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

Running Title: Covid-19 and depression risk in older adults

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Abstract

Background

The coronavirus disease 2019 (COVID-19) has serious physiological and psychological consequences. The longer-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 symptomology in community-dwelling older adults with metabolic syndrome within the framework of the PREDIMED-Plus cohort

Methods

Participants (n=5,486) aged 55-75y were included in this longitudinal cohort. COVID-19 status(positive/negative) determined by tests (e.g., PCR SARS-Cov-2, IgG) was confirmed via event adjudication (410 cases). Pre- and post-COVID-19 depressive symptomatology were 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 symptomology.

Results

COVID-19 in older adults was associated with higher post-COVID-19 BDI-II scores measured at a median (IQR) of 29 (15-40) weeks post-infection (fully adjusted β=0.65 points,95%CI (Confidence Interval): 0.15, 1.15; p= 0.011). This association was particularly prominent in women (β=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 (OR: 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, longer-term

evaluations of the impact of COVID-19 on mental health and preventive public health initiatives are warranted in older adults.

Key Words:

Depression; Older adults; COVID-19; PREDIMED-Plus; SARS-CoV-2

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 recognised(Sparks et al., 2020). Long-term physical and mental health consequences of COVID-19 are increasingly understood as more data becomes 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 19y, 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 to 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. And 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 6,874 community-dwelling older adults with overweight/obesity and metabolic syndrome. At enrollment, 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=3,982) of the PREDIMED-Plus participants who had undergone serology testing with SARS-CoV-2 IgG ELISA Kits. These tests obtained between March 3rd, 2020, and December 25th, 2021, classified participants as COVID-19-negative (n= 3,698)/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 assessments of depressive symptomatology 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 and a post-COVID-19 measurement was 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 (31st 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 31st January 2020 indicated pre-COVID-19 measurement and those from the subsequent visit were used as post-COVID-19 measurement (Supplementary Figure 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).

Categorising 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. Additionally, 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 BMI (kg/m^2). For other confounders including sex (man/woman), education (<high school, high school, 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), 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 December 31st, 2021. All other data (depression outcomes and confounder data) were sourced from the database that was updated until November 4th, 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 prior to 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/m2), 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 (Table 2). Alcohol consumption was used as

a quadratic term in the model to accommodate for a non-linear relationship with the outcome. All analyses were conducted with robust estimates of the variance to correct for intra-cluster 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 (Supplementary Figure 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 >70y], 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 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 5,486 PREDIMED-Plus participants (51.7% men) with a median (IQR) age of 69.7 (7.4) y (Figure 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 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 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 versus 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% CI): 0.65 (0.15 to 1.15, p= 0.011).

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(OR 95% CI: 1.13 to 2.30, p= 0.008).

These results remained unchanged in the supplementary analysis using a minimal adjustment model (Supplementary Analysis 1: Supplementary Table S1). Additionally, 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 (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 (Supplementary Figure 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 Supplementary Figure 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 to 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 to 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 to 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 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= 3,801, 284 cases of COVID-19) (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).

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-

445 inducing traumatic event, and patients who experience traumatic events are known to
446 have higher inflammation markers(Fernández-Sevillano et al., 2022). Proinflammatory
447 cytokines are associated with the development of depression, irrespective of baseline
448 scores, indicating that inflammation temporally precedes and increases depression
449 risk(Martínez-Cengotitabengoa et al., 2016). Additionally, increased depression risk in
450 Middle East Respiratory Syndrome (MERS) patients quarantined in the hospital was
451 ascribed to psychological factors including tension, fear, anger, mistrust, uncertainty,
452 and depressed mood due to the infection itself and the subsequent isolation during
453 quarantine(Kim, Yoo, Lee, Lee, & Shin, 2018), socio-economic and family
454 consequences. These mechanisms could collectively explain the association of
455 COVID-19 with increased depressive symptomatology. Additionally, the pandemic
456 nature of the COVID-19 outbreak and the widespread adoption of public health
457 measures could have compounded the association of COVID-19 with depressive
458 symptoms. Therefore, it is likely that the magnitude of the impact of COVID-19 on
459 mental health, specifically among the vulnerable including older adults, is more
460 prominent in comparison to common acute illnesses.

461

462 While the association between COVID-19 and depression risk was statistically
463 significant, the effect size was small, hence its clinical significance is debatable.
464 Nevertheless, the effect of COVID-19 on depressive symptoms is in line with the
465 repeated calls for mental health interventions in older adults, particularly in older
466 women surviving COVID-19(Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et
467 al., 2021). Moreover, contrary to the existing understanding that prior mental health
468 conditions make individuals particularly vulnerable to the psychological impact of
469 COVID-19(Mazza et al., 2020; Meng et al., 2020; Renaud-Charest et al., 2021), we
470 found that COVID-19 was significantly associated with elevated depressive risk post-
471 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 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 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 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. Thirdly, 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 maximising 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 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 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 27th 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.

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Conflict of Interest

None. The authors have no competing 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.

Authorship and Contributorship

All authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for the important intellectual concept; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

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Table and Figure Legends

Table 1. Participant characteristics according to COVID-19 status

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

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

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 or β coefficients and 95% CI)

Figure 1. Flow diagram for PREDIMED-PLUS participants included in the analysis to evaluate the impact of COVID-19 on depression.

Figure 1 Legend:

Abbreviations: BDI-II, Beck Depression Inventory-II, COVID-19, coronavirus disease 2019.

[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: 12/5,486 (0.2%) missing data. Missing data were replaced with the mode of the variable for the cohort.

Alcohol consumption-15/5,486 (0.3%) missing data. Missing data were replaced with cohort mean consumption by gender (* men= 17.47276; women= 4.599879 g/day). Mini-Mental State Examination (MMSE) data:135/5,486 missing data (2.4%). No imputation was performed for missing data.

Supporting information

Supplementary Methods: Outlines details on study participants and statistical analysis

Supplementary Table S1: Association of COVID-19 status with depressive symptomatology in the PREDIMED-Plus cohort - Results of supplementary analysis using minimal adjustment models and BDI-II ≥ 12 to describe depressive symptomatology

Table S1 Legend

Abbreviations: BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019, MMSE, Mini-Mental State Examination
[#]Reference category for all analysis: COVID-19 negative status
Supplementary analysis 1: Uses a minimal adjustment set identified using directed acyclic graphs (supplementary figure 2)
Minimal adjustment model A uses linear regression with Post BDI-II scores as the outcome, COVID-19 infection as the exposure, adjusting for BDI-II scores pre-COVID-19. Effect size presented as β coefficients (95% CI).
Minimal adjustment model B uses logistic regression with post-COVID-19 elevated depression risk (BDI-II ≥ 14) as the outcome, COVID-19 status as exposure, adjusting for BDI-II scores pre-COVID-19. Effect size presented as Odds ratio (OR and 95% CI).
Supplementary analysis 2: Uses logistic regression with post-COVID-19 elevated depression risk (BDI-II ≥ 12) as the outcome, COVID-19 status as exposure. Effect size presented as Odds ratio (OR and 95% CI).
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 randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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

Supplementary Table S2: Association of COVID-19 status with depressive symptomatology in the PREDIMED-Plus cohort, stratified by time of post-COVID-19 depression assessment.

Table S2 Legend

β coefficient (95% CI) was calculated using linear regression models. Exposure= COVID-19 status (Positive or negative); Outcome: Post COVID BDI-II scores
[δ]OR: Odds Ratio (95% CI) was calculated using logistic regression models. Exposure= COVID-19 status (Positive or negative); Outcome: elevated depression risk symptomatology Post COVID-19 (yes/no).

Elevated depression risk symptomatology is defined as BDI-II score ≥ 14, absence of elevated depression risk symptomatology 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 randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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

Supplementary Table S3: Association of COVID-19 (status determined using serology) with depressive symptomatology assessments in the sub-study of PREDIMED-Plus cohort merging the information of COVID-19 ascertained cases and positive serology information (mean beta [95%CI] or OR [95%CI], n= 3,801)

Table S3 Legend

[#]β coefficient (95% CI) were calculated using linear regression models. Exposure: COVID-19 status (Positive or negative); Outcome: Post-COVID-19 BDI-II scores
[δ]OR: Odds Ratio and (95% CI) were calculated using logistic regression models. Exposure: COVID-19 status (Positive or negative); Outcome: Elevated depression risk symptomatology Post COVID-19 (yes/no). 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 evaluate post-COVID-19 depressive symptomatology
Reference category: COVID-19 negative status.
***Model 1:** Adjusted for age, sex, education, marital status, intervention group, cluster randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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

Minimal adjustment model adjusts only for BDI-II scores pre-COVID-19

Supplementary Figure S1: Timing of pre- and post-COVID-19 depression assessments in the participants

Legend: *The figure shows the timing of pre- and post-COVID-19 depression measurements in the participants. The calendar period of these measurements is shown in the Gantt chart below. Q1- Q4 represents the four quarters of the year. The shaded regions depict the pre and post-COVID-19 time of assessments of depressive assessments of the participants. Pre-COVID-19 measurements in COVid-19 negative participants are measured before the first case of COVID-19 was reported in Spain. In Covid-19 positive participants, Pre-COVID-19 measurements are those from before the date of Covid-19 diagnosis. Post-COVID-19 measurements are those obtained in the subsequent follow-up. Red bars show the timing of assessment in the COVID-19 positive and blue bars in COVID-19 negative participants. The orange bar below shows the timing and duration of the lockdown in Spain as a public health measure to prevent the spread of COVID-19.*
Explanatory Note: *20% of post-COVID-19 assessments for the COVID-19 positive participants and 83% of the post-COVID-19 assessments for the COVID-19 negative participants occurred during the lockdown*

in Spain (14/3/20 to 1/1/2021). Assuming that the COVID-19 lockdown could have increased the BDI-II scores, it is expected that the current estimates for the impact of COVID-19 obtained in this analysis are attenuated since more COVID-19 negative participants had their post-COVID-19 assessments performed during this time.

Supplementary Figure S2: Directed acyclic graph to identify minimal adjustments to evaluate the impact of COVID-19 on depression measures in PREDIMED-Plus participants

Supplementary Figure S3: Interactions between potential factors and COVID-19 in impacting depression assessments post-COVID-19

Legend: Beta coefficients from linear regression and odds ratios calculated from logistic regression in fully adjusted models are shown with their 95% CI in this stratified analysis.
p values for interaction derived from the log-likelihood ratio test.
BDI-II scores, Beck Depression Inventory-II. Depressive symptomatology is defined as BDI-II score ≥ 14*, absence of depressive symptomatology was described as scoring < 14.*

Supplementary Figure S4. Predicted post-COVID-19 BDI-II scores and probabilities of elevated depression risk post-COVID-19 in stratified regression analysis using fully adjusted models

Legend: BDI-II, Beck Depression Inventory-II, COVID-19, coronavirus disease 2019. Predicted post-COVID-19 BDI-II was calculated using linear regression; predicted probabilities for depressive symptomatology post-COVID-19 were calculated using logistic regression. Both analyses show the fully adjusted models (Adjusted for age, sex, education, marital status, intervention group, cluster randomisation, recruitment centre, pre-COVID-19 BDI-II scores, time since infection for post-COVID-19 depression assessments, presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition, adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption. Red square markers indicate COVID-19-positive status and blue dots indicate COVID-19-negative status within the strata. Error bars indicate 95% CI. BDI-II scores have a potential range between 0 and 63 and predicted probabilities between 0 and 1.

Table 1. Participant characteristics according to COVID-19 status

Characteristics	Full sample n = 5,486	COVID-19 Status		P-value[a]
		Positive n = 410	Negative n = 5,076	
Sociodemographic data				
Age at pre-COVID visit, years[#]	69.7 (7.4)	69.7 (7.6)	69.7 (7.3)	0.64
Men, n (%)	2836 (51.7)	239 (58.3)	2,597 (51.2)	<0.01
Education level, n (%) [b]				0.14
Less than high school	2,730 (49.8)	188 (45.9)	2,542 (50.1)	
High school or equivalent	1,560 (28.4)	118 (28.8)	1,442 (28.4)	
University	1,196 (21.8)	104 (25.4)	1,092 (21.5)	
Civil status, n (%)[t]				0.43
Single or divorced	678 (12.4)	52(12.7)	626 (12.3)	
Married	4,135 (75.4)	316 (77.1)	3,819 (75.2)	
Widow/Widower	673 (12.3)	42 (10.2)	631 (12.4)	
Intervention group (Group B)	2,649 (48.3)	195 (47.6)	2,454 (48.4)	0.76
Lifestyle habits				
Smoking habit, n (%) [b]				<0.01
Never smoker	2,477 (45.1)	163 (39.8)	2,314 (45.6)	
Former smoker	2,352 (42.9)	205 (50.0)	2,147(42.3)	
Current smoker	657 (12.0)	42 (10.2)	615 (12.1)	
17-item MedDiet score$_1$ [t#]	12(4)	12(4)	12(4)	0.97
Total physical activity, METs min/week[t#]	2545 (2853)	2654 (3040)	2544 (2853)	0.75
Alcohol consumption, g/day [t#]	4.0 (11.3)	4.5 (12.6)	3.8 (11.3)	0.06
Anthropometry, clinical and cognitive data				
BMI, kg/m^2 [t#]	31.4 (5.3)	31.7 (5.3)	31.3(5.3)	0.09
Obesity; BMI≥30, n (%) [t]	3,515 (64.1)	275 (67.1)	3,240 (63.8)	0.18
Diabetes, n (%) [b]	1,621 (29.6)	122 (29.8)	1,499 (29.5)	0.92
Hypercholesterolemia, n (%) [b]	3,842 (70.0)	272 (66.3)	3,570 (70.3)	0.09
Hypertension, n (%) [b]	4,591 (83.7)	330(80.5)	4,261 (84.0)	0.08
MMSE scores$_1$ [b#]	29 (3)	29 (2)	29 (3)	0.31
Depression data				
BDI-II scores$_1$ [#]				
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 (%) [b]	1,077 (19.7)	71 (17.3)	1,006 (19.9)	0.21
Elevated depression risk, pre-COVID-19, n (%)[t]	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†	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†	29.4 (15- 39.7)	22.7 (11.1 – 37.1)	30.7 (15.6 - 39.9)	<0.001

Abbreviations: BDI-II scores, Beck Depression Inventory-II; BMI, body mass index; COVID-19, coronavirus disease 2019, MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination.

[1]Notes on scales: BDI-II Scores range between 0 and 63. Elevated depression risk is described as BDI-II scores ≥ 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.

Data are n (%) or median (IQR) for categorical and quantitative variables, respectively, unless specified [#] Data presented as median (IQR)). [†] Duration data presented as median (25^{th} – 75^{th} percentile) [b] Data from study baseline [t] Data from pre-COVID-19 measurement.

[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.

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=5,486)			Men (n = 2, 836)			Women (n = 2, 650)		
	β[#]	95% CI	P value	B[#]	95% CI	P value	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 to 2.30)	0.03
Model 1[b]	0.70	(0.21 to 1.19)	0.01	0.07	(-0.44 to 0.59)	0.79	1.56	(0.66 to 2.46)	<0.01
Model 2	0.64	(0.14 to 1.14)	0.01	0.11	(-0.41 to 0.63)	0.67	1.40	(0.47 to 2.34)	<0.01
Model 3	0.65	(0.15 to 1.15)	0.01	0.13	(-0.39 -to 0.65)	0.63	1.40	(0.45 to 2.34)	<0.01

Abbreviations: BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019, MMSE, Mini-Mental State Examination.

[#]β (95% CI) was calculated using linear regression models.

[a] Depression assessment from the first scheduled follow-up visit after COVID-19 was used to calculate post-COVID-19 BDI-II scores.

[b]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.

Linear regression model: exposure= COVID-19 status (Positive or negative); outcome: post-COVID-19 BDI-II score. Reference category: COVID-19-negative status.

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 randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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.

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=5,486)			Men (n = 2, 836)			Women (n = 2, 650)		
	OR[#]	95% CI	P value	OR[#]	95% CI	P value	OR[#]	95% CI	P value
Unadjusted Crude Model	1.22	(0.91 to 1.63)	0.18	1.11	(0.68 to 1.81)	0.69	1.47	(1.01 to 2.13)	0.04
Model 1 [b]	1.67	(1.19 to 2.34)	<0.01	1.40	(0.78 to 2.50)	0.26	1.92	(1.26 to 2.95)	<0.01
Model 2	1.59	(1.11 to 2.27)	0.01	1.36	(0.74 to 2.49)	0.32	1.82	(1.16 to 2.84)	<0.01
Model 3	1.62	(1.13 to 2.30)	<0.01	1.38	(0.76 to 2.53)	0.30	1.83	(1.17 to 2.87)	<0.01

Abbreviations: BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019, MMSE, Mini-Mental State Examination.

[#]OR: Odds Ratio (95% CI) was calculated using logistic regression models.

[a] 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 categorise post-COVID-19 depressive symptomatology.

[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.

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 randomisation, 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.

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[#] or β[δ] coefficients and 95% CI)

	Elevated depression risk at pre-COVID-19 visit (n = 758)			Minimal risk at pre-COVID-19 visit (n = 4,728)		
	Effect size	95% CI	P value	Effect size	95% CI	P value
Post COVID BDI-II scores (β [95%CI])[#]						
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])[δ]						
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

Abbreviations: BDI-II scores, Beck Depression Inventory-II, COVID-19, coronavirus disease 2019, MMSE, Mini-Mental State Examination.

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.

[#]β coefficient (95% CI) was calculated using linear regression models. Exposure= COVID-19 status (positive or negative); Outcome: Post-COVID-19 BDI-II scores.

[δ]OR: Odds Ratio (95% CI) was calculated using logistic regression models. Exposure= COVID-19 status (positive or negative); Outcome = Elevated depressive risk post-COVID-19 (yes/no).

Reference category: COVID-19-negative status.

***Model 1:** Adjusted for age, sex, education, marital status, intervention group, cluster randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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.

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

Supplementary Methods

PREDIMED-Plus Participants

In brief, 23 centres across Spain recruited participants from several primary healthcare facilities affiliated with the National Health System. Candidates were community-dwelling adults (men aged 55–75y; women aged 60–75y). Participants were eligible for study enrolment if they were overweight or obese (body mass index [BMI] between 27 and 40 kg/m^2) and satisfied a minimum of three criteria for metabolic syndrome (Alberti et al., 2009). At enrolment, participants were free from CVD. Further inclusion and exclusion criteria are detailed in the protocol(Martínez-González et al., 2019) and accessible at http://predimedplus.com/.

Ascertainment of Variables

1. *Exposure: SARS-CoV-2 infection*

A COVID-19 event (SARS-CoV-2 infection) was confirmed as per the following definitions: a) Confirmed COVID-19 was defined as a positive response to any one of the following tests: PCR SARS-CoV-2 (acute infection), Ag SARS-CoV-2 (acute infection), Ab SARS-CoV-2, total or IgG (past infection) and b) Probable COVID-19 infection was defined as Ab SARS-CoV-2, IgM +

without a subsequent increase in IgG (IgG -) or a clinical presentation compatible diagnosis of COVID-19 by an attending physician treating COVID-19, without analytical testing at or after the acute moment. COVID-19 events adjudicated and confirmed until December 31st, 2021, were used in this analysis. Overall, 409 participants were confirmed COVID-19 cases and 1 participant was a probable case of COVID-19. Owing to only one of the COVID-19 positive cases designated as probable, both confirmed and probable cases of COVID-19 were pooled for this analysis as COVID-19 positive. Participants who did not have a confirmed or probable positive diagnosis of SARS-CoV-2 infection were considered COVID-19 negative, i.e., they were assumed to have not experienced the infection

2. Serology Analysis in a sub-sample for supplementary analysis

Participants were first tested for SARS-CoV-2 IgG using SARS-CoV-2 IgG ELISA Kit – (Enzo Biochem, New York, USA) (sensitivity: 100% and specificity: 96.5%) by duplicate. Participants who tested negative for the SARS-CoV-2 IgG were confirmed as COVID-19 negative. Participants whose serum tested positive in the above test were submitted to a second test using Technozym anti-SARS-CoV-2 RBD IgG test kit (Diapharma, West Chester, USA) (sensitivity: 99.3% and specificity: 100%). Those testing negative in the second test by duplicate were classified as COVID-19 negative and others were confirmed as COVID-19 positive.

Assessment of confounder variables

PREDIMED-Plus has a scheduled collection of data that facilitates adjustments for potentially relevant confounders. Sociodemographic data (age, sex, educational level, marital status) and lifestyle information including physical activity (Molina et al., 2017), alcohol consumption and health status (e.g. presence or treatment for diabetes, hypercholesterolemia)were self-reported by the participants at face-to-face interviews at the baseline visit of the PREDIMED-

Plus Trial and during the annual follow-ups. Anthropometric data were collected yearly, and BMI was calculated as weight in kg divided by the square of height in m^2. Adherence to an energy-reduced Mediterranean diet was assessed during annual visits by using a validated 17-item energy-restricted Mediterranean Adherence Screener (er-MEDAS)(Schröder et al., 2021). Cognitive assessments were performed using a Spanish-validated version of the Mini-Mental State Examination (MMSE) questionnaire, commonly used as a cognitive screening test(Blesa, 2001; Folstein et al., 1975; Lobo et al., 2002). A higher MMSE score indicates better cognitive performance.

Statistical Analysis

1. *Preliminary cross-sectional exploration*

A preliminary cross-sectional exploration of the data at the pre-COVID-19 visit was undertaken, descriptive statistics for continuous variables are shown as the median and interquartile range (IQR), and categorical data are displayed as count and percentages. To compare the pre-Covid-19 characteristics of COVID-19 negative and positive participants, Chi-square test and Mann-Whitney U test (owing to the skewed nature of the distribution) were used, as appropriate.

2. *Models used for primary analysis*

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 (Table 2). Alcohol consumption was used as a quadratic term in the model to

accommodate for a non-linear relationship with the outcome. All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation. This procedure was used to control for the allocation of household members into the same intervention group without randomization.

3. *Secondary Analysis*

A secondary analysis was performed with post-COVID-19 elevated depression risk as a binary outcome using BDI-II cut-offs of ≥ 14 (Table 3). Logistic regression was used to calculate Odds Ratios (ORs) and their 95% confidence intervals (CIs), considering the COVID-19 negative status as the reference category. The results were adjusted for the same confounding factors noted above, using the three same models developed for the main linear regression analysis.

4. *Supplementary Analysis*

a. *Evaluation of minimal adjustment*

In order to evaluate the effect of over-adjustments, a directed acyclic graph (DAG) was modelled (Supplementary Figure S2) based on existing literature (Textor et al., 2016). A minimal adjustment set to quantify the total direct effect of COVID-19 on depression measures included only pre-COVID-19 depression scores. Minimal linear and logistic regression models were accordingly tested as supplementary analysis (Supplementary analysis 1: Supplementary Table S1).

b. *Lower BDI-II cut off to identify elevated depression risk*

Evaluating the use of BDI-II in Spain over 50 years, Sanchez (2013) proposed that for the non-institutionalised Spanish population, a cut-off ≥ 12 had an adequate specificity index and diagnostic concordance and could detect major depressive episodes in 93% of individuals(Sanz Fernández, 2013). Thus, a supplementary analysis using a cut-off ≥ 12 was also conducted to categorise the outcome variable, namely the elevated risk of depression post-COVID-19. An

additional supplementary logistic regression analysis was undertaken using a BDI-II score ≥ 12 as the cut-off for elevated depression risk (Supplementary analysis 2: Supplementary Table S1).

c. Evaluation of effect modification

Next, in order to assess the possible effect modification of association by potential confounders (age group [≤70 or <70 years], sex, intervention group, disease conditions and time elapsed post-COVID-19), product-terms were introduced in the different multivariable models. P-values for interaction were calculated with the likelihood ratio test and coefficient plots were generated to visualize the trends by strata (Supplementary Figure S2). Sub-analyses that stratified the results by factors that showed significant interaction (sex (Tables 2, 3)), presence of pre-COVID-19 high depression risk (Table 4) and time elapsed post-COVID-19 during depression assessments (Supplementary Table S2) were undertaken to identify strata specific trends. Post-estimation was performed for the final model to obtain predicted post-COVID-19 BDI-II scores. These were generated for the strata that showed significant interactions (Supplementary Figure S4). Finally, supplementary linear and logistic analyses were conducted in the sub-sample with serology results to ascertain COVID-19 status (Supplementary Table S3).

References

Sanz Fernández, J. (2013). *50 years of the Beck Depression Inventory: Recommendations for using the Spanish adaptation of the BDI-II in clinical practice* [Info:eu-repo/semantics/article]. Consejo General de la Psicología de España. https://eprints.ucm.es/id/eprint/36450/

Textor, J., van der Zander, B., Gilthorpe, M. S., Liśkiewicz, M., & Ellison, G. T. (2016). Robust causal inference using directed acyclic graphs: The R package 'dagitty.' *International Journal of Epidemiology*, *45*(6), 1887–1894. https://doi.org/10.1093/ije/dyw341

Supplementary Table S1: Longitudinal association of COVID-19 status with depressive symptomatology in the PREDIMED-Plus cohort - Results of supplementary analysis using minimal adjustment models and BDI-II ≥ 12 to describe elevated depression risk

	Effect Size#	95% CI	P value
Supplementary analysis 1			
Minimal adjustment Model A (β [95%CI]) #	0.57	(0.07 to 1.07)	0.03
Minimal adjustment Model B (OR [95%CI]) #	1.59	(1.13 to 2.19)	<0.01
Supplementary analysis 2 (OR [95%CI]) #			
Unadjusted Crude Model	1.22	(0.95 to 1.57)	0.12
Model 1	1.60	(1.19 to 2.15)	<0.01
Model 2	1.57	(1.16 to 2.13)	<0.01
Model 3	1.59	(1.17 to 2.15)	<0.01

Abbreviations: BDI-II scores, Beck Depression Inventory-II; COVID-19, coronavirus disease 2019, MMSE, Mini-Mental State Examination

#Reference category for all analysis: COVID-19 negative status

Supplementary analysis 1: Uses a minimal adjustment set identified using directed acyclic graphs (supplementary figure 2)

Minimal adjustment model A uses linear regression with Post BDI-II scores as the outcome, COVID-19 infection as the exposure, adjusting for BDI-II scores pre-COVID-19. Effect size presented as β coefficients (95% CI).

Minimal adjustment model B uses logistic regression with post-COVID-19 elevated depression risk (BDI-II ≥ 14) as the outcome, COVID-19 status as exposure, adjusting for BDI-II scores pre-COVID-19. Effect size presented as Odds ratio (OR and 95% CI).

Supplementary analysis 2: Uses logistic regression with post-COVID-19 elevated depression risk (BDI-II ≥ 12) as the outcome, COVID-19 status as exposure. Effect size presented as Odds ratio (OR and 95% CI).

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 randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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

Supplementary Table S2: Longitudinal association of COVID-19 status with depressive symptomatology in the PREDIMED-Plus cohort, stratified by time of post-COVID-19 depression assessment

	Post-COVID-19 assessment <= 12 weeks (n = 1,025)			Post-COVID-19 assessment > 12 weeks (n = 4,461)		
	Effect size	95% CI	P value	Effect size	95% CI	P value
Post COVID BDI-II scores (β [95%CI]) #						
Unadjusted Crude Model	-0.10	(-1.45 to 1.25)	0.88	0.22	(-0.51 to 0.96)	0.55
Model 1	0.31	(-0.83 to 1.45)	0.60	0.79	(0.25 to 1.32)	<0.001
Model 2	0.38	(- 0.79 to 1.56)	0.52	0.70	(0.15 to 1.24)	0.01
Model 3	0.41	(- 0.77 to 1.58)	0.50	0.71	(0.17 to 1.25)	0.01
Elevated depression risk symptomatology Post-COVID19 (OR [95%CI]) δ						
Unadjusted Crude Model	1.33	(0.77 to 2.82)	0.30	1.15	(0.82 to 1.64)	0.40
Model 1	1.65	(0.81 to 3.35)	0.17	1.65	(1.13 to 2.43)	0.01
Model 2	1.74	(0.85 to 3.59)	0.13	1.53	(1.02 to 2.30)	0.04
Model 3	1.67	(0.82 to 3.43)	0.16	1.56	(1.04 to 2.34)	0.03

#β coefficient (95% CI) was calculated using linear regression models. Exposure= COVID-19 status (Positive or negative); Outcome: Post COVID BDI-II scores

δOR: Odds Ratio (95% CI) was calculated using logistic regression models. Exposure= COVID-19 status (Positive or negative); Outcome: elevated depression risk symptomatology Post COVID-19 (yes/no).

Elevated depression risk symptomatology is defined as BDI-II score ≥ 14, absence of elevated depression risk symptomatology 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 randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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

Supplementary Table S3: Longitudinal association of COVID-19 (status determined using serology) with depressive symptomatology assessments in the sub-study of PREDIMED-Plus cohort (beta [95%CI] or OR [95%CI], n= 3,801)

Supplementary Analysis 1	B#	95% CI	P value
Crude Model	0.64	(-0.19 to 1.48)	0.13
Model 1a	0.92	(0.23 to 1.61)	<0.01
Model 2	0.95	(0.26 to 1.65)	<0.01
Model 3	0.95	(0.26 to 1.64)	<0.01
Minimal adjustment	1.00	(0.37 to 1.62)	<0.01

Supplementary Analysis 2	ORδ	95% CI	P value
Crude Model	1.04	(0.70 to 1.54)	0.85
Model 1 a	1.27	(0.79 to 2.05)	0.33
Model 2	1.29	(0.80 to 2.08)	0.30
Model 3	1.29	(0.79 to 2.08)	0.31
Minimal adjustment	1.33	(0.84 to 2.10)	0.22

[#]β coefficient (95% CI) was calculated using linear regression models. Exposure: COVID-19 status (Positive or negative); Outcome: Post-COVID-19 BDI-II scores

[δ]OR: Odds Ratio and (95% CI) were calculated using logistic regression models. Exposure: COVID-19 status (Positive or negative); Outcome: Elevated depression risk symptomatology Post COVID-19 (yes/no). 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 evaluate post-COVID-19 depressive symptomatology

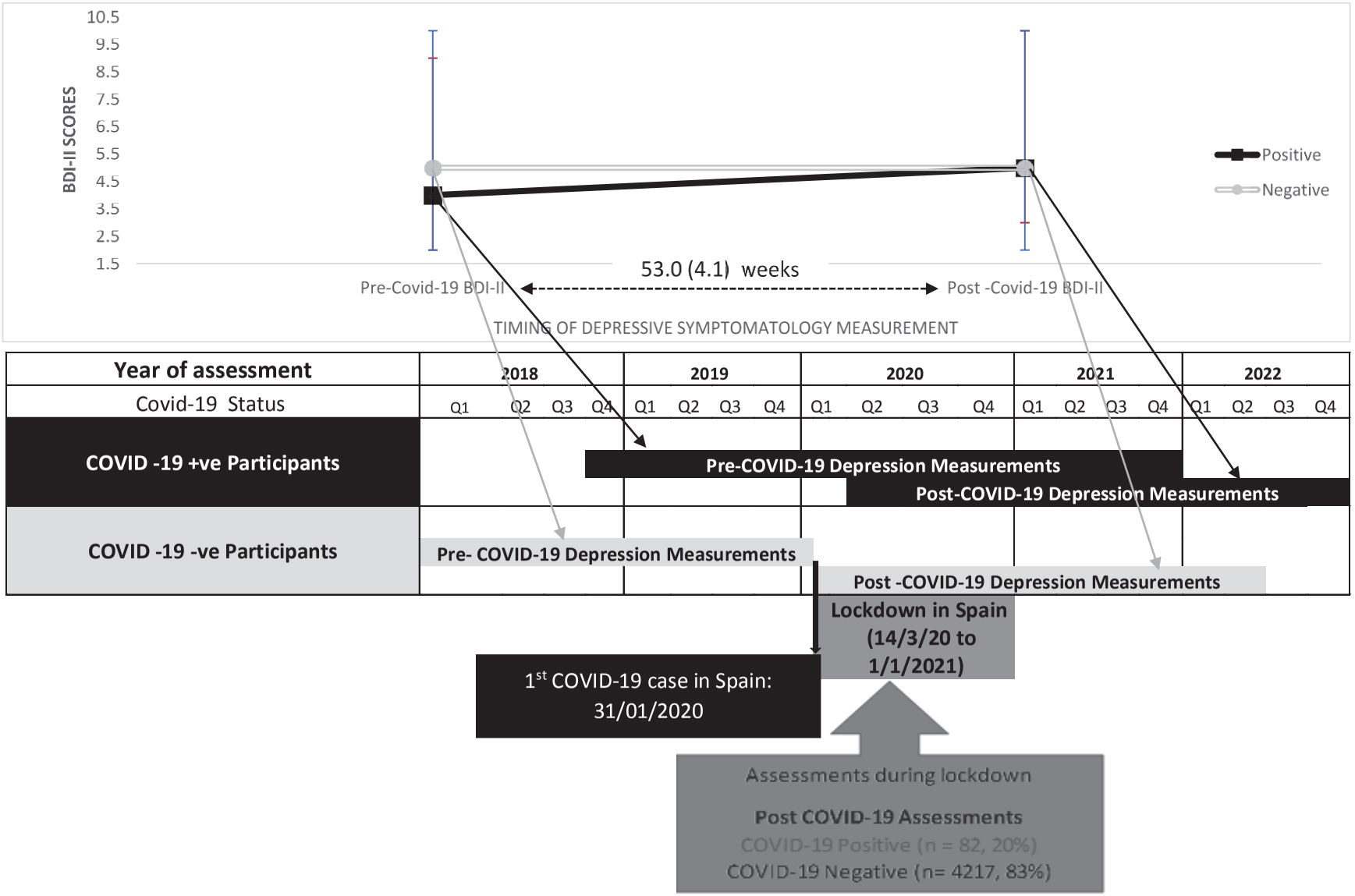
Reference category: COVID-19 negative status.

***Model 1:** Adjusted for age, sex, education, marital status, intervention group, cluster randomisation, recruitment centre size, pre-COVID-19 BDI-II scores, 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

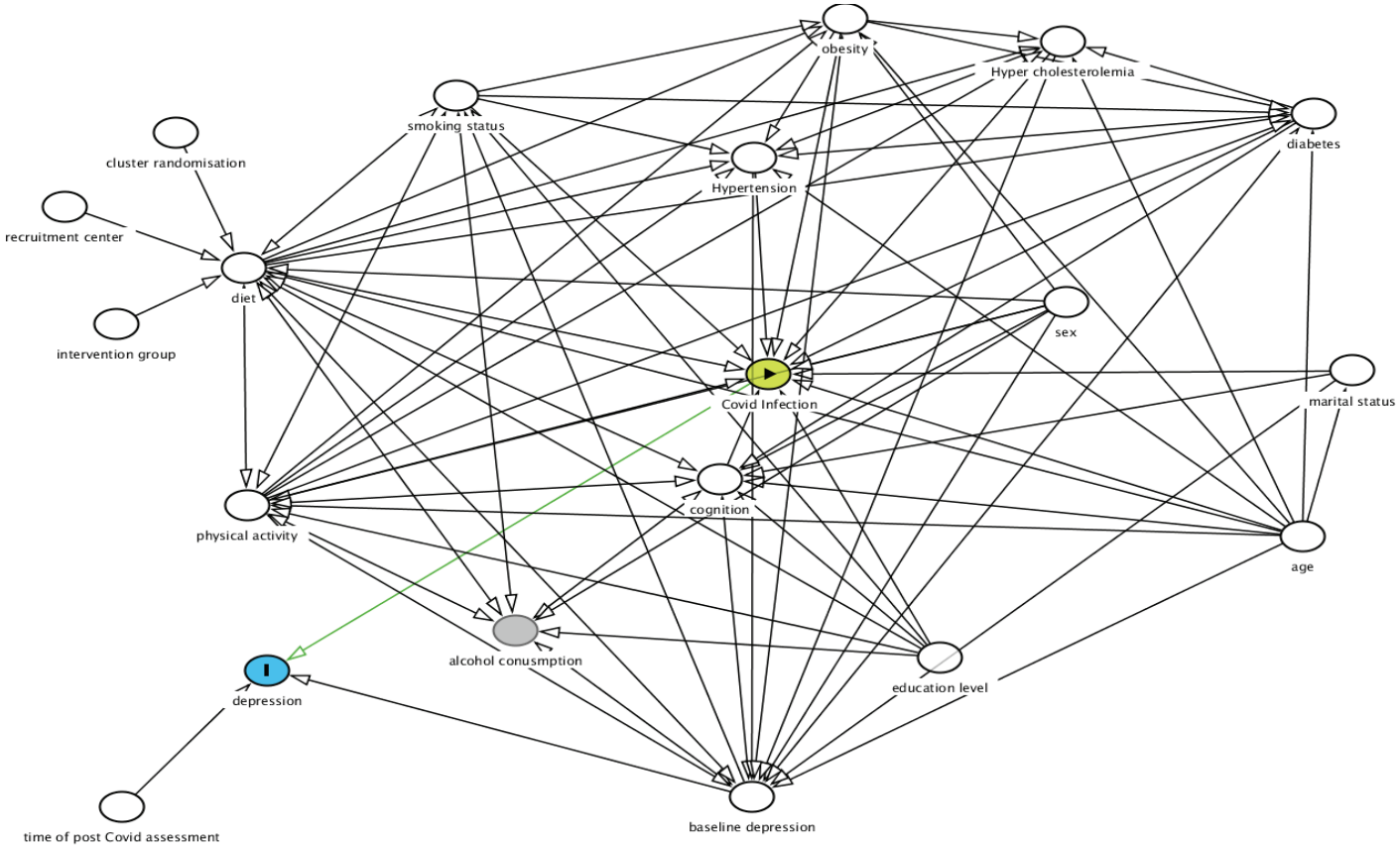
Minimal adjustment model adjusts only for BDI-II scores pre-COVID-19



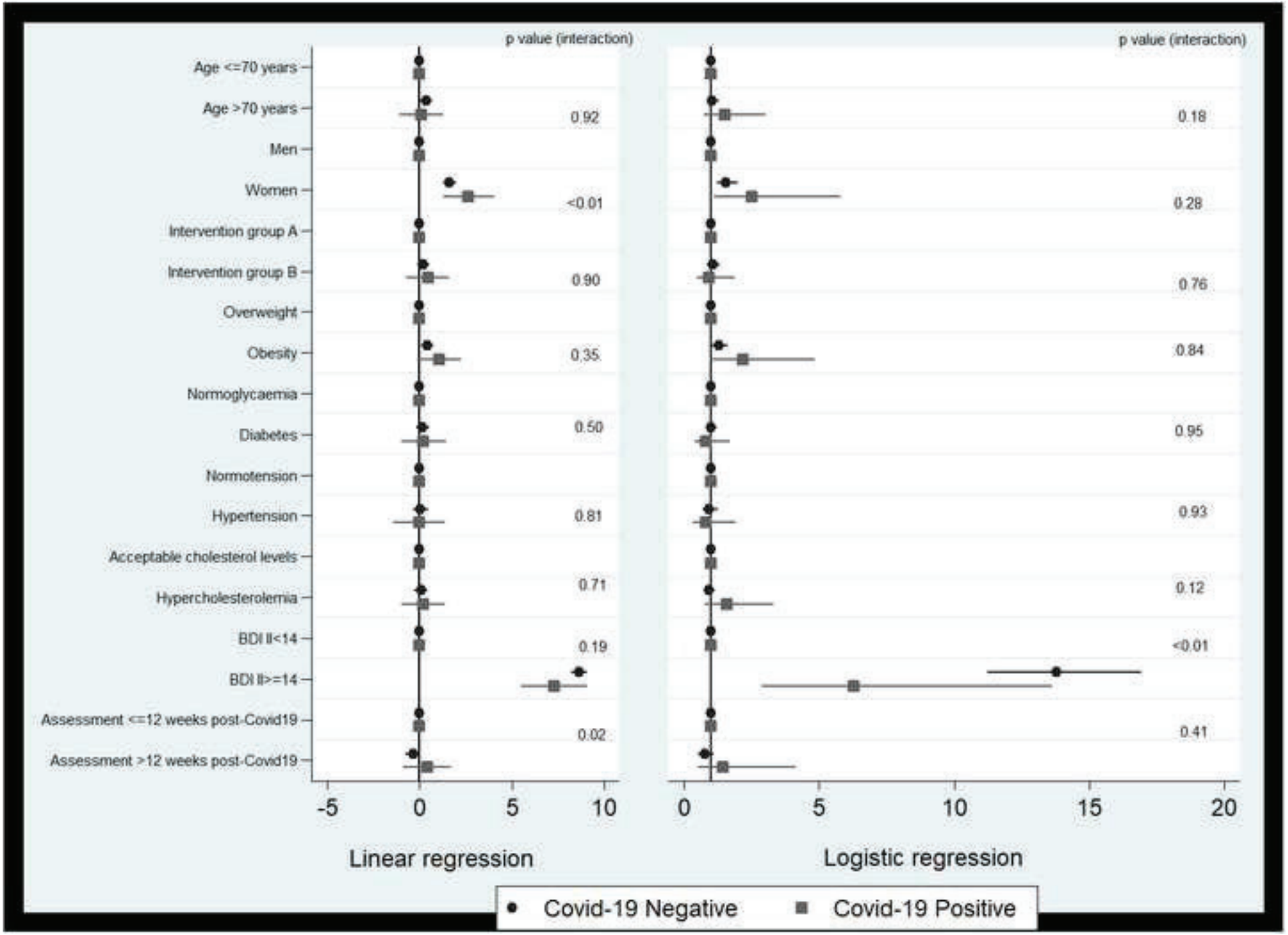
Supplementary Figure S1: Timing of pre- and post-COVID-19 depression assessments in the participants

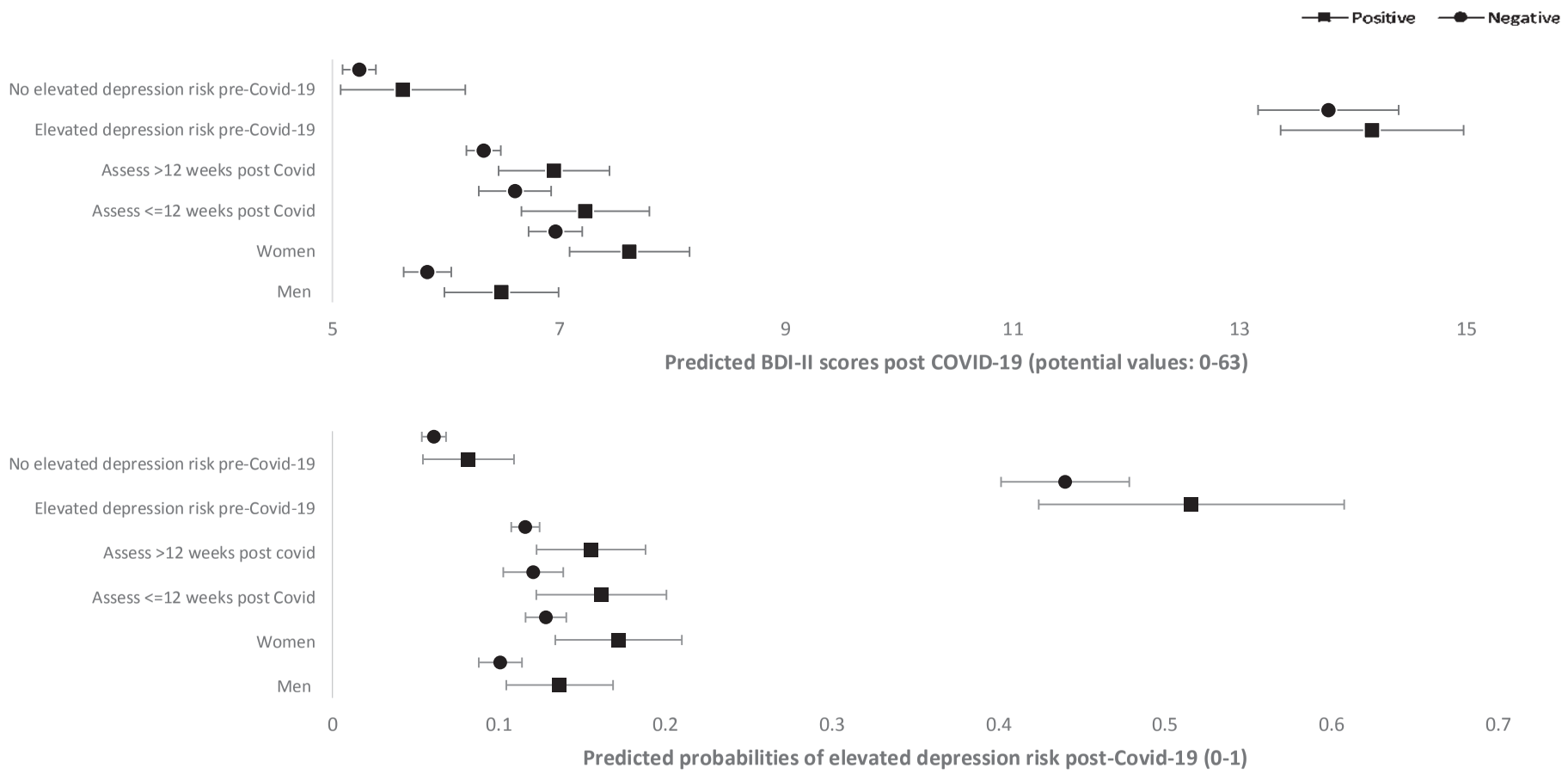
Legend: *The figure shows the timing of pre- and post-COVID-19 depression measurements in the participants. The calendar period of these measurements is shown in the Gantt chart below. Q1- Q4 represents the four quarters of the year. The shaded regions depict the pre and post-COVID-19 time of assessments of depressive assessments of the participants. Pre-COVID-19 measurements in COVid-19 negative participants are measured before the first case of COVID-19 was reported in Spain. In Covid-19 positive participants, Pre-COVID-19 measurements are those from before the date of Covid-19 diagnosis. Post-COVID-19 measurements are those obtained in the subsequent follow-up. Red bars show the timing of assessment in the COVID-19 positive and blue bars in COVID-19 negative participants. The orange bar below shows the timing and duration of the lockdown in Spain as a public health measure to prevent the spread of COVID-19.*

Explanatory Note: *20% of post-COVID-19 assessments for the COVID-19 positive participants and 83% of the post-COVID-19 assessments for the COVID-19 negative participants occurred during the lockdown in Spain (14/3/20 to 1/1/2021). Assuming that the COVID-19 lockdown could have increased the BDI-II scores, it is expected that the current estimates for the impact of COVID-19 obtained in this analysis are attenuated since more COVID-19 negative participants had their post-COVID-19 assessments performed during this time.*



Supplementary Figure S2: Directed acyclic graph to identify minimal adjustments to evaluate the impact of COVID-19 on depression measures in PREDIMED-Plus participants





Supplementary Figure S4. Predicted post-COVID-19 BDI-II scores and probabilities of elevated depression risk post-COVID-19 in stratified regression analysis using fully adjusted models

Legend: *BDI-II, Beck Depression Inventory-II, COVID-19, coronavirus disease 2019. Predicted post-COVID-19 BDI-II was calculated using linear regression; predicted probabilities for depressive symptomatology post-COVID-19 were calculated using logistic regression. Both analyses show the fully adjusted models (Adjusted for age, sex, education, marital status, intervention group, cluster randomisation, recruitment centre, pre-COVID-19 BDI-II scores, time since infection for post-COVID-19 depression assessments, presence of obesity, diabetes mellitus, hypertension, hypercholesterolemia, and baseline cognition, adherence to Mediterranean diet scores, smoking status, physical activity, and alcohol consumption. Red square markers indicate COVID-19-positive status and blue dots indicate COVID-19-negative status within the strata. Error bars indicate 95% CI. BDI-II scores have a potential range between 0 and 63 and predicted probabilities between 0 and 1.*