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4 1 **Title: Intensive Weight-Loss Lifestyle Intervention using Mediterranean Diet and COVID-**  
5 2 **19 Risk in Older Adults: Secondary Analysis of PREDIMED-Plus Trial**  
6 3

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11 He has received support for travel or meetings or conference organization from ERAB, Belgium,  
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1 Title: **Intensive Lifestyle Intervention for Weight-Loss using Mediterranean Diet and**  
2 **COVID-19 Risk in Older Adults: Analysis of PREDIMED-Plus Trial**

3 **ABSTRACT**

4 **Objectives:** We tested the effects of a weight loss intervention encouraging energy-reduced  
5 MedDiet and PA in comparison to ad libitum MedDiet on COVID-19 incidence in older adults.

6 **Design:** Secondary analysis of PREDIMED-Plus, a prospective, ongoing, multicentre  
7 randomized controlled trial

8 **Setting:** Community-dwelling, free-living participants in PREDIMED-Plus trial

9 **Participants:** 6,874 Spanish older adults (55-75 years, 49% women) with overweight/obesity  
10 and metabolic syndrome

11 **Intervention:** Participants were randomised to Intervention (IG) or Control (CG) Group. IG  
12 received intensive behavioural intervention for weight loss with an energy-reduced MedDiet  
13 intervention and PA promotion. CG was encouraged to consume *ad libitum* MedDiet without PA  
14 recommendations.

15 **Measurements:** COVID-19 was ascertained by an independent Event Committee until  
16 December 31, 2021. COX regression models compared the effect of PREDIMED-Plus  
17 interventions on COVID-19 risk.

18 **Results:** Overall, 653 COVID-19 cases were documented (IG:317; CG:336) over a median  
19 (IQR) follow-up of 5.8 (1.3) years (inclusive of 4.0 (1.2) years before community transmission of  
20 COVID-19) in both groups. A significantly lowered risk of COVID-19 incidence was not evident  
21 in IG, compared to CG (fully-adjusted HR (95% CI): 0.96 (0.81,1.12)).

22 **Conclusions:** There was no evidence to show that an intensive weight-loss intervention  
23 encouraging energy-reduced MedDiet and PA significantly lowered COVID-19 risk in older

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24 adults with overweight/obesity metabolic syndrome in comparison to *ad libitum* MedDiet.  
25 Recommendations to improve adherence to MedDiet provided with or without lifestyle  
26 modification suggestions for weight loss may have similar effects in protecting against COVID-  
27 19 risk in older adults with high cardiovascular risks.

28  
29 **Trial registration:** This study is registered at International Standard Randomized Controlled  
30 Trial (ISRCT) ISRCTN89898870 (<http://www.isrctn.com/ISRCTN89898870>).

31  
32 **Keywords:** COVID-19; SARS-CoV2; PREDIMED-Plus; Mediterranean diet; Older adults

33  
34 **Abbreviations:**  
35 CG: Control Group; COVID-19: Coronavirus disease; IG: Intervention Group, MedDiet:  
36 Mediterranean diet; PA: Physical activity

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4 38 **INTRODUCTION**

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7 39 The Coronavirus Disease 2019 (COVID-19) emerged as a pandemic with unprecedented global  
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9 40 impact (1). Older age, excessive body weight, and elevated cardiometabolic risks have been  
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12 41 associated with increased COVID-19 risk (2). The increased risk associated with these conditions  
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14 42 has been ascribed to senescence and/or obesity-related inflammation that attenuates immune  
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16 43 response (2). With climate change and globalisation, the emergence and transmission of novel  
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19 44 diseases are expected to accelerate (3). Thus, there is an urgent need to understand how  
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22 45 modifiable risks including excessive body weight can be targeted for future prevention.  
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27 47 Lifestyle habits are among the modifiable factors to improve immunocompetence. In individuals  
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29 48 with overweight/obesity weight loss could improve immunocompetence (4). We have shown that  
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32 49 clinically significant weight loss achieved 5-6 years before the onset of the pandemic was  
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34 50 associated with reduced COVID-19 risk among older adults with overweight/obesity and  
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36 51 metabolic syndrome enrolled in the PREDIMED-Plus cohort (5). Additionally, observational  
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39 52 evidence has associated higher adherence to the Mediterranean diet (MedDiet) with a lower  
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42 53 COVID-19 risk (6–8). Furthermore, adherence to physical activity (PA) recommendations in the  
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44 54 2 years preceding the pandemic was associated with a lower risk of COVID-19-related  
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46 55 hospitalization and death (9). Hence, we hypothesized that in comparison to *ad libitum* MedDiet,  
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49 56 an intensive lifestyle intervention for weight loss through improving adherence to an energy-  
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52 57 reduced MedDiet pattern and PA recommendations would further reduce COVID-19 incidence  
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54 58 in older adults with overweight/obesity. In the absence of existing randomized controlled trials  
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56 59 (RCTs), we tested this hypothesis in PREDIMED-Plus participants.  
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4 60 **METHODS**

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7 61 **Setting:**

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9 62 The PREDIMED-Plus is an ongoing, multicentre, open-labelled RCT in 6,874 community-  
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11 63 dwelling Spanish women and men, aged 55–75 years at enrolment, with overweight/obesity and  
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13 64 metabolic syndrome, but without cardiovascular disease (CVD) (10). The trial aims to assess the  
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15 65 effectiveness of an intensive lifestyle intervention using an energy-reduced MedDiet pattern and  
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17 66 PA promotion on the primary prevention of CVD in comparison to usual care (*ad libitum*  
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19 67 MedDiet) in older adults with high cardiometabolic risks in the Meditterarean region.  
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26 69 **Intervention:**

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28 70 The PREDIMED-Plus was approved by institutional review board approvals of the participating  
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30 71 centres. The study is registered at the International Standard RCT Registry (ISRCT;  
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32 72 <http://www.isrctn.com/ISRCTN89898870>) and the protocol has been published previous (10).  
33  
34 73 In brief, 6,874 PREDIMED-Plus participants were randomly allocated on a 1:1 ratio to either an  
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36 74 intervention (IG) or control (CG) group, stratified by sex, age (<65, 65–70, >70) and centre (10).  
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38 75 CG participants were encouraged to follow a traditional MedDiet based on PREDIMED study  
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40 76 (11) without caloric restrictions or PA recommendations. IG received advice to adhere to a  
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42 77 healthy, energy-reduced MedDiet and improve PA ( $\geq 45$  min/day) (10).  
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47 78 The trial randomization began in 2013, with all trial participants completing the 6-year  
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49 79 intervention in 2023. The additional 2-year in-person annual follow-up is currently ongoing, and  
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51 80 trial is scheduled for completion in 2025.  
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4 **82 Outcome: COVID-19 incidence**

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7 83 COVID-19 event was adjudicated by the independent Trial Clinical Event Ascertainment  
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9 84 Committee, based on participant medical records reviewed annually by the participating  
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11 85 physicians. According to the study protocol, COVID-19 event (SARS-CoV-2 infection) in the  
12  
13 86 PREDIMED-Plus is confirmed as per the following definitions: a) Confirmed COVID-19 was  
14  
15 87 defined as a positive response to any one of the following tests: PCR SARS-CoV-2 (acute  
16  
17 88 infection), Ag SARS-CoV-2 (acute infection), Ab SARS-CoV-2, total or IgG (past infection) and b)  
18  
19 89 Probable COVID-19 infection was defined as Ab SARS-CoV-2, IgM + without a subsequent  
20  
21 90 increase in IgG (IgG -) or a clinical presentation compatible diagnosis of COVID-19 by an  
22  
23 91 attending physician treating COVID-19, without analytical testing at or after the acute moment.  
24  
25 92 COVID-19 events confirmed (incident/not-incident) from the emergence of the pandemic until  
26  
27 93 December 31, 2021, were used in this analysis. In this analysis, both confirmed (n=652) and  
28  
29 94 probable (n=1) COVID-19 diagnoses were pooled together as COVID-19 incident cases (n= 653).  
30  
31 95 Others were treated as having COVID-19 non-incident status (n=6,221). Thus COVID-19 status  
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33 96 was defined as a dichotomous variable (incident/not-incident).  
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44 **98 Covariates:**

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46 99 The cohort has baseline data on socio-demography (age, sex, education level, marital status),  
47  
48 100 lifestyle (dietary and physical activity), and clinical status (body mass index (BMI), prevalence  
49  
50 101 of type 2 diabetes, hypercholesterolemia, hypertension) that could confound the relationship  
51  
52 102 between the intervention and COVID-19. The cohort has also documented from the medical  
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54 103 records of participants the use of angiotensin-converting enzyme (ACE) inhibitors and whether  
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4 104 at least one dose of a COVID-19 vaccine was administered before censoring, enabling additional  
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7 105 adjustments for these potential confounders.  
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9 106

## 107 **Statistical Analysis**

108 We constructed Kaplan–Meier cumulative-incidence curves according to the intervention  
109 allocation and calculated Hazard Ratios (HR) on an intention-to-treat basis, with CG as the  
110 reference, using a Cox proportional regression model. The follow-up time for each participant  
111 started at randomization and ended at COVID-19 diagnosis or date of death or last contact prior  
112 to 31 December 2021, whichever occurred first.

113 The results are presented as Hazard Ratio (HR) with 95% Confidence Intervals (CI) calculated  
114 from a crude model without adjustments and two additional models. Model 1 was adjusted for  
115 age at enrolment (y), sex (male/female), education (primary or less/ secondary/university),  
116 marital status (single or divorced or separated/married/widow(er)), and recruitment centre  
117 (location). Model 2 was additionally adjusted for baseline data for smoking status  
118 (never/former/current), BMI, Mediterranean diet adherence score (17-point scale), total PA  
119 (METs.min/week), alcohol intake (g/d as a quadratic term), previous diagnosis of chronic  
120 diseases (diabetes, hypertension, hypercholesterolemia (Yes/No)), ACE-inhibitor use (Yes/No),  
121 and receipt of at least one COVID-19 vaccine dose (Yes/No) prior to censoring. We used robust  
122 variance estimators to account for intra-cluster correlations in all models, considering members  
123 of the same household and the participants in a recruitment centre as a cluster. Stata (Ver 14.2)  
124 was used to perform all analyses with the statistical significance set at 5%.

125 Sensitivity analyses were carried out after excluding participants (n=108) who had deceased  
126 before COVID-19 emergence (November 30, 2019) and using a minimal adjustment set

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127 identified with a directed acyclic graph (Supplementary Figure S1). For the present study, we  
128 used the PREDIMED-Plus database updated until December 2021

129

## 130 **RESULTS**

131 Participant characteristics are presented in Table 1. At censoring, a total of 653 (9.7%) COVID-  
132 19 cases (CG:336; IG:317) were documented. In both groups, the median (IQR) follow-up  
133 duration was 5.8 (1.3) years and this included 4.0 (1.2) years prior to community transmission of  
134 COVID-19 in Spain. There was no evidence to show that IG significantly lowered COVID-19  
135 risk versus CG (Table 2, Supplementary Figure S2). Sensitivity analyses performed removing  
136 108 individuals in the study who had deceased prior to the onset of the pandemic, confirmed the  
137 results (Table 2). No significant interaction with any factor of interest was apparent  
138 (Supplementary Figure S3).

139

## 140 **DISCUSSION**

141 We found in Spanish older adults with overweight/obesity and metabolic syndrome, the effect on  
142 COVID-19 risk of an intensive lifestyle intervention encouraging energy-reduced MedDiet and  
143 PA for weight loss was not significantly different from that of *ad libitum* MedDiet. It is  
144 interesting to juxtapose these results with previous observational findings in middle-aged adults  
145 that showed the benefit of MedDiet (6-8) and our observation that weight loss  $\geq 5\%$  significantly  
146 reduced COVID-19 risk in this cohort of older adults with overweight/obesity (5). One potential  
147 explanation for our results is that the CG participants in our trial also consumed MedDiet albeit  
148 without instruction to energy restriction/increase PA. It is possible that CG participants also lost  
149 body weight as a result of improving their eating habits, i.e. through increased adherence to a

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150 MedDiet (12). The beneficial effects of MedDiet emphasising specific food groups such a nuts  
151 and olive oil on body weight could have attenuated the treatment effect (12). Additionally,  
152 improving PA to potentiate negative energy balance for weight loss may be more feasible earlier  
153 in life. Thus, while the weight loss at the pre-COVID-19 visit was significantly lower in the IG  
154 vs CG ( $p<0.001$ ), this difference does not seem to be sufficient to significantly reduce COVID-  
155 19 risk (See Table 1). Moreover, the health benefits of MedDiet have been ascribed to  
156 mechanisms beyond weight loss, and primarily to the overall composition of the diet (13), which  
157 may explain the lack of significant difference between IG and CG whose interventions were  
158 based on MedDiet.

159  
160 This analysis have several strengths, being among the first RCT evidence to evaluate the  
161 effectiveness of an intensive weight loss intervention using MedDiet and PA recommendations  
162 on COVID-19 risk in older adults with overweight/obesity. The RCT design and blinding of the  
163 investigators to the outcomes are major strengths of this analysis. This analysis considers  
164 COVID-19 ascertainment data from 2020 and 2021, when testing for the infection was rigorous  
165 and systematic. The PREDIMED-Plus database also facilitated adjustments for several potential  
166 variables, providing a more reliable estimate.

167  
168 We also acknowledge potential limitations. First, asymptomatic infections could have been  
169 missed. Since the trial is underway, endpoints on chronic diseases such as diabetes or cancer are  
170 not available. This could have added to several other residual confounders relating to  
171 susceptibility to infection including the adoption of hygiene and sanitary precautions. COVID-19  
172 is an unexpected event that could not be accounted for in the original statistical analysis plan of

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4 173 the study, and the trial may have been underpowered to identify the small reduction in risks,  
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7 174 given the current <10% incidence of COVID-19 in the cohort, which however was similar to the  
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9 175 national incidence rate during the period (14). Finally, caution is required when generalising  
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11 176 results from an RCT to the general population.  
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## 16 178 **CONCLUSION**

19 179 There was no evidence to show that in comparison to an *ad libitum* MedDiet, an intensive  
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21 180 lifestyle intervention encouraging energy-reduced MedDiet and PA to promote weight loss had a  
22  
23 181 significantly greater reduction in COVID-19 risk among Spanish older adults with  
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25 182 overweight/obesity and metabolic syndrome. These findings require cautious interpretation  
26  
27 183 considering the limitations of this analysis, and our previous results which showed that clinically  
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29 184 significant weight loss in this cohort was associated with lower COVID-19 risk. We recommend  
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31 185 future evaluations on the effectiveness of weight loss interventions on infection severity,  
32  
33 186 recurrence or hospitalisation in older adults, as these outcomes may be more nutrition-sensitive.  
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35 187 Similar evaluations of lifestyle interventions for weight loss are required in younger populations  
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37 188 in whom increasing PA may be more feasible.  
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3 Martínez-González, Dolores Corella, J. Alfredo Martínez, Ángel M. Alonso-Gómez, Julia  
4 Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J  
5 Tinahones, José Lapetra, J. Luís Serra-Majem, Aurora Bueno-Cavanillas, Josep A. Tur, Vicente  
6 Martín Sánchez, Xavier Pintó, Pilar Matía-Martín, Josep Vidal, Clotilde Vázquez, Lidia Daimiel,  
7 Emili Ros, Fernando Fernandez-Aranda, Miguel Delgado-Rodríguez, María del Mar Alcarria,  
8 Eva M Asensio, Cristina Bouzas, M. Angeles Zulet, Elena Rayó, Rosa Casas, Sandra Martin-  
9 Pelaez, Lucas Tojal-Sierra, Bernal-López MR, Silvia Carlos, Albert Goday, Patricia J. Peña-  
10 Orihuela, Sonia Eguaras, María Dolors Zomeño, Jesús Francisco García-Gavilán, Indira Paz-  
11 Graniel, Stephanie K Nishi, Nancy Babio, Sangeetha Shyam. Formal Analysis & Methodology;  
12 Sangeetha Shyam, Nancy Babio, Jordi Salas-Salvadó. Funding acquisition; Jordi Salas-Salvadó,  
13 Montse Fitó , Miguel Ángel Martínez-González, Dolores Corella, J. Alfredo Martínez, Ángel M.  
14 Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon  
15 Estruch, Francisco J Tinahones, José Lapetra, J. Luís Serra-Majem, Aurora Bueno-Cavanillas,  
16 Josep A. Tur, Vicente Martín Sánchez, Xavier Pintó, Pilar Matía-Martín, Josep Vidal, Lidia  
17 Daimiel, Emili Ros, Fernando Fernandez-Aranda, and Miguel Delgado-Rodríguez. Project  
18 Administration; Resources; Software; Supervision; Jordi Salas-Salvadó & Montserrat Fitó.  
19 Writing - original draft; Sangeetha Shyam, Jordi Salas-Salvadó. Writing - review & editing: All  
20 authors.

21  
22 **ETHICS DECLARATIONS**

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4 **1 Ethics approval and consent to participate**

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6  
7 2 The studies involving human participants were reviewed and approved by the study was  
8  
9 3 conducted according to the guidelines of the Declaration of Helsinki. The study was approved by  
10  
11 4 the Institutional Review Boards of all participating centres as follows: (Facultad de Medicina de  
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14 5 Málaga:CEI Provincial de Málaga-Servicio Andaluz de Salud :O01\_feb\_PR2 - Predimedplus  
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16 6 nodo 1, Centro Salud San Pablo de Sevilla:CEI de los Hospitales Universitarios Virgen  
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18 7 Macarena y Virgen del Rocío-Servicio Andaluz de Salud:PI13/00673, Nutrición y Farmacia,  
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21 8 Univ. De Navarra:CEIC Universidad de Navarra:053/2013,Hospital Son Espases de  
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24 9 Mallorca:CEI de las Illes Balears - Conselleria de Salut Direcció General de Salut Publica i  
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26 10 Consum:IB 2242/14 PI, Hospital Clinic de Barcelona:CEIC del Hospital Clínic de  
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29 11 Barcelona:HCB/2016/0287,IMIM, Barcelona:CEIC Parc de Salut Mar y IDIAP Jordi  
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32 12 Gol:PI13/120,Universitat Rovira i Virigili:CEIC del Hospital Universitari Sant Joan de Reus y  
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34 13 IDIAB Jordi Gol:13-07-25/7proj2,Universida de Granda:CEI de la Provincia de Granada-  
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36 14 Servicio Andaluz de Salud:MAB/BGP/pg,Fundación Jiménez Díaz:CEIC de la Fundacion  
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38 15 Jiménez Díaz:EC 26-14/IIS-FJD,Facultad de Mecina, Univ. De Navarra:CEIC Universidad de  
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41 16 Navarra:053/2013,Hospital Txagorritxu, Vitoria:CEIC Euskadi:PI2014044,Facultad de Mecina  
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44 17 de Valencia:CEIC Corporativo de Atención Primaria de la Comunitat Valenciana :2011-005398-  
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46 18 22,Universidad de las Palmas de Gran Canaria:CEI Humana de la Universidad de las Palmas de  
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48 19 Gran Canaria:CEIH-2013-07,Hospital Universitari de Bellvitge:CEIC del Hospital de  
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51 20 Bellvitge:PR240/13,Universida de Córdoba:CEI de Cordoba-Junta de Salud:3078,IMDEA,  
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53 21 Madrid:CEI de la Fundación IMDEA Alimentación:PI-012, Hospital Clínico de Madrid:CEIC  
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56 22 Hospital Clínico San Carlos de Madrid-Piloto-CEIC Servicio Madrileño de salud-General  
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58 23 :30/15,Hospital de Málaga:CEI Provincial de Málaga-Servicio Andaluz de Salud :,Universitat de  
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1 les Illes Balears:CEI de las Illes Balears - Conselleria de Salut Direcció General de Salut  
2 Publica i Consum:IB 2251/14 PI,Endocrinología, Hospital Clínic de Barcelona:CEIC del  
3 Hospital Clínic de Barcelona:HCB/2017/0351,Universidad Miguel Hernandez de Alicante:CEIC  
4 del Hospital General Universitario de Alicante:CEIC PI2017/02, Universidad de Jaén:CEIC de la  
5 Investigación Biomédica de Andalucía (CCEIBA),Universidad de León:CEI de la Universidad  
6 de León:ÉTICA-ULE-014-2015). The patients/participants provided their written informed  
7 consent to participate in this study.

8  
9 **Conflict of interest:**

10 Fernandez-Aranda acknowledges consulting fees from Novo Nordisk and Wiley as EIC for the  
11 European Eat Dis Rev. He has also received honoraria for lectures and support for  
12 travel/meetings from Novo Nordisk. He discloses his honorary participation in the Data Safety  
13 Monitoring Board or Advisory Board of Sustain-Consortium-Germany. Emilio Ros has received  
14 honoraria for presentations and support for attending meetings/travel from the California Walnut  
15 Commission, Alexion and the Spanish Atherosclerosis Society. He has also received consulting  
16 fees from Alexion. He participates in the Data Safety Monitoring Board or Advisory Board of  
17 the PREDIMED-Plus Clinical Trial. Ramon Estruch has received research grants from Instituto  
18 de Salud Carlos III, Madrid, Spain. He has received honoraria for presentations from Fundacion  
19 Cerveza y Salud, Spain; Instituto Cervantes, Albuquerque, USA; Instituto Cervantes, Milan,  
20 Italy; Instituto Cervantes, Tokyo, Japan; Fundacion Bosch i Gimpera, Spain; Wine and Culinary  
21 International Forum; Pernaud Richart; Mexico; Fundacion Dieta Mediterranea, Barcelona, Spain.  
22 He has received support for travel or meetings or conference organization from ERAB, Belgium,  
23 Brewers of Europe, Belgium, and Sociedad Española de Nutrición (SEN). He has served on the

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4 1 Advisory Board of Cerveza y Salud, Spain. Jordi Salas-Salvadó reported receiving consulting  
5  
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7 2 fees from Eroski Foundation. He has also received grants and support for attending  
8  
9 3 meetings/travel from Nut and Dried Fruit Foundation. He is an honorary Member of the  
10  
11 4 International Advisory Board of the Project “Effect of cashew nut supplementation on glycemie  
12  
13 5 status and lipid profile in type 2 diabetes subjects”, Member of the Scientific Advisory  
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15 6 Committee of the European PEGASO project (Personalized Guidance Services for Optimizing  
16  
17 7 lifestyle management in teenagers through awareness, motivation and engagement) and Member  
18  
19 8 of the Scientific Committee of Danone Institute International. He received personal fees for  
20  
21 9 serving as a Member of the Institute Danone Advisory Board. Sangeetha Shyam has received  
22  
23 10 consulting fees from Abbott Sdn Bhd. Stephanie K. Nishi is a volunteer member of Plant-Based  
24  
25 11 Canada, a non-profit organization. Other authors (Jesús Francisco García-Gavilán, Indira Paz-  
26  
27 12 Graniel, José J Gaforio<sup>4</sup> Miguel Ángel Martínez-González, Dolores Corella, J. Alfredo Martínez,  
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29 13 Ángel M. Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda,  
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31 14 Francisco J Tinahones, José Lapetra, J. Luís Serra-Majem, Aurora Bueno-Cavanillas, Josep A.  
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33 15 Tur, Vicente Martín Sánchez, Xavier Pintó, Pilar Matía-Martín, Josep Vidal, María del Mar  
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35 16 Alcarria, Lidia Daimiel, Óscar García Regata, Rafael Perez Araluce, Eva M Asensio, Olga  
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37 17 Castañer, Antonio Garcia-Rios, Alejandro Oncina-Cánovas, Cristina Bouzas, M. Angeles  
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39 18 Zulet, Elena Rayó, Rosa Casas<sup>1,16,17</sup>, Sandra Martin-Pelaez, Lucas Tojal-Sierra, Bernal-López  
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41 19 MR, Silvia Carlos, Jose V.Sorlí, Albert Goday, Patricia J. Peña-Orihuela, Ana Pastor-  
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43 20 Morel, Sonia Eguaras, María Dolors Zomeño, Miguel Delgado-Rodríguez, Nancy Babio, and  
44  
45 21 Montserrat Fitó) declared no potential conflict of interest.  
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4 **1 TABLES**

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7 **2 TABLE 1: PREDIMED-PLUS PARTICIPANT BASELINE CHARACTERISTICS**

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10 **3 STRATIFIED BY INTERVENTION GROUP**

	Control Group (CG) (n=3,468)	Intervention Group (IG) (n=3,406)
Age (years)	65 (8)	65 (8)
Men, n (%)	1,781(51.4)	1,758(51.6)
Education level, n (%)		
Primary school or less	1,736(50.1)	1,626(47.7)
High school or equivalent	948(27.3)	1,038(30.5)
University	784(22.6)	742(21.8)
Marital status, n (%)		
Single or divorced or separated	444(12.8)	458(13.5)
Married	2,583(74.5)	2,498 (73.3)
Widowed	441(12.7)	450(13.2)
Lifestyle habits		
Smoking habit, n (%)		
Never smoker	1,508(43.5)	1,526(44.8)
Former smoker	1,563(45.1)	1,420(41.7)
Current smoker	397(11.5)	460 (13.5)
MedDiet score 17-item <sup>a</sup>	9(3)	8(3)
Total physical activity, METs. min./day	1958(2573)	1762(2442)
Alcohol consumption, g/d	3.8 (11.9)	3.1 (11.5)
Anthropometry and clinical data		
BMI, kg/m <sup>2</sup>	32.2(5.1)	32.2(5.1)
Waist circumference, cm	107 (13)	107 (13)
Obesity; BMI $\geq$ 30 kg/m <sup>2</sup> , n (%)	2,545(73.4)	2,501 (73.4)
Diabetes, n (%)	1,060 (30.6)	1,061 (31.2)
Hypercholesterolemia, n (%)	2,400(69.2)	2,413(70.9)
Hypertension, n (%)	2,890 (83.3)	2,868 (84.2)
Use of ACE inhibitors, n (%) <sup>b</sup>	1,315 (38.5)	1,206 (36.0)
Received at least 1 dose of vaccine, n(%) <sup>2</sup>	1,764 (50.9)	1,739(51.1)
COVID-19 Positive ascertainment	336 (9.7)	317(9.3)
Time in trial prior to COVID-19 (years) <sup>c</sup>	4.0 (3.6-4.8)	4.1 (3.6-4.8)
Total follow-up period at censoring (years)	5.8 (5.3- 6.6)	5.8 (5.3- 6.6)
Body weight change (kg)	-0.6 (6.2)	-2.9 (6.6)
Percentage body weight change	-0.7 (7.3)	-3.4 (7.5)

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1 **Abbreviations:** ACE, angiotensin-converting enzyme; BMI, body mass index; COVID-19,  
2 coronavirus disease 2019, IQR, interquartile range; MedDiet, Mediterranean diet; MET,  
3 metabolic equivalents.

4 Data are n (%) or median (IQR) for categorical and quantitative variables, respectively, unless  
5 specified

6 Notes:

7 <sup>a</sup> Possible MedDiet scores range between 0 and 17. Higher MedDiet scores represent higher  
8 adherence to Mediterranean diet.

9 <sup>b</sup> Data from measurement at the last visit prior to censoring.

10 <sup>c</sup> Time in trial prior to COVID-19 was calculated from baseline until 8th March 2020, when  
11 community transmission became widespread in Spain.

12 Age, sex, education, intervention group, recruitment centre, baseline PA, anthropometry,  
13 prevalence of diabetes, hypertension and hypercholesterolemia had no missing data for this  
14 analysis. Baseline smoking status: 28/6,874 (0.4% missing data); marital status: 27/6874 (0.4%)  
15 missing data. Missing data for these two variables were replaced with the mode of the variable  
16 for the cohort. Alcohol consumption at baseline: 36/6,784 (0.5%) missing data. Missing data was  
17 replaced with sex-specific cohort mean consumption (men= 17.47276; women= 4.599879  
18 g/day). Mediterranean diet adherence: 5/6,784 missing (<0.1%) missing data. Missing data was  
19 replaced with cohort mean.

**TABLE 2: PREDIMED-PLUS INTERVENTION AND RISK OF COVID-19  
INCIDENCE (HR & 95%CI)**

Overall main analysis	
Crude Model	0.95 (0.81, 1.11)
Model 1	0.94 (0.81, 1.11)
Model 2	0.96 (0.81, 1.12)
Minimal adjustment#	0.95 (0.81, 1.11)
Sensitivity analysis excluding participants deceased prior to the onset of pandemic	
Crude Model	0.95 (0.81, 1.11)
Model 1	0.94 (0.80, 1.11)
Model 2	0.95 (0.81, 1.12)
Minimal adjustment#	0.95 (0.81, 1.11)

Associations were not statistically significant

- The crude model has no adjustments
- Model 1 is adjusted for age (y), sex (male/female), education (primary or less/secondary/university), marital status (single or divorced/married/widow(er), and recruitment centre (location).
- Model 2 additionally adjusted for baseline smoking status (never/former/current), body mass index, Mediterranean diet adherence score (17-point scale), total physical activity (METs. min./day), alcohol intake (g/d as a quadratic term), and trial baseline diagnosis of chronic diseases (diabetes, hypertension
- #A minimal adjustment set was identified using a directed acyclic graph and included adjustment only for the recruitment centre (location).

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1 **SUPPLEMENTARY MATERIALS:**

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- 3 • Supplementary Figure S1: Directed acyclic graph to identify minimal adjustment sets  
4 required to identify the causal effect of the intervention on COVID-19 incidence
- 5 • Supplementary Figure S2. Kaplan–Meier Estimates of the Cumulative Incidence of End-  
6 Point Events in the Total Study Population
- 7 • Supplementary Figure S3: Plot showing the strata-wise effect of PREDIMED-PLUS  
8 intervention and the risk of COVID-19 incidence (HR & 95%CI)
- 9 • Appendix: CONSORT-Checklist