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Coronavirus disease 2019 is associated with long-term depressive symptoms in Spanish older adults with overweight/obesity and metabolic syndrome

Sangeetha Shyam[1,2,3], Carlos Gómez-Martínez[1,2,3], Indira Paz-Graniel[1,2,3], José J. Gaforio[4,5], Miguel Ángel Martínez-González[1,6,7], Dolores Corella[1,8], Montserrat Fitó[1,9], J. Alfredo Martínez[1,10,11], Ángel M. Alonso-Gómez[1,12], Julia Wärnberg[1,13], Jesús Vioque[4,14], Dora Romaguera[1,15], José López-Miranda[1,16], Ramon Estruch[1,17], Francisco J. Tinahones[1,18], José Manuel Santos-Lozano[1,19], J. Luís Serra-Majem[1,20], Aurora Bueno-Cavanillas[4,21], Josep A. Tur[1,22], Vicente Martín Sánchez[4,11,23], Xavier Pintó[1,24], María Ortiz Ramos[25], Josep Vidal[26,27], Maria Mar Alcarria[28], Lidia Daimiel[1,29,30], Emilio Ros[1,31], Fernando Fernandez-Aranda[1,32,33], Stephanie K. Nishi[1,2,3,34], Oscar García Regata[35], Estefania Toledo[1,6], Jose V. Sorli[1,8], Olga Castañer[9], Antonio Garcia-Rios[1,16], Rafael Valls-Enguix[36], Napoleon Perez-Farinos[1,13], M. Angeles Zulet[1,10], Elena Rayó-Gago[15], Rosa Casas[1,17], Mario Rivera-Izquierdo[21], Lucas Tojal-Sierra[1,12], Miguel Damas-Fuentes[18], Pilar Buil-Cosiales[1,6,37], Rebeca Fernández-Carrion[1,8], Albert Goday[9], Patricia J. Peña-Orihuela[1,16], Laura Compañ-Gabucio[4,14], Javier Diez-Espino[1,6,37], Susanna Tello[9], Ana González-Pinto[38], Víctor de la O[1,6], Miguel Delgado-Rodríguez[11,39], Nancy Babio[1,2,3] and Jordi Salas-Salvadó[1,2,3]

Original Article

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Corresponding author:
Sangeetha Shyam;
Email: Sangeetha.shyam@urv.cat;
Nancy Babio;
Email: nancy.babio@urv.cat

Abstract

Background. The coronavirus disease 2019 (COVID-19) has serious physiological and psychological consequences. The long-term (>12 weeks post-infection) impact of COVID-19 on mental health, specifically in older adults, is unclear. We longitudinally assessed the association of COVID-19 with depression symptomatology in community-dwelling older adults with metabolic syndrome within the framework of the PREDIMED-Plus cohort.

Methods. Participants ($n = 5486$) aged 55–75 years were included in this longitudinal cohort. COVID-19 status (positive/negative) determined by tests (e.g. polymerase chain reaction severe acute respiratory syndrome coronavirus 2, IgG) was confirmed via event adjudication (410 cases). Pre- and post-COVID-19 depressive symptomatology was ascertained from annual assessments conducted using a validated 21-item Spanish Beck Depression Inventory-II (BDI-II). Multivariable linear and logistic regression models assessed the association between COVID-19 and depression symptomatology.

Results. COVID-19 in older adults was associated with higher post-COVID-19 BDI-II scores measured at a median (interquartile range) of 29 (15–40) weeks post-infection [fully adjusted $\beta = 0.65$ points, 95% confidence interval (CI) 0.15–1.15; $p = 0.011$]. This association was particularly prominent in women ($\beta = 1.38$ points, 95% CI 0.44–2.33, $p = 0.004$). COVID-19 was associated with 62% increased odds of elevated depression risk (BDI-II ≥ 14) post-COVID-19 when adjusted for confounders (odds ratio; 95% CI 1.13–2.30, $p = 0.008$).

Conclusions. COVID-19 was associated with long-term depression risk in older adults with overweight/obesity and metabolic syndrome, particularly in women. Thus, long-term evaluations of the impact of COVID-19 on mental health and preventive public health initiatives are warranted in older adults.

Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) evolved into a global pandemic since its emergence in 2019

(Guo et al., 2022). Despite largely affecting the respiratory system, COVID-19's impact on the cardiovascular, gastrointestinal, and neurologic systems has been recognized (Sparks et al., 2020). Long-term physical and mental health consequences of COVID-19 are increasingly understood as more data become available (Lopez-Leon et al., 2021).

Depression is a potentially serious mental health consequence of COVID-19, with its prevalence post-COVID-19 depending on the individual's age and the timing of depression assessment in relation to the infection (Pano et al., 2021). While depression is common in the acute 4-weeks post-infection, there are scarce data on its long-term prevalence (>12 weeks after the diagnosis of COVID-19) (Mazza et al., 2020; Renaud-Charest et al., 2021). Recently, a meta-analysis determined the frequency of depressive symptoms ≥ 12 weeks post-infection in COVID-19-positive men and women aged over 19 years, with varying degrees of COVID-19 severity, including both hospitalized and non-hospitalized populations and those with and without comorbidities. In this heterogeneous group, the frequency of depressive symptoms ranged between 11% and 28%, while clinically significant depression and/or severe depressive symptoms affected 3–12% of the participants, at >12 weeks after COVID-19 (Renaud-Charest et al., 2021). While the long-term impact of COVID-19 on depression in the general population may be small, the effects appear to be severe in older age groups (Klaser et al., 2021), specifically in older women and those with prior depressive tendencies (Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et al., 2021).

Older age and cardiometabolic risks increase susceptibility to severe COVID-19 (Channappanavar & Perlman, 2020; Mueller, McNamara, & Sinclair, 2020; Wee, 2021), and depression is more prevalent in those with metabolic syndrome and diabetes (Dunbar et al., 2008; Khaledi, Haghighatdoost, Feizi, & Aminorroaya, 2019). The mental health consequence of COVID-19 in older adults with metabolic disturbances is of specific concern because depression is associated with lower adherence to treatment (Castro et al., 2021), poorer prognosis (Dunbar et al., 2008; Khaledi et al., 2019), and higher risk of mortality in community-dwelling older adults (Wei et al., 2019). While affecting mortality and quality of life in older adults with high cardiometabolic risk, the long-term impact of COVID-19 on depression symptoms will also represent a burden for healthcare systems. Therefore, understanding the impact of COVID-19 on older adults with comorbidities will facilitate early identification and management of the mental health sequelae of COVID-19 in this population. Existing evidence on the topic is highly heterogeneous in terms of the location, age, and sex of individuals and time of depressive symptoms assessment post-COVID-19. Few studies include an unexposed control group to quantify the impact of COVID-19 on depression (Renaud-Charest et al., 2021). These limitations make it challenging to inform practice with existing information.

Thus, we examined the association of COVID-19 with depressive symptomatology in older adults with overweight/obesity and metabolic syndrome enrolled in the PREDIMED-Plus trial in Spain. We hypothesized that a positive diagnosis of COVID-19 would be associated with higher post-COVID-19 scores for depressive symptoms in comparison to a COVID-19 negative status. We also investigated if sex, time of post-COVID-19 depression assessment, and pre-existing depressive symptomatology affected this association.

Methods

Study design and participants

This analysis involved older women and men enrolled in the PREDIMED-Plus trial, a multicentre, randomized controlled clinical trial in Spain (Martínez-González et al., 2019). PREDIMED-Plus is an existing longitudinal cohort of 6874 community-dwelling older adults with overweight/obesity and metabolic syndrome. At enrolment, participants were free from cardiovascular disease, cancers, major depressive disorder, and other major chronic conditions. The trial aims to assess in this cohort the effectiveness of an energy-reduced Mediterranean diet, physical activity, and behavioural support intervention on the primary prevention of cardiovascular disease in comparison to an *ad libitum* Mediterranean diet without advice to increase physical activity or reduce energy intake. The ongoing trial began its recruitment in 2013 and is scheduled to be completed in 2024. A detailed study protocol has been published earlier (Martínez-González et al., 2019; Salas-Salvadó et al., 2018) (see supplementary methods).

The PREDIMED-Plus protocol has been approved by the institutional review boards of all participating centres in accordance with the Declaration of Helsinki. All enrolled participants provided written informed consent. This study is registered at the International Standard Randomized Controlled Trial (ISRCT; http://www.isrctn.com/ISRCTN89898870).

The cohort has validated assessments of depression that were obtained before the onset of the COVID-19 pandemic as well as ongoing follow-up measurements. The PREDIMED-Plus database also contains data on demography and clinical status that could confound the relationship between COVID-19 and depression. Thus, the PREDIMED-Plus cohort provides a unique opportunity to evaluate the association of COVID-19 with depressive symptomatology in older adults with overweight/obesity and metabolic syndrome.

Ascertainment of variables

Exposure: SARS-CoV-2 infection

For the primary analysis, the main exposure was a confirmed COVID-19 event in a participant (positive/negative) as adjudicated by the Clinical Event Ascertainment Committee of the trial. The clinical event determination was based on the information from participant medical records reviewed annually by the participating physicians (CDC, 2020). Overall, 410 participants in this analysis were COVID-19 positive. Participants who did not have a confirmed/probable COVID-19-positive diagnosis were considered COVID-19 negative (i.e. assumed to have not experienced the infection). The COVID-19 status accordingly established as a dichotomous variable (positive/negative) was used to define the exposure.

A supplementary analysis was performed using a subsample ($n = 3982$) of the PREDIMED-Plus participants who had undergone serology testing with SARS-CoV-2 IgG ELISA Kits. These tests obtained between 3 March 2020, and 25 December 2021, classified participants as COVID-19 negative ($n = 3698$)/COVID-19 positive ($n = 287$). COVID-19 status was accordingly defined as a dichotomous predictor variable in the supplementary analysis (see supplementary methods for details).

Outcome: depression assessment

Depression assessment in the PREDIMED-Plus. As per the PREDIMED-Plus protocol, participants' complete annual

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assessments of depressive symptomatology were performed using the validated 21-item Spanish version of the Beck Depression Inventory-II (BDI-II) (Fernández, Valverde, & Perdigón, 2003). Each item in the BDI-II has four possible answers with scores ranging from 0 to 3 in accordance with symptom severity. Thus, the sum total of the BDI-II score ranges between 0 and 63 points, with higher scores indicating a higher propensity for depression.

Identifying pre- and post-COVID-19 measurements. From the annual assessments of depressive symptomatology, a pre-COVID-19 and a post-COVID-19 measurements were identified for each participant based on their COVID-19 event status. For COVID-19-positive participants, the last available BDI-II assessment prior to the COVID-19 diagnosis date was ascertained as the pre-COVID-19 measurement. In these participants, the BDI-II score available from the first post-COVID-19 follow-up visit was ascertained as the post-COVID-19 BDI-II score. For COVID-19-negative participants, the date of identification of the first COVID-19 case in Spain (31 January 2020) was used as a hinge to identify BDI-II scores from comparable time points as COVID-19-positive participants. Thus, in COVID-19-negative participants, BDI-II scores from a visit before 31 January 2020 indicated pre-COVID-19 measurement and those from the subsequent visit were used as post-COVID-19 measurement (online Supplementary Fig. S1). The duration between pre- and post-COVID-19 depression measurements and the time elapsed from the COVID-19 event at post-COVID-19 depression measurements were calculated in weeks. Time elapsed at post-COVID-19 depression measurement was further categorized as ≤12 weeks and >12 weeks to stratify the time-dependent effects of COVID-19 on depression (Klaser et al., 2021; Renaud-Charest et al., 2021).

Categorizing post-COVID-19 depression risk as the outcome variable. For the primary analysis, the post-COVID-19 BDI-II score was used as a continuous outcome. BDI-II scores have also been categorized to identify the risk of depression: scores 0–13 indicate minimal risk, and scores ≥ 14 identify elevated risk (Becker, Steer, & Brown, 1996). For a secondary analysis, we categorized elevated depression risk accordingly and treated it as a binary outcome. In addition, since a cut-off ≥ 12 had an adequate specificity index and diagnostic concordance and detects major depressive episodes in 93% of Spanish individuals (Sanz Fernández, 2013), a supplementary analysis using a cut-off ≥ 12 was also conducted.

Assessment of confounder variables

Data on potentially relevant confounders were also obtained from the PREDIMED-Plus database (See supplementary methods). Pre-COVID-19 visit covariates used in the models included age (years), marital status (levels: single/divorced, married or widow/widower), adherence to the Mediterranean diet (er-MEDAS score), alcohol consumption (g/day), total physical activity (METs min/week), and body mass index (BMI; kg/m^2). For other confounders including sex (man/woman), education (<high school, high school, and university), intervention group (A/B), recruitment centre size (>400, 300–400, 250–300, and <250), smoking status (never/former smoker/current smoker), the prevalence of type 2 diabetes mellitus (yes/no), hypercholesterolemia (yes/no), hypertension (yes/no), and cognitive performance [Mini-Mental State Examination (MMSE) scores], and study baseline data were used to reduce missing data. Since the time elapsed since COVID-19 can impact depression assessments (Renaud-Charest et al., 2021), this duration (weeks) was adjusted for confounding in regression models. Since pre- and post-COVID-19 BDI-II scores were highly correlated, pre-COVID-19 BDI-II scores were adjusted as a covariate in all models.

Statistical analyses

The present analysis was conducted as a prospective cohort study using the PREDIMED-Plus database with the COVID-19 event status updated until 31 December 2021. All other data (depression outcomes and confounder data) were sourced from the database that was updated until 4 November 2022. This allowed for sourcing depression assessments before and after COVID-19 and enabled the inclusion of both acute (<12 weeks) and long-term (≥12 weeks) associations of COVID-19 on depressive symptomatology. We included participants who had completed depression questionnaire assessments both before and after the ascertainment of COVID-19 event status.

In a preliminary cross-sectional exploration, we compared the characteristics and the timing of depression assessment of COVID-19-negative and positive participants using the Chi-Square and Mann–Whitney *U* tests, as appropriate.

The primary analysis evaluated the longitudinal relationship of COVID-19 on post-infection depression symptomatology (BDI-II scores) using linear regression models, considering the COVID-19-negative status as the reference category. In addition to the unadjusted crude model, three other models were tested. Model 1 adjusted for age, sex, education, marital status, intervention group, recruitment centre size, pre-COVID-19 BDI-II scores, and time since COVID-19 for depression assessments as confounders. Model 2 additionally adjusted for the presence of obesity (BMI ≥ 30 kg/m^2), type 2 diabetes mellitus, hypertension, hypercholesterolemia, and cognitive performance on recruitment to the trial. Model 3 also adjusted for lifestyle factors including scores of adherence to the Mediterranean diet, total physical activity levels, smoking status, and alcohol consumption. Alcohol consumption was used as a quadratic term in the model to accommodate for a nonlinear relationship with the outcome. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. This procedure was used to control for the allocation of household members into the same intervention group without randomization.

A secondary logistic regression analysis using the same models developed for the main analysis was performed with elevated depression risk post-COVID-19 (BDI-II cut-off ≥ 14) as a binary outcome.

Furthermore, to negate over-adjustments, a directed acyclic graph (DAG) (Textor, van der Zander, Gilthorpe, Liśkiewicz, & Ellison, 2016) was modelled (online Supplementary Fig. S2) and a minimal adjustment set was identified for both the linear and logistic regression models. This minimal model adjusted only for pre-COVID-19 depression scores. An additional supplementary logistic regression analysis was undertaken using a BDI-II score ≥ 12 as the cut-off for elevated depression risk.

Effect modification of the association by potential confounders [age group (≤70 or >70 years), sex, intervention group, disease conditions, and time elapsed post-COVID-19] was assessed by introducing product terms in the multivariable model. Further, sub-analyses that stratified results by factors that showed significant interaction (sex, presence of pre-COVID-19 high depression risk, and time elapsed post-COVID-19 during depression

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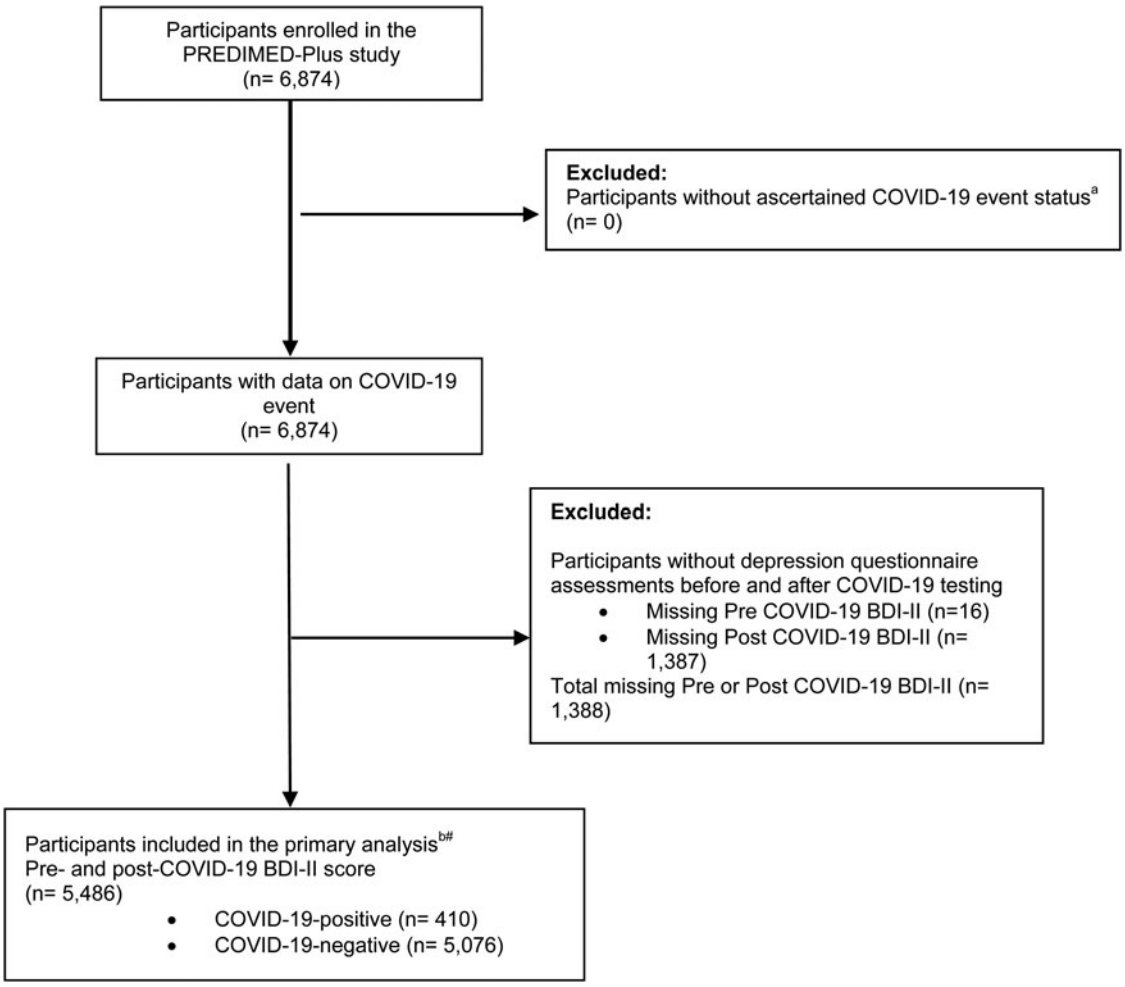

Figure 1. Flow diagram for PREDIMED-Plus participants included in the analysis to evaluate the impact of COVID-19 on depression. BDI-II, Beck Depression Inventory-II; BMI, body mass index; COVID-19, coronavirus disease 2019; MMSE, Mini-Mental State Examination. [a]Analysis used COVID-19 event confirmation data from the PREDIMED-Plus database updated until December 2021. [b]Analysis used depressive and covariate assessments from the PREDIMED-Plus database updated until November 2022. [#]Age, sex, education, intervention group, recruitment centre, smoking status, physical activity, adherence to the Mediterranean diet, BMI, prevalence of baseline diabetes, hypertension, and hypercholesterolemia had no missing data for this analysis. Marital status: 12/5486 (0.2%) missing data. Missing data were replaced with the mode of the variable for the cohort. Alcohol consumption: 15/5486 (0.3%) missing data. Missing data were replaced with cohort mean consumption by gender (*men = 17.47; women = 4.59 g/day). MMSE data: 135/5486 missing data (2.4%). No imputation was performed for missing data.

assessments) were undertaken. Finally, supplementary linear and logistic analyses were conducted in the sub-sample with serology results to ascertain COVID-19 status.

Data were analysed using the Stata 14 software (StataCorp, College Station, TX, USA), and statistical significance was set at a two-tailed p value <0.05 (see supplementary methods for details).

Results

This analysis included a total of 5486 PREDIMED-Plus participants (51.7% men) with a median [interquartile range (IQR)] age of 69.7 (7.4) years (Fig. 1). Table 1 shows their characteristics stratified by COVID-19 event status. At the pre-COVID-19 visit, participants had a median (IQR) BDI-II score of 5 (8), and these scores did not significantly differ by COVID-19 status. Approximately 14% of the participants included in this analysis had elevated depression risk at the pre-COVID-19 visit with no significant difference in the prevalence between COVID-19-positive and COVID-19-negative individuals. A COVID-19-positive status was associated with the male sex. COVID-19-positive participants were also more likely to report having been former smokers. All other factors evaluated were comparable in COVID-19-positive and COVID-19-negative individuals at the pre-COVID-19 visit.

Post-COVID-19 depression assessments in COVID-19-positive participants were on average assessed 23 weeks post-infection. The duration between pre- and post-COVID-19 depression assessments was significantly shorter in COVID-19-positive *v.* COVID-19-negative participants ($p < 0.001$, Table 1). However, the mean difference in duration between pre- and post-COVID-19 depression assessments between those who had and did not have the infection was <5 days.

Table 2 evaluates the longitudinal association of COVID-19 on BDI-II scores over a median (IQR) duration of 29.4 (24.7) weeks post-COVID-19 in the cohort. In the fully adjusted model, SARS-CoV-2 infection was significantly associated with post-COVID-19 BDI-II scores [β (95% confidence interval (CI)) 0.65 (0.15–1.15), $p = 0.011$].

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Table 1. Participant characteristics according to COVID-19 status

Characteristics	Full sample ($n = 5486$)	COVID-19 status		p Value[a]
		Positive ($n = 410$)	Negative ($n = 5076$)	
Sociodemographic data				
Age at pre-COVID visit, years[b]	69.7 (7.4)	69.7 (7.6)	69.7 (7.3)	0.64
Men, *n* (%)	2836 (51.7)	239 (58.3)	2597 (51.2)	<0.01
Education level, *n* (%)[c]				0.14
Less than high school	2730 (49.8)	188 (45.9)	2542 (50.1)	
High school or equivalent	1560 (28.4)	118 (28.8)	1442 (28.4)	
University	1196 (21.8)	104 (25.4)	1092 (21.5)	
Civil status, *n* (%)[d]				0.43
Single or divorced	678 (12.4)	52(12.7)	626 (12.3)	
Married	4135 (75.4)	316 (77.1)	3819 (75.2)	
Widow/widower	673 (12.3)	42 (10.2)	631 (12.4)	
Intervention group (Group B)	2649 (48.3)	195 (47.6)	2454 (48.4)	0.76
Lifestyle habits				
Smoking habit, *n* (%)[c]				<0.01
Never smoker	2477 (45.1)	163 (39.8)	2314 (45.6)	
Former smoker	2352 (42.9)	205 (50.0)	2147(42.3)	
Current smoker	657 (12.0)	42 (10.2)	615 (12.1)	
17-item MedDiet score[b,d,e]	12(4)	12(4)	12(4)	0.97
Total physical activity, METs min/week[b,d]	2545 (2853)	2654 (3040)	2544 (2853)	0.75
Alcohol consumption, g/day[b,d]	4.0 (11.3)	4.5 (12.6)	3.8 (11.3)	0.06
Anthropometry, clinical and cognitive data				
BMI, kg/m^{2}[b,d]	31.4 (5.3)	31.7 (5.3)	31.3(5.3)	0.09
Obesity; BMI $\geq$ 30, *n* (%)[d]	3515 (64.1)	275 (67.1)	3240 (63.8)	0.18
Diabetes, *n* (%)[c]	1621 (29.6)	122 (29.8)	1499 (29.5)	0.92
Hypercholesterolaemia, *n* (%)[c]	3842 (70.0)	272 (66.3)	3570 (70.3)	0.09
Hypertension, *n* (%)[c]	4591 (83.7)	330(80.5)	4261 (84.0)	0.08
MMSE scores[b,c,e]	29 (3)	29 (2)	29 (3)	0.31
Depression data				
BDI-II scores[b,c]				
Pre-COVID-19	5 (8)	4 (8)	5 (8)	0.14
Post-COVID-19	5 (7)	5 (8)	5 (7)	0.62
Elevated depression risk, *n* (%)[c]	1077 (19.7)	71 (17.3)	1006 (19.9)	0.21
Elevated depression risk, pre-COVID-19, *n* (%)[d]	758 (13.8)	53 (12.9)	705 (13.9)	0.65
Elevated depression risk, post-COVID-19, *n* (%)	661 (12.1)	58 (14.2)	603 (11.9)	0.18
Time between pre- and post-COVID-19 depression measurements, weeks[f]	53.0 (51.0–55.1)	52.3 (50.0–54.6)	53.0 (51.1–53.3)	<0.001
Time elapsed from COVID-19 at post-COVID-19 depression assessment, weeks[f]	29.4 (15–39.7)	22.7 (11.1–37.1)	30.7 (15.6–39.9)	<0.001

BDI-II scores, Beck Depression Inventory-II; BMI, body mass index; COVID-19, coronavirus disease 2019; IQR, interquartile range; MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination.
Data are *n* (%) or median (IQR) for categorical and quantitative variables, respectively, unless specified.
[a]p Values for comparisons between groups were tested using the Mann–Whitney test (owing to the skewed nature of the distribution) or χ^2, as appropriate.
[b]Data are presented as median (IQR).
[c]Data are from study baseline.
[d]Data from pre-COVID-19 measurement.
[e]Notes on scales: BDI-II Scores range between 0 and 63. Elevated depression risk is described as BDI-II scores $\geq$ 14. MMSE scores range between 0 and 30; the higher the scores greater the cognitive performance. Possible MedDiet scores range between 0 and 17. Higher MedDiet scores represent higher adherence to the Mediterranean diet.
[f]Duration data are presented as median (25th–75th percentile).

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Table 2. Longitudinal association of COVID-19 status with post-infection depression assessments (BDI-II scores)[a] in the PREDIMED-Plus cohort (β [95% CI])

	Total ($n = 5486$)			Men ($n = 2836$)			Women ($n = 2650$)		
	β[b]	95% CI	p value	β[b]	95% CI	p value	β[b]	95% CI	p value
Unadjusted crude model	0.19	−0.46 to 0.83	0.57	−0.20	−0.91 to 0.52	0.59	1.21	0.13–2.30	0.03
Model 1[c]	0.70	0.21–1.19	0.01	0.07	−0.44 to 0.59	0.79	1.56	0.66–2.46	<0.01
Model 2	0.64	0.14–1.14	0.01	0.11	−0.41 to 0.63	0.67	1.40	0.47–2.34	<0.01
Model 3	0.65	0.15–1.15	0.01	0.13	−0.39 to 0.65	0.63	1.40	0.45–2.34	<0.01

BDI-II, Beck Depression Inventory-II; CI, confidence interval; COVID-19, coronavirus disease 2019; MMSE, Mini-Mental State Examination.
Linear regression model: exposure = COVID-19 status (positive or negative); outcome: post-COVID-19 BDI-II score. Reference category: COVID-19-negative status.
The crude model only uses COVID-19 status (positive or negative) as the predictor variable in the model.
Model 1: Adjusted for age, sex, education, marital status, intervention group, cluster randomization, recruitment centre size, pre-COVID-19 BDI-II scores, and time since infection for post-COVID-19 depression assessments.
Model 2: Model 1 in addition adjusted for the presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition (MMSE scores).
Model 3: Model 2 in addition adjusted for adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption.
[a]Depression assessment from the first scheduled follow-up visit after COVID-19 was used to calculate post-COVID-19 BDI-II scores.
[b]β (95% CI) was calculated using linear regression models.
[c]Sex is included as a predictor for the analysis of the total sample in Model 1. A stratified analysis by sex was conducted to determine differences, if any, in the impact of COVID-19 on depression measurements.

Table 3 summarises the positive association between a SARS-CoV-2 infection and elevated depression risk post-COVID-19 in this group of older adults at high cardiometabolic risk. In the final model, COVID-19 was associated with a 62% increase in the odds of observing elevated depression risk post-COVID-19 in the cohort [odds ratio (OR), 95% CI 1.13–2.30, $p = 0.008$].

These results remained unchanged in the supplementary analysis using a minimal adjustment model (online Supplementary Analysis 1: Supplementary Table S1). In addition, the results of logistic regression quantifying the longitudinal association between COVID-19 and elevated depression risk post-COVID-19 remained unchanged when the cut-off for BDI-II to identify the heightened risk was lowered to 12 points (online Supplementary Analysis 2, Supplementary Table S1).

Evaluation of interactions

Significant interactions ($p < 0.01$) with COVID-19 were observed for sex and the presence of pre-COVID-19 elevated depression risk (online Supplementary Fig. S3). Fully adjusted predicted post-COVID-19 BDI-II scores and probabilities of elevated depression risk in the stratified sub-analysis undertaken for these factors are visualised in online Supplementary Fig. S4.

Sex

At the pre-COVID visit, 68% of the participants who exhibited depressive symptomatology were women ($p < 0.001$). In women, a positive COVID-19 event was associated with an increase in BDI-II scores measured post-COVID-19 [β (95% CI) 1.38 (0.44–2.33), $p = 0.004$, Table 2] in the fully adjusted model. Similarly, a positive COVID-19 status in women was associated with an 82% increase in heightened depression risk post-COVID-19, even when controlled for potential confounders including pre-COVID-19 BDI-II scores (OR, 95% CI 1.17–2.86; $p = 0.008$, Table 3). However, these associations were not significant in men.

Elevated depression risk pre-COVID-19

Elevated depression risk pre-COVID-19 was positively associated with a similar assessment at the post-COVID-19 visit. Approximately 50% ($n = 377$) of those who recorded BDI-II scores ≥14 ($n = 758$) and 6% ($n = 284$) of those who scored <14 at the pre-COVID-19 visit exhibited elevated depression risk at their post-COVID-19 visit. Table 4 stratifies the prospective association between SARS-CoV-2 infection and elevated depression risk post-COVID-19, by pre-COVID-19 depression risk levels. In individuals with BDI-II scores <14 at the prior visit, a positive COVID-19 event was associated with a 72% increase in the risk of elevated depression post-COVID-19, in the fully adjusted model (OR, 95% CI 1.17–2.62; $p = 0.008$, Table 4).

A significant interaction was also observed between the timing of depression assessment and COVID-19 status ($p < 0.05$). Results stratified by timing of post-COVID-19 depression assessment are shown in online Supplementary Table S2. While the directionality of the relationship between a COVID-19-positive status and depression scores remained consistent, these associations were statistically significant only among participants who had their depression assessment conducted after 12 weeks following COVID-19 diagnosis (COVID-19-positive participants) or after 12 weeks following the first confirmed case of COVID-19 in Spain (COVID-19-negative participants).

In the replication analysis in the subsample with serology results to confirm COVID-19 status, the directionality of the results remained unchanged. However, the association was no longer statistically significant ($n = 3801$, 284 cases of COVID-19) (online Supplementary Table S3).

Discussion

We examined the association of COVID-19 with depressive symptomatology in older adults with overweight/obesity and metabolic syndrome enrolled in the PREDIMED-Plus trial in Spain. Spain with an increasingly ageing population was among the European countries most affected by the pandemic (Pollán et al., 2020). COVID-19 was associated with a small but significant and persistent increase in post-infection depression scores in this population. These findings add to the existing global evidence on the mental health consequences of COVID-19 (Deng et al., 2021; Klaser et al., 2021; Meng et al., 2020; Renaud-Charest et al., 2021).

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Table 3. Longitudinal association between COVID-19 status and post-infection elevated depression risk in the PREDIMED-Plus cohort [OR (95% CI)]

Depressive symptomatology	Total ($n = 5486$)			Men ($n = 2836$)			Women ($n = 2650$)		
	OR[a]	95% CI	p Value	OR[a]	95% CI	p Value	OR[a]	95% CI	p Value
Unadjusted crude model	1.22	0.91–1.63	0.18	1.11	0.68–1.81	0.69	1.47	1.01–2.13	0.04
Model 1[b]	1.67	1.19–2.34	<0.01	1.40	0.78–2.50	0.26	1.92	1.26–2.95	<0.01
Model 2	1.59	1.11–2.27	0.01	1.36	0.74–2.49	0.32	1.82	1.16–2.84	<0.01
Model 3	1.62	1.13–2.30	<0.01	1.38	0.76–2.53	0.30	1.83	1.17–2.87	<0.01

BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.
Logistical regression model: exposure = COVID-19 status (positive or negative); outcome = elevated depression risk post-COVID-19. Reference category: COVID-19-negative status.
Model 1: Adjusted for age, sex, education, marital status, intervention group, cluster randomization, recruitment centre size, pre-COVID-19 BDI-II scores, duration post-COVID-19 measurements.
Model 2: Model 1 additionally adjusted for the presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition (MMSE scores).
Model 3: Model 2 additionally adjusted for adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption.
[a]OR (95% CI) was calculated using logistic regression models.
[b]Sex included as a predictor for the analysis of the total sample in Model 1. A stratified analysis by sex was conducted to determine differences, if any, in the impact of COVID-19 on depression measurements.
[c]Elevated depression risk is defined as BDI-II score ≥ 14, absence of elevated depression risk as BDI-II score < 14. Depression assessment from the first scheduled follow-up visit after the COVID-19 infection was used to categorize post-COVID-19 depressive symptomatology.

Post-infection increases in depressive symptomatology associated with infections that have a prolonged convalescence have biological and psychological bases (Kim, Yoo, Lee, Lee, & Shin, 2018). Biologically, the escalation of depressive symptoms after COVID-19 stems from increased inflammation (Lyra e Silva, Barros-Aragão, De Felice, & Ferreira, 2022; Mazza et al., 2020). COVID-19 is a hyperinflammatory disease with systemic and brain inflammation, leading to acute and persistent neurological and psychological disturbances (Lyra e Silva et al., 2022). COVID-19 could also be a stress-inducing traumatic event, and patients who experience traumatic events are known to have higher inflammation markers (Fernández-Sevillano et al., 2022). Proinflammatory cytokines are associated with the development of depression, irrespective of baseline scores, indicating that inflammation temporally precedes and increases the depression risk (Martínez-Cengotitabengoa et al., 2016). In addition, the increased depression risk in Middle East Respiratory Syndrome (MERS) patients quarantined in the hospital was ascribed to psychological factors including tension, fear, anger, mistrust, uncertainty, and depressed mood due to the infection itself and the subsequent isolation during quarantine (Kim et al., 2018), socioeconomic and family consequences. These mechanisms could collectively explain the association of COVID-19 with increased depressive symptomatology. In addition, the pandemic nature of

Table 4. Longitudinal association between COVID-19 status and depressive symptomatology in the PREDIMED-Plus cohort, stratified by depression risk at pre-COVID-19 assessment (OR[a] or β[b] coefficients and 95% CI)

	Elevated depression risk at pre-COVID-19 visit ($n = 758$)			Minimal risk at pre-COVID-19 visit ($n = 4728$)		
	Effect size	95% CI	p Value	Effect size	95% CI	p Value
Post COVID BDI-II scores [β (95% CI)][a]						
Unadjusted crude model	−0.10	−2.47 to 2.26	0.93	0.33	−0.19 to 0.86	0.21
Model 1	0.27	−1.92 to 2.45	0.81	0.53	−0.02 to 1.08	0.06
Model 2	−0.06	−2.37 to 2.25	0.96	0.48	−0.08 to 1.03	0.09
Model 3	0.17	−2.78 to 2.52	0.90	0.50	−0.05 to 1.05	0.08
Depressive symptomatology post-COVID19 [OR (95% CI)][b]						
Unadjusted crude model	0.97	0.56 to 1.70	0.92	1.61	1.09 to 2.36	0.02
Model 1	1.00	0.56 to 1.79	1.00	1.78	1.19 to 2.65	<0.01
Model 2	0.87	0.47 to 1.61	0.66	1.73	1.15 to 2.60	<0.01
Model 3	0.92	0.49 to 1.72	0.78	1.74	1.16 to 2.62	<0.01

BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.
Elevated depression risk is defined as BDI-II score ≥ 14, minimal depression risk as BDI-II score < 14. Depression assessment from the first scheduled follow-up visit after the COVID-19 infection was used to evaluate post-COVID-19 depressive symptomatology.
Reference category: COVID-19-negative status.
Model 1: Adjusted for age, sex, education, marital status, intervention group, cluster randomization, recruitment centre size, pre-COVID-19 BDI-II scores, and time since infection for post-COVID-19 depression assessments.
Model 2: Model 1 additionally adjusted for the presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition (MMSE scores).
Model 3: Model 2 additionally adjusted for adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption.
[a]β coefficient (95% CI) was calculated using linear regression models. Exposure = COVID-19 status (positive or negative); outcome: post-COVID-19 BDI-II scores.
[b]OR (95% CI) was calculated using logistic regression models. Exposure = COVID-19 status (positive or negative); outcome = elevated depressive risk post-COVID-19 (yes/no).

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the COVID-19 outbreak and the widespread adoption of public health measures could have compounded the association of COVID-19 with depressive symptoms. Therefore, it is likely that the magnitude of the impact of COVID-19 on mental health, specifically among the vulnerable including older adults, is more prominent in comparison to common acute illnesses.

While the association between COVID-19 and depression risk was statistically significant, the effect size was small, and hence, its clinical significance is debatable. Nevertheless, the effect of COVID-19 on depressive symptoms is in line with the repeated calls for mental health interventions in older adults, particularly in older women surviving COVID-19 (Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et al., 2021). Moreover, contrary to the existing understanding that prior mental health conditions make individuals particularly vulnerable to the psychological impact of COVID-19 (Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et al., 2021), we found that COVID-19 was significantly associated with elevated depressive risk post-infection in PREDIMED-Plus participants without a similar risk at the pre-COVID-19 visit. These results provide new insights into the need for holistic management of COVID-19 in older adults who were more vulnerable to infection and had poorer survival rates in the initial phases of the pandemic, owing to senescence and comorbidity-related changes in the immune system (Mueller et al., 2020). Aging attenuates coping strategies (Meng et al., 2020), while self-awareness of the aging-related increased the risk of mortality from the pandemic and poorer coping tendencies could contribute to increased and persistent depressive tendencies in older adults experiencing COVID-19. Furthermore, poorer physical health increases the risk for poorer mental health post-COVID-19 (Robinson, Sutin, Daly, & Jones, 2022). Hence, among older adults at high cardiometabolic health risk, preventive mental health interventions to manage depressive symptomatology may be required irrespective of pre-COVID-19 mental health status.

Previous reports suggest that the mental health effects of COVID-19 are transitory and attenuate 12 weeks after the infection (Klaser et al., 2021; Renaud-Charest et al., 2021). However, we found no evidence to support this contention. The observed lack of significance of the results in the group with post-COVID-19 assessments conducted within 12 weeks of the date of infection could be due to insufficient statistical power in this group. Nevertheless, consistent results in the group that had their depression assessments performed 12 weeks or later after SARS-CoV-2 infection confirms that COVID-19 posed an extended mental health risk in this group of older adults with heightened metabolic risks, even in the absence of depression in pre-COVID-visits.

We could attribute this extended mental health consequence of COVID-19 to both the physiological consequences of COVID-19 and the prolonged lockdown instituted as public health measures to stem the spread of the disease. However, we have recently shown, albeit in a sub-sample of this cohort, that the lockdown was not associated with an increase in depressive symptomatology (Paz-Graniel et al., 2023). Thus, it is highly likely that the persistent depressive symptomatology seen in this group is predominantly a consequence of the disease. These findings reemphasize that COVID-19-induced increases in depressive symptoms could be larger and more persistent in comparison to smaller changes observed for anxiety disorder symptoms and overall mental health functioning measures (Robinson et al., 2022). With the increasing concern over 'Long-COVID', it is important to further monitor the long-term psychological impact of COVID-19 in older adults, specifically concerning depressive symptoms, even in the absence of depression in pre-COVID-visits.

Our study has limitations. First, BDI-II scores were self-reported and are not interpreted as a bonafide diagnosis of the presence/absence of depression. Nevertheless, BDI-II has been validated and used widely in Spain with sufficient specificity to identify individuals at the heightened risk for depression (Sanz Fernández, 2013). Second, while social and economic outcomes of the pandemic contribute to depression post-COVID-19 (Renaud-Charest et al., 2021), this analysis did not account for regional variation in lockdown severity and its economic/social consequences. We believe that with adjustments for the recruitment centre size and education, we could have partially accounted for these factors. Third, some COVID-19-negative patients may have had asymptomatic infections that went undiagnosed, resulting in misclassification of cases. This is unlikely because we scrutinized all medical records during 2020 and 2021 when public health strategies for COVID-19 testing were stringent as the nation was in the process of maximizing vaccination coverage. We also recognize that protecting the integrity of the main trial precludes obtaining updated data for covariates such as the prevalence of diabetes, hypercholesterolemia, or hypertension for this analysis. However, the minimal adjustment model shows that the association may be independent of these variables. Furthermore, the results from the sub-sample with positive serology go in the same direction as the primary analysis, suggesting minimal effects of misclassification on this analysis. Finally, this analysis uses data from participants in a clinical trial and may not be widely generalizable.

Nevertheless, this analysis adds strong data to the existing evidence on the mental health sequelae of COVID-19 in a vulnerable group of older adults with overweight/obesity and metabolic syndrome. The sufficiently large PREDIMED-Plus cohort with scheduled data assessments from before the onset of the pandemic and after helps establish the impact of COVID-19 on depressive symptomatology in the cohort while adjusting for the time for depression determinations, an important confounder of this relationship (Renaud-Charest et al., 2021). Furthermore, the similar time frame within which the pre- and post-COVID-19 assessments were obtained in all participants controls for many extraneous factors that could have increased the depression risk, independently of infection status. Moreover, COVID-19 event adjudication was performed by an independent committee removing any potential bias in the ascertainment of cases. Supplementary analyses using a lower cut-off for depression risk and serology results from a sub-sample confirmed the directionality of the results from the main analysis. Finally, we believe that the identification of a minimal adjustment set using a DAG to investigate the relationships involved in this analysis also removes concerns of over-adjustments in the models.

Our analyses do not consider vaccination status and type, the severity of COVID-19 infection, the infection strain or the treatment modality used, or the need for hospitalization among the COVID-19-positive participants. However, current evidence for the impact of these factors on post-COVID-19 depressive symptoms is inconsistent (Chen, Aruldass, & Cardinal, 2022; Mazza et al., 2020; Renaud-Charest et al., 2021). It is possible that the severity of COVID-19 in the early days of the pandemic differed from those that occurred later. We found that while several of the strains reported in 2020 and 2021 caused severe infections, the

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omicron variant reported after November 2021 produced milder disease. However, only 46 cases in our cohort were diagnosed after November 2021, and we do not possess data on strain causing COVID-19 in our cohort to tease out these effects. Also, vaccination in Spain started on 27 December 2020, and the possibility that it might have influenced depression outcomes is restricted to approximately 4% of our population who had received at least one dose of the vaccine at the time of post-COVID-19 depression measurements. Nevertheless, considering these factors in future analyses will facilitate identifying sub-groups that would specifically benefit from mental health interventions. We also propose that future studies investigate the trajectory of depressive symptoms in COVID-19 patients using repeated measurements post-infection. Such an evaluation will help better understand the time-dependent mental health effects of COVID-19.

Implications for practice

Overall, our findings support a call for mental health interventions to tackle increased depressive tendencies post-COVID-19 infection in older adults, particularly in women. Furthermore, in this Spanish cohort of older adults with overweight/obesity and metabolic syndrome, the association between COVID-19 and depressive symptoms was persistent and observable after 12 weeks post-COVID-19. Importantly, strategies to mitigate depression should be extended to older adults with cardiometabolic health risks, who do not exhibit heightened depressive symptomatology prior to a SARS-CoV-2 infection.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002313.

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Competing interest. The authors have no conflict of interests to declare.

Ethical standards. The authors assert that the studies involving human participants were reviewed and approved by the study and were conducted in compliance with the guidelines of the Declaration of Helsinki. The study was approved by the Institutional Review Boards of all participating centres. The patients/participants provided their written informed consent to participate in this study.

[1]Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain; [2]Departament de Bioquímica i Biotecnologia, Grup Alimentació, Nutrició, Desenvolupament i Salut Mental, Unitat de Nutrició Humana, Universitat Rovira i Virgili, Reus, Spain; [3]Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain; [4]CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [5]Departamento de Ciencias de la Salud, Instituto Universitario de Investigación en Olivar y Aceites de Oliva, Universidad de Jaén, Jaén, Spain; [6]Department of Preventive Medicine and Public Health, Instituto de Investigación Sanitaria de Navarra (IdiSNA), University of Navarra, Pamplona, Spain; [7]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [8]Department of Preventive Medicine, University of Valencia, Valencia, Spain; [9]Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Médica (IMIM), Barcelona, Spain; [10]Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain; [11]Precision Nutrition and Cardiometabolic Health Program, IEA Food, CEI UAM + CSIC, Madrid, Spain; [12]Bioaraba Health Research Institute, Cardiovascular, Respiratory and Metabolic Area; Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain; [13]EpiPHAAN Research Group, School of Health Sciences, University of Málaga – Instituto de Investigación Biomédica en Málaga (IBIMA), Málaga, Spain; [14]Instituto de Investigación Sanitaria y Biomédica de Alicante, Universidad Miguel Hernández (ISABIAL-UMH), Alicante, Spain; [15]Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain; [16]Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain; [17]Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; Institut de Recerca en Nutrició i Seguretat Alimentaria (INSA-UB), University of Barcelona, Barcelona, Spain; [18]Department of Endocrinology, Virgen de la Victoria Hospital, Instituto de Investigación Biomédica de Málaga (IBIMA), University of Málaga, Málaga, Spain;

[19]Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain; [20]Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria & Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI), Canarian Health Service, Las Palmas de Gran Canaria, Spain; [21]Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain; [22]Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands, Palma de Mallorca, Spain; [23]Institute of Biomedicine (IBIOMED), University of León, León, Spain; [24]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IDIBELL, Hospitalet de Llobregat – Barcelona, Barcelona, Spain; [25]Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain; [26]CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [27]Department of Endocrinology, Institut d`Investigacions Biomédiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; [28]Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz, Instituto de Investigaciones Biomédicas IISFJD, University Autonoma, Madrid, Spain; [29]Nutritional Control of the Epigenome Group, Precision Nutrition and Obesity Program, IMDEA Food, CEI UAM + CSIC, Madrid, Spain; [30]Departamento de Ciencias Farmacéuticas y de la Salud, Faculty de Farmacia, Universidad San Pablo-CEU, CEU Universities, Boadilla del Monte, Spain; [31]Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain; [32]Psychoneurobiology of Eating and Addictive Behaviors Group, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain; [33]Department of Psychiatry, University Hospital of Bellvitge and University of Barcelona, Barcelona, Spain; [34]Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Toronto, ON, Canada; [35]Department of Internal Medicine, OSI ARABA, University Hospital Araba, Vitoria-Gasteiz, Spain; [36]Health Care Centre Raval-Elche, Elche, Spain; [37]Atención Primaria, Servicio Navarro de Salud, Pamplona, Spain; [38]Department of Psychiatry, Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU, CIBERSAM, Vitoria-Gasteiz, Spain and [39]Division of Preventive Medicine, Faculty of Medicine, University of Jaén, Jaén, Spain

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