

## Effect of a dietary intervention based on the Mediterranean diet on the quality of life of patients recovered from depression: Analysis of the PREDIDEP randomized trial

Beatriz M. Cabrera-Suárez<sup>a</sup>, Francisca Lahortiga-Ramos<sup>b,c</sup>, Carmen Sayon-Orea<sup>d</sup>, Jose L. Hernández-Fleta<sup>a</sup>, Ana González-Pinto<sup>d,e</sup>, Patricio Molero<sup>b,c</sup>, Rosario Vega-Pérez<sup>a</sup>, Almudena Sánchez-Villegas<sup>c,d,f,\*,\*\*,\*\*\*</sup>, PREDI-DEP investigators

<sup>a</sup> Psychiatry and Clinical Psychology Service, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

<sup>b</sup> Department of Psychiatry and Medical Psychology, University Clinic of Navarra, Pamplona, Spain

<sup>c</sup> IdiSNA, Instituto de Investigación Sanitaria de Navarra, Spain

<sup>d</sup> Centro de Investigación Biomédica en Red (CIBER), Instituto de Salud Carlos III, Madrid, Spain

<sup>e</sup> BIOARABA, Hospital Universitario de Alava, UPV/EHU, Spain

<sup>f</sup> ISFOOD - Institute for Innovation & Sustainable Development in Food Chain, Universidad Pública de Navarra (UPNA), Spain

### ARTICLE INFO

#### Keywords:

Mediterranean diet  
Quality of life  
Depression  
Olive oil  
Clinical trial

### ABSTRACT

**Introduction:** There is substantial evidence supporting that improving diet quality leads to improved health-related quality of life (HRQoL). Our major aim was to assess the effectiveness of a Mediterranean diet-based nutritional intervention to improve HRQoL in the context of a secondary prevention trial of depression. Secondarily to assess its effectiveness among adults aged 60 or more years.

**Methods:** The PREDIDEP study is a 2-year multicentre, randomized, single-blinded nutritional trial. At baseline and at 1-year and 2-year follow-up, SF-36 health survey questionnaire was collected to evaluate participants' HRQoL (total and specific range for each of the 8 dimensions: 0 to 100 points). Mixed effect linear models were used to assess changes in HRQoL according to adherence to the Mediterranean diet. The trial was registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) NCT03081065.

**Results:** After 2 years of intervention, the Mediterranean Diet intervention group compared to control group (without nutritional intervention, only usual clinical care) showed an improvement in some dimensions of HRQoL such as Mental Health (7.22; 95 % CI = 2.22–12.22) (between-group difference: 6.79; 95 % CI –0.14–13.73,  $p = 0.055$ ); Vitality (9.51; 95 % CI = 4.00–15.03) (between-group difference: 9.00; 95 % CI 1.75–16.25,  $p = 0.020$ ); Mental Summary Component (2.83; 95 % CI = 0.55–5.11) (between-group difference: 1.17; 95 % CI = –1.96–4.30,  $p = 0.462$ ); and General Health (10.70; 95 % CI = 5.58–15.81) (between-group difference: 6.20; 95 % CI = –0.89–13.28,  $p = 0.086$ ). Similar results were observed for participants aged 60 or more years.

**Conclusion:** The intervention based on Mediterranean diet in patients with previous depression seems to be effective in improving HRQoL, especially the mental dimensions. This effect is also observed among participants aged 60 or more years.

**Abbreviations:** BMI, body mass index; BP, bodily pain; CIs, Confidence Intervals; DALYs, disability-adjusted life years; DS, standard deviation; GH, General Health; HELFIMED, Mediterranean-style dietary intervention supplemented with fish oil; HRQoL, health-related quality of life; MEDAS, Mediterranean Diet Adherence Screener; MET, metabolic equivalent; MH, Mental Health; MSC, Mental Summary Component; PF, physical functioning; PREDIDEP, Prevention of depression with Mediterranean Diet (Prevención con Dieta Mediterránea de Depresión); PSC, Physical Summary Component; RE, role emotional; SDs, standard deviations; SF, social functioning; SF-36, The Short Form-36 Health Survey; VT, vitality; YLD, Years Lived with Disability.

\* Corresponding author at: IdiSNA, Instituto de Investigación Sanitaria de Navarra, Spain.

\*\* Corresponding author at: ISFOOD - Institute for Innovation & Sustainable Development in Food Chain, Universidad Pública de Navarra (UPNA), Pamplona, Spain.

\*\*\* Corresponding author at: Centro de Investigación Biomédica en Red (CIBER), Instituto de Salud Carlos III, Madrid, Spain.

E-mail address: [almudena.sanchez@unavarra.es](mailto:almudena.sanchez@unavarra.es) (A. Sánchez-Villegas).

<https://doi.org/10.1016/j.exger.2023.112149>

Received 13 December 2022; Received in revised form 11 March 2023; Accepted 14 March 2023

Available online 20 March 2023

0531-5565/© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

The World Health Organization defines quality of life concept as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals expectations, standards and concerns (World Health Organization Quality of Life assessment, 1995). Unipolar depression is a prevalent and disabling condition that negatively influences quality of life. Patients with depression are more vulnerable to have a poorer health-related quality of life (HRQoL) (Papakostas et al., 2004). Moreover, factors such as the age of onset of depression, lack of therapeutic adherence, the existence of comorbid diseases, poor social support, perceived self-stigma, and positive family history influence in depressed patients' HRQoL (Priebe et al., 2010). This situation is particularly dramatic in older patients. In this population, severity of depression has been also associated to poorer HRQoL, and this association has been found to be stable over time (Sivertsen et al., 2015). Depression is one of the leading global causes of quality of life impairment measured in disability-adjusted life years (DALYs) and Years Lived with Disability (YLD) (GBD 2019 Mental Disorders Collaborators, 2022). Quality of life is an important component and prognostic indicator of mental illness, and it is recommended to be integrated into the clinical assessment and interventions of people with severe mental illness. In depression, HRQoL is affected by the nature of the symptoms (depressed mood, anhedonia, apathy, low self-esteem, psychomotor retardation, among others), comorbid diseases, and social, occupational and cognitive deterioration (ulHaq et al., 2016).

There is substantial evidence supporting the relationship between high adherence to Mediterranean diet and low risk for depression (Lassale et al., 2019) or improvement in HRQoL (Muñoz et al., 2009; Galilea-Zabalza et al., 2018). The specific biological mechanisms that link depression, HRQoL, and diet are still unknown. It is a challenge for Public Health policies to identify new strategies to increase depressed patients' quality of life to reduce their substantial resource expenditure and personal and familiar suffering.

The principal objective of this study was to assess the effect of 2-year intervention with Mediterranean Diet enriched with extravirgin olive oil on HRQoL improvement in the context of a secondary prevention trial of depression particularly among participants older than 60 years.

## 2. Material & methods

### 2.1. Study population

The PREDIDEP study was a multicentre, randomized, controlled, single-blind trial. The study design and methodology has been described previously in detail elsewhere (Sánchez-Villegas et al., 2019). Briefly, study participants were randomly assigned to one of two groups (Mediterranean diet or control) once their data were included in a centralized data management system by the specialists. Various stratification factors were considered for randomization, sex, age group (<65 years or ≥65 years), and recruitment centre. At baseline, psychiatrists and clinical psychologists were blinded to the allocation of participants, following the CONSORT guidelines for randomized trials to prevent information biases.

The PREDIDEP study included 52 men and 144 women between 18 and 86 years old who had suffered at least one depression episode and who were in a stage of clinical remission. Between March 2017 and December 2020, 222 patients from different Spanish regions or provinces (Alava, Navarra, Madrid, and Las Palmas) were invited to participate in the study by their specialists. Of them, although 208 patients were recruited and randomized, 196 started the intervention. The number of dropouts was 17, and the retention rate was 92.9 % among participants with follow-up over 12 months (182/196), and 91.3 % with follow-up over 24 months (179/196).

In a secondary analysis, we included all participants who had already

been followed up for at least 2 years (n = 157). Among them, 134 had successfully fulfilled the information about HRQoL collected in SF-36 questionnaires (Fig. 1).

Additional analyses were carried out to assess the role of the dietary intervention in HRQoL among participants aged 60 or more years who completed the trial (n = 29 in the control group and n = 26 in the intervention group).

All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The trial was registered at ClinicalTrials.gov NCT03081065. The Research Ethics Committees at each recruitment centre approved the protocol. All participants provided written informed consent after they received the information sheet and an additional verbal explanation of the study characteristics.

### 2.2. Description of the intervention

The aim of the nutritional intervention of the PREDIDEP study was to improve adherence to the Mediterranean diet in recovered depressed patients. In the PREDIDEP study, we used a remote nutritional intervention rather than an in-person approach. This remote intervention was conducted by a team of registered dietitians by phone and on the internet, and participants had access to web-based information on a website and printed materials. Each participant in the intervention group also received extravirgin olive oil for free. The nutritional intervention has been described previously in detail elsewhere (Sánchez-Villegas et al., 2019). Participants in the control group received usual clinical care but not a nutritional intervention.

### 2.3. Outcome assessment

HRQoL was assessed at baseline and yearly during follow-up (by phone or through the web page) with the validated Spanish version of the SF-36 Health Survey. This instrument is useful to evaluate the relationship between lifestyle habits and non-disease-specific quality of life (Alonso et al., 1998).

This questionnaire contains 36 items, which measure eight multiitem dimensions of health status: physical functioning, role limitations because of physical health problems (role-physical), bodily pain (tolerance), general health perceptions, vitality, social functioning, role limitations because of emotional problems (role emotional) and mental health. The first four domains deal with physical aspects, and the next four reflect psychological features. For each dimension, the scores are coded, summed, and transformed to a scale from 0 (the worst possible condition) to 100 (the best possible condition) (Brazier et al., 1992).

Change in HRQoL was measured for each dimension as the difference between one-year follow-up and baseline scores (short-term change) or two years follow-up and baseline scores (long-term change).

### 2.4. Other covariate assessment

At baseline, the dietitians also collected information about socio-demographic characteristics (education level, civil status, and working status), smoking habits, and anthropometric measurements (self-reported weight and height). During this phone call, information about physical activity was also collected with a physical activity questionnaire validated for the Spanish population (Martínez-González et al., 2005).

Depressive symptoms were assessed through the Beck Depression Inventory. In case of suspected recurrence (score Beck Depression Inventory >18), participants were examined by care providers and they were excluded if they suffered a depression recurrence.

2.5. Sample size calculation and statistical analysis

To detect a mean yearly difference of 5 points in the physical and mental summary components with a standard deviation equal to 10 in each group with a 5 % significance level and 80 % power, a sample size of 126 participants was calculated. Considering an attrition of 15 %, the final number of required participants was 150.

The main analysis of the study included all randomized participants with baseline data, regardless of whether they had incomplete information at follow-up visits, with multiple imputation procedures for missing data (intention to treat analysis). Multiple imputation methods used an iterative Markov chain Monte Carlo method (STATA “mi” command). We generated 20 imputations for each missing measurement. Imputed missing values were used for follow-up data but not for baseline data. The imputation models included sex, age, smoking status, body mass index (BMI), civil status, education level, total energy intake, physical activity, depressive symptoms (baseline Beck score), intervention group, and the baseline value of the variable that was imputed as a predictor. Secondary analyses included only participants with complete information available at each follow-up visit (completers only).

Quantitative variables were expressed as means and standard deviations (SDs), whereas categorical variables were described as number and percentages (n [%]). The Student *t*-test for continuous variables and the chi-square test for categorical variables were applied to test differences in baseline characteristics between the intervention groups.

Mixed effects linear models were used to assess changes in HRQoL from baseline to 12- and 24-month follow-up visits in all randomized participants and completer-only analyses. A 2-level mixed linear model with random intercepts at the recruitment centre and participants was fitted.

The analyses were performed using STATA (v 12.0, StataCorp LP). The significance level (2-tailed) was set at p values lower than 0.05.

3. Results

Among the 196 patients who started the intervention, 73.5 % were women and the mean age was 51.1 years (SD 14.2). Table 1 shows the demographic, anthropometric, and lifestyle baseline characteristics of participants according to the randomized groups (intervention or control). No baseline significant differences between intervention groups

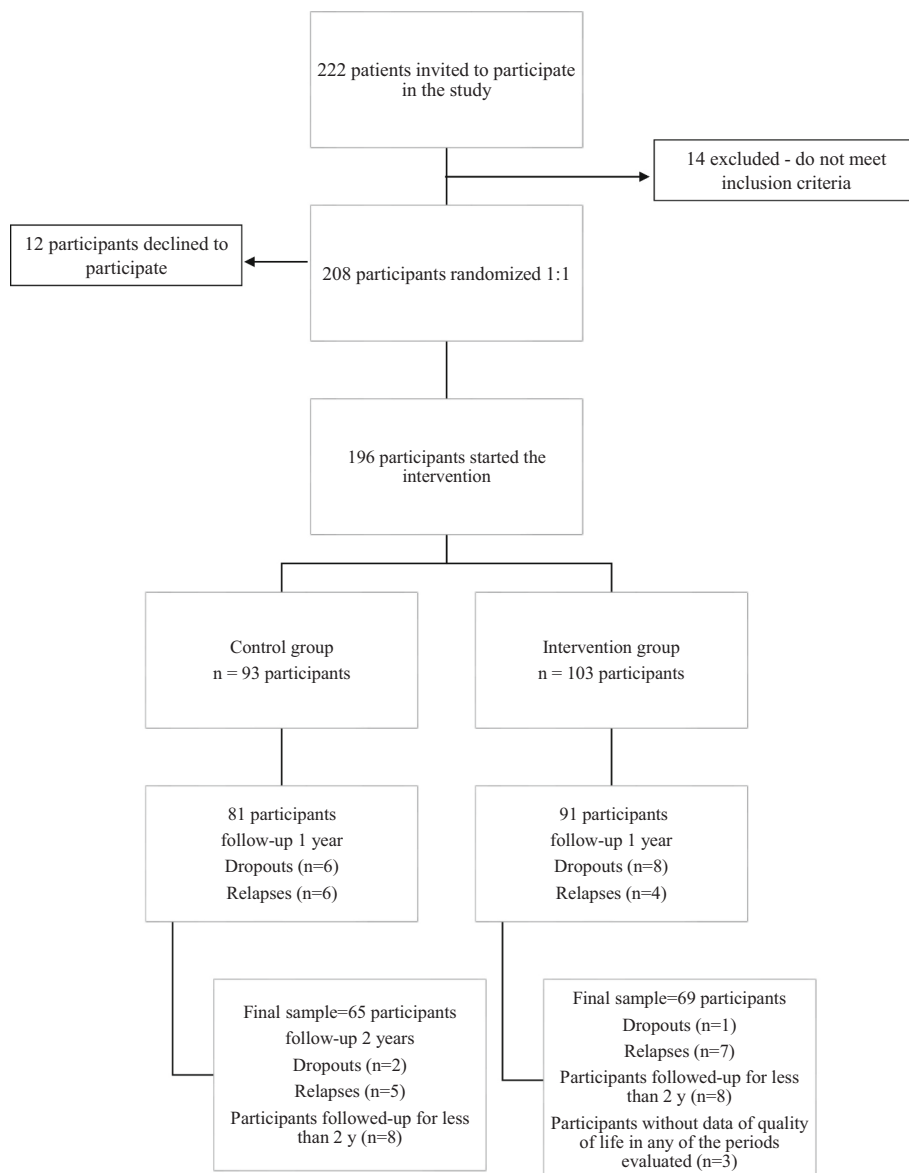


Fig. 1. Flow-chart of participant screening, recruitment, and randomization.

were found. When the analysis was restricted to those participants aged 60 years or more, baseline characteristics were also similar between comparison groups (data not shown).

### 3.1. HRQoL changes by intervention groups

The effect of dietary intervention on changes in mental dimensions of HRQoL is shown in Table 2.

After one year of follow-up, the intervention group showed a significant increase in Vitality [mean absolute 1-y change for this domain was 5.41 points (95 % CI = 0.51–10.31)] and in Mental Summary Component [2.48 (95 % CI = 0.54–4.41)], with no mean absolute changes in the control group. However, between group differences did not reach statistical significance. The results for Vitality and Mental Summary Component were similar in the analyses including only completers.

After two years of intervention, there was a significant increase in Mental Health [mean absolute 2-y change was 7.22 (95 % CI =

**Table 1**

Baseline characteristics of the participants in the prevention of recurrent depression with Mediterranean diet trial.

Characteristics	Control (n = 93)	Intervention (n = 103)	p value*
Age, years, mean (SD)	51.48 (14.7)	51.16 (13.79)	0.8647
Sex, n (%)			0.588
Men	23 (24.73)	29 (28.16)	
Women	70 (75.27)	74 (71.84)	
Depressive episodes, n (%)			0.274
1	42 (45.16)	35 (33.98)	
2	21 (22.58)	27 (26.21)	
3 or more	30 (32.26)	41 (39.81)	
Somatic diseases, n (%)	28 (30.43)	26 (25.24)	0.419
Antidepressants use, n (%)	70 (75.27)	81 (78.64)	0.575
Civil status, n (%)			0.558
Single	33 (35.87)	34 (33.01)	
Married	37 (40.22)	49 (47.57)	
Others	22 (23.91)	20 (19.41)	
Education, n (%)			0.613
Secondary or less	48 (52.17)	50 (48.54)	
University	44 (47.82)	53 (51.45)	
Working status, n (%)			0.826
Working	39 (42.39)	47 (45.63)	
Retired	16 (17.39)	19 (18.45)	
Others	37 (40.22)	37 (35.92)	
BMI (kg/m <sup>2</sup> )	26.04 (5.29)	26.09 (4.78)	0.945
Smoking status, n (%)	24 (26.09)	24 (23.30)	0.457
Illegal drugs, n (%)	8 (8.6)	9 (8.74)	0.973
Beck score	5.78 (5.24)	6.41 (5.84)	0.428
Physical activity (MET-hours/week)	16.30 (19.19)	18.13 (24.99)	0.5694
MEDAS score (14 items)	7.01 (2.1)	7.04 (1.97)	0.8959
HRQoL mental dimensions			
- MSC	37.07 (7.13)	37.85 (7.00)	0.4462
- MH	62.70 (1.99)	67.02 (1.81)	0.1090
- VT	53.10 (2.30)	54.02 (2.16)	0.7705
- SF	75.54 (3.29)	81.74 (2.90)	0.1582
- RE	29.35 (4.40)	23.53 (3.90)	0.3219
HRQoL physical dimensions			
- PSC	47.81 (7.35)	48.36 (7.21)	0.6002
- GH	60.67 (2.64)	60.62 (2.54)	0.9878
- BP	70.11 (2.95)	73.04 (2.85)	0.4761
- PF	88.26 (1.78)	90.00 (1.60)	0.4676
- RP	21.74 (4.00)	20.34 (3.71)	0.7982
Energy intake (kcal/day)	2531 (809)	2683 (874)	0.2094

BMI: body mass index; BP: Bodily pain; GH: General Health; HRQoL: Health Related Quality of Life; MET: Metabolic equivalent; MEDAS: Mediterranean Diet Adherence Screener; MH: Mental Health; MSC: Mental Summary Component; PF: Physical functioning; PSC: Physical Summary Component; RE: Role emotional; RP: Role physical; SF: Social functioning; VT: Vitality.

\* p-value obtained through the Student's t-test (quantitative variables) or the Chi-square (qualitative variables).

2.22–12.22)], Vitality [9.51 (95 % CI = 4.00–15.03)], and Mental Summary Component [2.83 (95 % CI = 0.55–5.11)] in the intervention group with Mediterranean Diet enriched with extravirgin olive oil, with no changes in control group. In addition, significant differences between groups were observed for Vitality (between-group difference: 9.00; 95 % CI = 1.75–16.25,  $p = 0.015$ ). In the analyses including only completers, the results did not substantially differ also finding a significant difference between groups in Mental Health after two years of intervention (between-group difference: 7.37; 95 % CI = 0.82–13.92,  $p = 0.027$ ).

The effect of the nutritional intervention on the physical dimensions of HRQoL is showed in Table 3. After one year of follow-up, intervention group showed a significant improvement in General Health [5.05 (95 % CI = 0.63–9.47)] and Role physical [14.00 (95 % CI = 2.88–25.11)] with no changes in control group. After two years of intervention, there was a significant increase in General Health [10.70 (95 % CI = 5.58–15.81)] in the intervention group with Mediterranean Diet enriched with extravirgin olive oil, with no changes in control group. Results were very similar in the analysis including only completers.

Results for the analysis restricted to older participants were similar (Supplemental Tables 1 and 2). Among participants that completed the overall follow-up period, those assigned to the Mediterranean dietary pattern showed a significant increment in the Vitality dimension (10.49; 95 % CI = 1.96–19.03) and in the Mental Summary Component (3.50; 95 % CI = 0.79–6.21) after two years of follow-up although, in these cases, the differences between groups were not significant. Regarding physical dimensions, important increment in General Health was observed for participants assigned to the Mediterranean diet at short term (one year of intervention): increment in 7.19 points (95 % CI = 0.28–14.10) and at long term (two years of intervention): increment in 11.41 points (95 % CI = 2.46–20.37), although only significant differences between groups were observed for this dimension after one year of follow up (9.27; 95 % CI = 1.07–17.46).

### 3.2. Adverse effects

Regarding the possible adverse effect, we did not find any harm or unintended effects in the group assigned to Mediterranean diet supplemented with extravirgin olive oil.

## 4. Discussion

### 4.1. Principal findings

This trial is, to our knowledge, the first multiprofessional intervention study which has evaluated the effect of a remote dietary intervention based on the Mediterranean diet enriched with extravirgin olive oil in increasing HRQoL in recovered depressed patients. This dietary intervention was specifically designed for patients in clinical remission who had suffered at least one depression episode and was based on personalized nutritional information through different remote access routes, in coordination with face-to-face interventions, carried out by psychiatrists and psychologists.

The intervention based on Mediterranean diet resulted in an improvement in quality of life, especially in General Health and in the mental domains of HRQoL: Mental Health and Vitality, as well as in Mental Summary Component. When the analyses were restricted to participants aged 60 or more years the results were consistent with significant increment in Vitality, Mental Summary Component and General Health after two years of intervention with Mediterranean diet.

Furthermore, it should be highlighted the great magnitude of the increment observed for Vitality and General Health scores after two years of intervention, higher than 8 points in both the overall sample and in the sub-analysis including only participants aged 60 or more years. There is a debate on how to define meaningful differences on the SF-36 scores in a clinical setting. Even absolute differences from 3 to 10 points have been suggested as relevant (Samsa et al., 1999; Norman

**Table 2**

Changes in the mental dimensions of the HRQoL at 12- and 24-month follow-up visits of all randomized PREDIDEP participants according to randomized treatment group.

HRQoL mental and physical dimensions	Control group, mean change (CI 95 %)		Intervention group, mean change (CI 95 %)		Control vs. Intervención			
	Intention-to-treat <sup>a</sup> (n = 93)	Completers-only <sup>b</sup> (n = 65)	Intention-to-treat <sup>a</sup> (n = 103)	Completers-only <sup>b</sup> (n = 69)	Intention-to-treat <sup>c</sup> (MI)	p value <sup>d</sup>	Completers-only <sup>c</sup>	p value <sup>d</sup>
<b>Mental Health</b>								
1-year change	-2.43 (-7.13-2.27)	-2.30 (-6.30-1.70)	2.73 (-1.63-7.09)	2.87 (-1.55-7.28)	5.16 (-1.26-11.59)	0.115	5.17 (-0.79-11.12)	0.089
2-year change	0.43 (-4.38-5.23)	0.23 (-4.28-4.74)	<b>7.22</b> <b>(2.22-12.22)</b>	<b>7.60</b> <b>(2.85-12.36)</b>	6.79 (-0.14-13.73)	0.055	<b>7.37 (0.82-13.92)</b>	<b>0.027</b>
<b>Vitality</b>								
1-year change	-0.53 (-5.81-4.75)	-0.56 (-5.54-4.42)	<b>5.41</b> <b>(0.51-10.31)</b>	<b>5.37</b> <b>(0.47-10.27)</b>	5.94 (-1.27-13.16)	0.106	5.93 (-1.06-12.92)	0.096
2-year change	0.43 (-4.90-5.76)	-0.22 (-5.18-4.74)	<b>9.51</b> <b>(4.00-15.03)</b>	<b>8.78</b> <b>(3.49-14.06)</b>	<b>9.09 (1.42-16.75)</b>	<b>0.020</b>	<b>9.00 (1.75-16.25)</b>	<b>0.015</b>
<b>Social functioning</b>								
1-year change	2.09 (-5.69-9.88)	2.12 (-5.59-9.83)	1.62 (-5.64-8.88)	1.35 (-5.16-7.86)	-0.47 (-11.13-10.18)	0.930	-0.77 (-10.87-9.32)	0.881
2-year change	1.35 (-6.54-9.25)	1.28 (-7.08-9.64)	3.95 (-4.15-12.06)	4.47 (-2.49-11.42)	2.60 (-8.75-13.96)	0.653	3.19 (-7.69-14.06)	0.566
<b>Role emotional<sup>e</sup></b>								
1-year change	4.65 (-6.42-15.72)	4.48 (-6.08-15.04)	7.13 (-3.25-17.52)	6.38 (-3.53-16.28)	2.48 (-12.61-17.57)	0.747	1.89 (-12.58-16.37)	0.798
2-year change	7.58 (-3.50-18.66)	7.44 (-4.53-19.40)	-3.38 (-14.93-8.16)	-3.39 (-13.87-7.09)	-10.96 (-26.86-4.93)	0.176	-10.83 (-26.73-5.07)	0.182
<b>Mental Summary Component</b>								
1-year change	0.54 (-1.52-2.60)	0.55 (-1.35-2.45)	<b>2.48 (0.54-4.41)</b>	<b>2.36 (0.55-4.17)</b>	1.94 (-0.98-4.77)	0.180	1.81 (-0.81-4.43)	0.176
2-year change	1.66 (-0.51-3.82)	1.57 (-0.66-3.81)	<b>2.83 (0.55-5.11)</b>	<b>2.84 (0.73-4.94)</b>	1.17 (-1.96-4.30)	0.462	1.26 (-1.81-4.33)	0.421

CI: Confidence Interval. HRQoL: Health-Related Quality of Life.

<sup>a</sup> Calculated using multiple imputation method with 20 imputations for each missing measurement.

<sup>b</sup> Calculated using mixed-effect models with centre as random factor.

<sup>c</sup> Calculated using mixed-effect models with site and intracluster correlations (couples) as random factors.

<sup>d</sup> p value between group intervention difference.

<sup>e</sup> Role emotional: convergence not achieved with the original model; thus, for this variable, the imputation model included sex, age, smoking status, body mass index (BMI), total energy intake, physical activity, depressive symptoms (baseline Beck score), intervention group, and the baseline value of role emotional. Marital status and education were excluded from the imputation method.

et al., 2003). Therefore, our results could be considered clinically significant.

#### 4.2. Comparison with prior work

The benefits of a high adherence to the Mediterranean Diet are more than those which evidence has already demonstrated for the general health population or in the prevention and prognosis of different kinds of pathologies (Sánchez-Sánchez et al., 2020). During the last years, the benefit of Mediterranean diet has been the focus on its relationship with quality of life. In fact, there are several studies that have analyzed the relationship between Mediterranean Diet and HRQoL. A recent meta-analysis (Vajdi and Farhangi, 2020) evaluated 13 studies with a total of 43,445 subjects. It determined that both a “healthy” and a “Mediterranean” diet pattern were related to better HRQoL scores.

The perceived benefits found for Mediterranean diet have been consolidated in culturally diverse populations and countries, such as Italy (Bonaccio et al., 2013) and Spain (Galilea-Zabalza et al., 2018), Greece, and the United Kingdom (Klonizakis et al., 2019), or the United States (Gigic et al., 2018), with improvements in various dimensions of

HRQoL in those individuals with greater adherence to the Mediterranean diet pattern. This universality also goes beyond issues such as population age profile. The evidence has been also replicated with these improvements in the adolescent (Costarelli et al., 2013) and elderly populations (Govindaraju et al., 2018).

However, we cannot forget that our study is based on adults affected by a medical condition, depression. Other studies have determined the benefits of high adherence to a Mediterranean diet on HRQoL for other pathologies, such as type 2 diabetes mellitus (Alcubierre et al., 2016) metabolic syndrome (Galilea-Zabalza et al., 2018) or individuals at cardiovascular risk (Sanchez-Aguadero et al., 2016). In these pathologies, improvements were found for both mental and physical dimensions of HRQoL. Depression shares with all of them a common pathophysiological process that makes them susceptible to all potential benefits of Mediterranean diet, such as a low-grade inflammatory state mediated by the gut microbiota (Hills et al., 2019).

Nevertheless, unlike the results of the aforementioned studies, in our analysis we observed benefits especially for the mental domains of HRQoL. Our participants are individuals with a potential risk of presenting a new depressive episode whose most affected HRQoL domains

**Table 3**

Changes in the physical dimensions of the HRQoL at 12- and 24-month follow-up visits of all randomized PREDIDEP participants according to randomized treatment group.

HRQoL mental and physical dimensions	Control group, mean change (CI 95 %)		Intervention group, mean change (CI 95 %)		Control vs. Intervención			
	Intention-to-treat <sup>a</sup> (n = 93)	Completers-only <sup>b</sup> (n = 65)	Intention-to-treat <sup>a</sup> (n = 103)	Completers-only <sup>b</sup> (n = 69)	Intention-to-treat <sup>c</sup> (MI)	p value <sup>d</sup>	Completers-only <sup>c</sup>	p value
<b>General Health</b>								
1-year change	0.67 (−4.08–5.41)	0.88 (−3.19–4.96)	<b>5.05 (0.63–9.47)</b>	<b>5.88 (1.92–9.83)</b>	4.39 (−2.11–10.88)	0.185	4.99 (−0.69–10.68)	0.085
2-year change	4.50 (−0.41–9.41)	4.76 (−0.29–9.82)	<b>10.70 (5.58–15.81)</b>	<b>10.92 (5.83–16.00)</b>	6.20 (−0.89–13.28)	0.086	6.15 (−1.02–13.32)	0.093
<b>Bodily pain</b>								
1-year change	<b>−7.90 (−14.84 to −0.96)</b>	<b>−7.51 (−13.28 to −1.73)</b>	<b>−9.20 (−15.64 to −2.77)</b>	<b>−9.11 (−15.67 to −2.54)</b>	−1.31 (−10.78–8.17)	0.787	−1.60 (−10.34–7.14)	0.720
2-year change	<b>−11.67 (−18.72 to −4.61)</b>	<b>−11.40 (−18.22 to −4.57)</b>	<b>−3.77 (−11.15–3.62)</b>	<b>−3.72 (−10.47–3.03)</b>	7.90 (−2.36–18.16)	0.131	7.68 (−1.92–17.28)	0.117
<b>Physical functioning</b>								
1-year change	−2.33 (−5.55–0.88)	−2.48 (−5.39–0.43)	−2.05 (−5.02–0.93)	−1.88 (−5.22–1.36)	0.29 (−4.11–4.68)	0.898	0.61 (−3.75–4.96)	0.785
2-year change	<b>−3.83 (−7.03 to −0.63)</b>	<b>−3.97 (−7.05 to −0.90)</b>	<b>−3.50 (−6.77 to −0.23)</b>	<b>−3.03 (−5.84 to −0.22)</b>	0.33 (−4.26–4.92)	0.888	0.94 (−3.22–5.10)	0.657
<b>Role physical</b>								
1-year change	7.30 (−4.65–19.24)	6.89 (−3.11–16.89)	<b>14.00 (2.88–25.11)</b>	<b>14.01 (2.87–25.16)</b>	6.70 (−9.65–23.05)	0.422	7.13 (−7.85–22.10)	0.351
2-year change	<b>14.79 (2.77–26.82)</b>	<b>13.54 (1.52–25.55)</b>	5.07 (−7.32–17.47)	4.60 (−6.42–15.62)	−9.72 (−26.87–7.43)	0.266	−8.94 (−25.25–7.37)	0.283
<b>Physical Summary Component</b>								
1-year change	−0.54 (−2.26–1.18)	−0.49 (−1.99–1.01)	−0.18 (−1.78–1.43)	−0.03 (−1.60–1.53)	0.36 (−2.00–2.73)	0.115	0.46 (−1.71–2.63)	0.681
2-year change	−0.47 (−2.22–1.27)	−0.56 (−2.33–1.20)	0.54 (−1.24–2.31)	0.47 (−1.19–2.14)	1.01 (−1.49–3.50)	0.055	1.04 (−1.39–3.47)	0.402

CI: Confidence Interval. HRQoL: Health-Related Quality of Life.

<sup>a</sup> Calculated using multiple imputation method with 20 imputations for each missing measurement.<sup>b</sup> Calculated using mixed-effect models with centre as random factor.<sup>c</sup> Calculated using mixed-effect models with site and intracluster correlations (couples) as random factors.<sup>d</sup> p value between group intervention difference.

are mental dimensions. Thus, we consider that the observed results are of special importance in the management of this kind of patients.

However, to our knowledge, only one previous study, the HELFIMED study, has directly evaluated changes in HRQoL in an intervention with a Mediterranean diet in patients with depression, with a shorter sample size and duration (Parletta et al., 2019). Similar to our results, this study concluded that the intervention with Mediterranean diet supplemented with fish oil improved Mental Health dimensions of HRQoL. We also found improvements in Vitality, Total Mental Score and General Health parameters in HRQoL.

#### 4.3. Strengths and limitations

There are several strengths and limitations of this study that should be considered when interpreting the results.

The main strength of this study is that, as far as we know, this is the first trial including such a high number of participants and that it has evaluated the effect of a dietary intervention based on the principles of the Mediterranean diet on the HRQoL of individuals recovered from depression for a large period of time, up to 2 years. That long duration has allowed us to accurately evaluate the medium-long-term effects of adherence to the Mediterranean diet on HRQoL. Moreover, HRQoL and adherence to Mediterranean diet-related data were evaluated by SF-36

and MEDAS, respectively, which were assessed at baseline and during the intervention. Thereby, the precision of the analyses and temporal consistency of the results are guaranteed.

Likewise, to evaluate low/high adherence to the Mediterranean diet according to MEDAS, we have used a widely used reference point for Spanish population (García-Conesa et al., 2020), which allows us to obtain comparable results with other populations. Finally, some analyses have been adjusted for a wide range of baseline characteristics that could have interfered with the results.

However, the results obtained in our study might not be applicable to the general population. Our study is based on patients with depression, who present worse HRQoL baseline scores (Papakostas et al., 2004).

Another possible limitation of this study is that SF-36 questionnaire is a self-reported measure, which is susceptible to information bias. It is possible that the association reflects a tendency to report outcomes as more favourable than they actually are (social desirability bias). Likewise, if there had been an information bias, this would be a non-differential one; and it would have biased the results towards null (lack of effectiveness). Therefore, it would be expected that the difference obtained would be even greater than that observed. Furthermore, the use of validated questionnaire such as SF-36 (Brazier et al., 1992) to assess information minimizes this possibility.

## 5. Conclusion

In conclusion, our results suggest that a Mediterranean diet-based nutritional intervention enriched with extravirgin olive oil compared with usual care, resulted in a significantly greater increase in HRQoL in recovered depressed patients. This association was greater for the mental dimensions rather than the physical dimensions of SF-36. The association was also observed for participants aged 60 or more years specially for Vitality and General Health domains.

Depression is an important condition for its high prevalence and economic cost, and the personal suffering that involves. For that reason, the evaluation of cost-effective, safe, and inexpensive interventions, such as Mediterranean Diet nutritional interventions, is mandatory. It reaches greater importance due to its impact on HRQoL, which affects the subsequent development and prognosis of depression, especially among older patients.

## Funding

This study was externally funded by the Spanish Ministry of Science and Innovation (Carlos III National Health Institute-ISCIII), PI16/01274. The Interprofesional del Aceite de Oliva-Aceites de Oliva de España (Madrid, Spain) donated the olive oil used in the study.

None of the funding sources played a role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

## CRedit authorship contribution statement

Almudena Sánchez-Villegas: Conceptualization.

Beatriz M Cabrera-Suárez, Francisca Lahortiga-Ramos, Jose L Hernández-Fleta, Ana González-Pinto, Patricio Molero, Rosario Vega-Pérez: Data curation.

Beatriz M Cabrera-Suárez; Carmen Sayon-Orea: Formal analysis.

Almudena Sánchez-Villegas: Funding acquisition.

Almudena Sánchez-Villegas, Beatriz M Cabrera-Suárez, Francisca Lahortiga-Ramos, Jose L Hernández-Fleta, Ana González-Pinto, Patricio Molero, Rosario Vega-Pérez: Methodology.

Beatriz M Cabrera-Suárez, Almudena Sánchez-Villegas: Roles/Writing - original draft.

All authors: Writing - review & editing.

## Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

## Data availability

Data will be made available on request.

## Acknowledgments

The authors are grateful to the PREDIDEP study participants.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.exger.2023.112149>.

## References

Alcubierre, N., Martínez-Alonso, M., Valls, J., Rubinat, E., Traveset, A., Hernández, M., Martínez-González, M.D., Granado-Casas, M., Jurjo, C., Vioque, J., Navarrete-Muñoz, E.M., Mauricio, D., 2016. Relationship of the adherence to the Mediterranean diet with health-related quality of life and treatment satisfaction in patients with type 2 diabetes mellitus: a post-hoc analysis of a cross-sectional study.

Health and Quality of Life Outcomes 14, 69. <https://doi.org/10.1186/s12955-016-0473-z>.

Alonso, J., Regidor, E., Barrio, G., Prieto, L., Rodríguez, C., de la Fuente, L., 1998. Population reference values of the Spanish version of the Health Questionnaire SF-36. In: *Valores poblacionales de referencia de la versión española del Cuestionario de Salud SF-36*, 111(11). *Medicina Clínica, Barc*, pp. 410–416.

Bonaccio, M., Di Castelnuovo, A., Bonanni, A., Costanzo, S., De Lucia, F., Pounis, G., Zito, F., Donati, M.B., de Gaetano, G., Iacoviello, L., Moli-sani project Investigators, 2013. Adherence to a Mediterranean diet is associated with a better health-related quality of life: a possible role of high dietary antioxidant content. *BMJ Open* 3 (8), e003003. <https://doi.org/10.1136/bmjopen-2013-003003>.

Brazier, J.E., Harper, R., Jones, N.M., O'Catlain, A., Thomas, K.J., Usherwood, T., Westlake, L., 1992. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *Br. Med. J.* 305 (6846), 160–164. <https://doi.org/10.1136/bmj.305.6846.160>.

Costarelli, V., Koretsi, E., Georgitsogianni, E., 2013. Health-related quality of life of Greek adolescents: the role of the Mediterranean diet. *Qual. Life Res.* 22 (5), 951–956.

Galilea-Zabalza, I., Buil-Cosiales, P., Salas-Salvadó, J., Toledo, E., Ortega-Azorín, C., Díez-Espino, J., Vázquez-Ruiz, Z., Zomeño, M.D., Vioque, J., Martínez, J.A., Romaguera, D., Perez-Farinos, N., López-Miranda, J., Estruch, R., Bueno-Cavanillas, A., Arós, F., Tur, J.A., Tinahones, F., Serra-Majem, L., et al., 2018. Mediterranean diet and quality of life: baseline cross-sectional analysis of the PREDIMED-PLUS trial. *PLoS One* 13 (6), e0198974. <https://doi.org/10.1371/journal.pone.0198974> eCollection 2018.

García-Conesa, M.T., Philippou, E., Pafilas, C., Massaro, M., Quarta, S., Andrade, V., Jorge, R., Chervenkov, M., Ivanova, T., Dimitrova, D., Maksimova, V., Smilkov, K., Ackova, D.G., Miloseva, L., Ruskovska, T., Deligiannidou, G.E., Kontogiorgis, C.A., Pinto, P., 2020. Exploring the validity of the 14-item Mediterranean Diet Adherence Screener (MEDAS): a cross-national study in seven European countries around the Mediterranean Region. *Nutrients* 12 (10), 2960. <https://doi.org/10.3390/nu12102960>.

GBD 2019 Mental Disorders Collaborators, 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Psychiatry* 9 (2), 137–150. [https://doi.org/10.1016/S2215-0366\(21\)00395-3](https://doi.org/10.1016/S2215-0366(21)00395-3).

Gigic, B., Boeing, H., Toth, R., Böhm, J., Habermann, N., Scherer, D., Schrotz-King, P., Abbenhardt-Martin, C., Skender, S., Brenner, H., Chang-Claude, J., Hoffmeister, M., Syrjala, K., Jacobsen, P.B., Schneider, M., Ulrich, A., Ulrich, C.M., 2018. Associations between dietary patterns and longitudinal quality of life changes in colorectal cancer patients: the ColoCare study. *Nutr. Cancer* 70 (1), 51–60. <https://doi.org/10.1080/01635581.2018.1397707>.

Govindaraju, T., Sahle, B.W., TA, McCaffrey, McNeil, J.J., Owen, A.J., 2018. Dietary patterns and quality of life in older adults: a systematic review. *Nutrients* 10 (8), 971. <https://doi.org/10.3390/nu10080971>, 2018.

Hills Jr, R.D., Pontefract, B.A., Mishcon, H.R., Black, C.A., Sutton, S.C., Theberge, C.R., 2019. Gut microbiome: profound implications for diet and disease. *Nutrients* 11 (7), 1613. <https://doi.org/10.3390/nu11071613>.

Klonizakis, M., Grammatikopoulou, M.G., Theodoridis, X., Milner, M., Liu, Y., Chourdakis, M., 2019. Effects of long-versus short-term exposure to the Mediterranean diet on skin microvascular function and quality of life of healthy adults in Greece and the UK. *Nutrients* 11 (10), 2487. <https://doi.org/10.3390/nu11102487>.

Lassale, C., Batty, G.D., Baghdadli, A., Jacka, F., Sánchez-Villegas, A., Kivimäki, M., Akbaraly, T., 2019. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Mol. Psychiatry* 24 (7), 965–986. <https://doi.org/10.1038/s41380-018-0237-8>.

Martínez-González, M.A., López-Fontana, C., Varo, J.J., Sánchez-Villegas, A., Martínez, J.A., 2005. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' health study and the health professionals' follow-up study. *Public Health Nutr.* 8 (7), 920–927. <https://doi.org/10.1079/phn2005745>.

Muñoz, M.A., Fito, M., Marrugat, J., Covas, M.I., Schröder, H., REGICOR and HERMES investigators, 2009. Adherence to the Mediterranean diet is associated with better mental and physical health. *British Journal of Nutrition* 101. <https://doi.org/10.1017/S0007114508143598>, 1821–1822.

Norman, G.R., Sloan, J.A., Wyrwich, K.W., 2003. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med. Care* 41 (5), 582–592. <https://doi.org/10.1097/01.MLR.0000062554.74615.4C>.

Papakostas, G.I., Petersen, T., Mahal, Y., Mischoulon, D., Nierenberg, A.A., Fava, M., 2004. Quality of life assessments in major depressive disorder: a review of the literature. *Gen. Hosp. Psychiatry* 26 (1), 13–17. <https://doi.org/10.1016/j.genhosppsych.2003.07.004>.

Parletta, N., Zarnowiecki, D., Cho, J., Wilson, A., Bogomolova, S., Villani, A., Itsiopoulos, C., Niyonsenga, T., Blunden, S., Meyer, B., Segal, L., Baune, B.T., O'Dea, K., 2019. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: a randomized controlled trial (HELFI-MED). *Nutr. Neurosci.* 22 (7), 474–487. <https://doi.org/10.1080/1028415X.2017.1411320>.

Priebe, S., Reininghaus, U., McCabe, R., Burns, T., Eklund, M., Hansson, L., Junghan, U., Kallert, T., van Nieuwenhuizen, C., Ruggeri, M., Slade, M., Wang, D., 2010. Factors influencing subjective quality of life in patients with schizophrenia and other mental disorders: a pooled analysis. *Schizophr. Res.* 121 (1–3), 251–258. <https://doi.org/10.1016/j.schres.2009.12.020>.

Samsa, G., Edelman, D., Rothman, M.L., Williams, G.R., Lipscomb, J., Matchar, D., 1999. Determining clinically important differences in health status measures: a general

- approach with illustration to the health utilities index mark II. *Pharmacoeconomics* 15, 141–155. <https://doi.org/10.2165/00019053-199915020-00003>.
- Sanchez-Aguadero, N., Alonso-Dominguez, R., Garcia-Ortiz, L., Agudo-Conde, C., Rodriguez-Martin, C., de Cabo-Laso, A., Sanchez-Salgado, B., Ramos, R., Maderuelo-Fernandez, J.A., Gomez-Marcos, M.A., Recio-Rodriguez, J.I., MARK Group, 2016. Diet and physical activity in people with intermediate cardiovascular risk and their relationship with the health-related quality of life: results from the MARK study. *Health and Quality of Life Outcomes* 14 (1), 169. <https://doi.org/10.1186/s12955-016-0572-x>.
- Sánchez-Sánchez, M.L., García-Vigara, A., Hidalgo-Mora, J.J., García-Pérez, M.A., Tarín, J., Cano, A., 2020. Mediterranean diet and health: a systematic review of epidemiological studies and intervention trials. *Maturitas* 136, 25–37. <https://doi.org/10.1016/j.maturitas.2020.03.008>.
- Sánchez-Villegas, A., Cabrera-Suárez, B., Molero, P., González-Pinto, A., Chiclana-Actis, C., Cabrera, C., Lahortiga-Ramos, F., Florido-Rodríguez, M., Vega-Pérez, P., Vega-Pérez, R., Pla, J., Calviño-Cabada, M.J., Ortuño, F., Navarro, S., Almeida, Y., Hernández-Fleta, J.L., 2019. Preventing the recurrence of depression with a Mediterranean diet supplemented with extra-virgin olive oil. The PREDI-DEP trial: study protocol. *BMC Psychiatry* 19 (1), 63. <https://doi.org/10.1186/s12888-019-2036-4>.
- Sivertsen, H., Bjørkløf, G.H., Engedal, K., Selbæk, G., Helvik, A.S., 2015. Depression and quality of life in older persons: a review. *Dement. Geriatr. Cogn. Disord.* 40 (5–6), 311–339. <https://doi.org/10.1159/000437299>. Epub 2015 Sep 12.
- ulHaq, N., Ahmed, N., Rasool, G., Ilyas, M., Nasim, A., 2016. Assessment of health related quality of life (HrQoL) of patients with severe mental illness attending tertiary care public hospitals of Quetta, Pakistan. *Value Health* 19 (7), A843. <https://doi.org/10.1016/j.jval.2016.08.751>.
- Vajdi, M., Farhangi, M.A., 2020. A systematic review of the association between dietary patterns and health-related quality of life. *Health Qual. Life Outcomes* 18 (1), 337. <https://doi.org/10.1186/s12955-020-01581-z>.
- World Health Organization, 1995. Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Social Science & Medicine* 41 (10), 1403–1409.