

Intensive Weight-Loss Lifestyle Intervention Using Mediterranean Diet and COVID-19 Risk in Older Adults: Secondary Analysis of PREDIMED-Plus Trial

S. Shyam^{1,2,3}, J.F. García-Gavilán^{1,2,3}, I. Paz-Graniel^{1,2,3}, J.J. Gaforio^{4,5}, M.Á. Martínez-González^{1,6,7}, D. Corella^{1,8}, J.A. Martínez^{9,10}, Á.M. Alonso-Gómez^{1,11}, J. Wärnberg^{1,12}, J. Vioque^{4,13}, D. Romaguera^{1,14}, J. López-Miranda^{1,15}, R. Estruch^{1,16,17}, F.J. Tinahones^{1,18}, J. Lapetra^{1,19}, J.L. Serra-Majem^{1,20}, A. Bueno-Cavanillas^{4,21}, J.A. Tur^{1,22}, V. Martín Sánchez^{4,23}, X. Pintó^{1,24}, P. Matía-Martín^{25,26}, J. Vidal^{27,28}, M. del Mar Alcarria²⁹, L. Daimiel^{1,30,31}, E. Ros^{1,32}, F. Fernandez-Aranda^{1,33,34}, S.K. Nishi^{1,2,3,35}, Ó. García-Regata¹¹, R. Perez Araluce⁶, E.M. Asensio^{1,8}, O. Castañer^{4,36}, A. Garcia-Rios^{1,15}, A. Oncina-Cánovas^{4,13}, C. Bouzas²², M.A. Zulet^{1,9}, E. Rayó¹⁴, R. Casas^{1,16,17}, S. Martín-Pelaez^{4,21}, L. Tojal-Sierra^{1,11}, M.R. Bernal-López^{1,37}, S. Carlos⁶, J.V. Sorlí^{1,8}, A. Goday^{1,36}, P.J. Peña-Orihuela^{1,15}, A. Pastor-Morel³⁸, S. Eguaras⁶, M.D. Zomeño^{1,36,39}, M. Delgado-Rodríguez^{1,10,40}, N. Babio^{1,2,3}, M. Fitó^{1,36,*}, J. Salas-Salvadó^{1,2,3,*}

1. CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain; 2. Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Grup Alimentació, Nutrició, Desenvolupament i Salut Mental, Unitat de Nutrició Humana, Reus, Spain; 3. Institut d'Investigació Sanitària Pere Virgili (ISPV), Reus, Spain; 4. CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; 5. Departamento de Ciencias de la Salud, Instituto Universitario de Investigación en Olivares y Aceites de Oliva, Universidad de Jaén, Jaén, Spain; 6. University of Navarra, Department of Preventive Medicine and Public Health, Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain; 7. Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; 8. Department of Preventive Medicine, University of Valencia, Valencia, Spain; 9. Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, IdiSNA, Pamplona, Spain; 10. Precision Nutrition and Cardiometabolic Health Program, IMDEA Alimentación, Madrid, Spain; and Medicine and Endocrinology, UVA, Valladolid, Spain; 11. Department of Internal Medicine Araba University Hospital; University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain; 12. EpiPHAAN research group, School of Health Sciences, University of Málaga - Instituto de Investigación Biomédica en Málaga (IBIMA), Málaga, Spain; 13. Instituto de Investigación Sanitaria y Biomédica de Alicante. Universidad Miguel Hernández (ISABIAL-UMH), Alicante, Spain; 14. Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain; 15. Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain; 16. Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; 17. Institut de Recerca en Nutrició i Seguretat Alimentària (INSA-UB). University of Barcelona, Barcelona, Spain; 18. Virgen de la Victoria Hospital, Department of Endocrinology, Instituto de Investigación Biomédica de Málaga (IBIMA). University of Málaga, Málaga, Spain; 19. Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain; 20. Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria & Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI), Canarian Health Service, Las Palmas de Gran Canaria, Spain; 21. Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain; 22. Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands, Palma de Mallorca, Spain; 23. Institute of Biomedicine (IBIOMED), University of León, León, Spain; 24. Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge-IDIBELL, Hospitalet de Llobregat - Barcelona, Spain; 25. Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain; 26. Medicine Department. Universidad Complutense, Madrid, Spain; 27. CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; 28. Department of Endocrinology, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; 29. Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz. Instituto de Investigaciones Biomédicas IISFJD. University Autónoma, Madrid, Spain; 30. Nutritional Control of the Epigenome Group. Precision Nutrition and Obesity Program. IMDEA Food. CEI UAM + CSIC, Madrid, Spain; 31. Departamento de Ciencias Farmacéuticas y de la Salud, Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities, Boadilla del Monte, Spain; 32. Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain; 33. Psychoneurobiology of Eating and Addictive Behaviors Group, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain; 34. Department of Clinical Psychology, University Hospital of Bellvitge and University of Barcelona, Barcelona, Spain; 35. Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit; Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Unity Health Toronto, ON, Canada; 36. Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain; 37. Internal Medicine Clinical Management Unit, Regional University Hospital of Malaga, Instituto de Investigación Biomédica de Málaga (IBIMA-Plataforma BIONAND), University of Malaga, Malaga, Spain; 38. Centro de Salud Cabo Huertas, Alicante, Spain; 39. Blanquerna-Ramon Llull University, Barcelona, Spain; 40. Division of Preventive Medicine, Faculty of Medicine, University of Jaén, Jaén, Spain; *Prof Jordi Salas-Salvadó and Prof Montserrat Fitó are joint senior-authors.

Corresponding Author: Prof Jordi Salas-Salvadó and Dr Sangeetha Shyam, Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Food, Nutrition, Development and Mental Health Group (ANUT-DSM), Human Nutrition Unit. C/Sant Llorenç 21, 43201, Reus, Spain. Email: jordi.salas@urv.cat and Sangeetha.shyam@urv.cat

Abstract

OBJECTIVES: We tested the effects of a weight-loss intervention encouraging energy-reduced MedDiet and physical activity (PA) in comparison to *ad libitum* MedDiet on COVID-19 incidence in older adults.

DESIGN: Secondary analysis of PREDIMED-Plus, a prospective, ongoing, multicentre randomized controlled trial.

SETTING: Community-dwelling, free-living participants in PREDIMED-Plus trial.

PARTICIPANTS: 6,874 Spanish older adults (55-75 years, 49% women) with overweight/obesity and metabolic syndrome.

INTERVENTION: Participants were randomised to Intervention (IG) or Control (CG) Group. IG received intensive behavioural intervention

for weight loss with an energy-reduced MedDiet intervention and PA promotion. CG was encouraged to consume *ad libitum* MedDiet without PA recommendations.

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

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

CONCLUSIONS: There was no evidence to show that an intensive weight-loss intervention encouraging energy-reduced MedDiet and PA significantly lowered COVID-19 risk in older adults with overweight/obesity and metabolic syndrome in comparison to *ad libitum* MedDiet. Recommendations to improve adherence to MedDiet provided with or without lifestyle modification suggestions for weight loss may have similar effects in protecting against COVID-19 risk in older adults with high cardiovascular risks.

Key words: COVID-19, SARS-CoV2, PREDIMED-Plus, Mediterranean diet, older adults.

Abbreviations: CG: Control Group; COVID-19: Coronavirus disease; IG: Intervention Group; MedDiet: Mediterranean diet; PA: Physical activity.

Introduction

The Coronavirus Disease 2019 (COVID-19) emerged as a pandemic with unprecedented global impact (1). Older age, excessive body weight, and elevated cardiometabolic risks have been associated with increased COVID-19 risk (2). The increased risk associated with these conditions has been ascribed to senescence and/or obesity-related inflammation that attenuates immune response (2). With climate change and globalisation, the emergence and transmission of novel diseases are expected to accelerate (3). Thus, there is an urgent need to understand how modifiable risks including excessive body weight can be targeted for future prevention.

Lifestyle habits are among the modifiable factors to improve immunocompetence. In individuals with overweight/obesity weight loss could improve immunocompetence (4). We have shown that clinically significant weight loss achieved 5-6 years before the onset of the pandemic was associated with reduced COVID-19 risk among older adults with overweight/obesity and metabolic syndrome enrolled in the PREDIMED-Plus cohort (5). Additionally, observational evidence has associated higher adherence to the Mediterranean diet (MedDiet) with a lower COVID-19 risk (6-8). Furthermore, adherence to physical activity (PA) recommendations in the 2 years preceding the pandemic was associated with a lower risk of COVID-19-related hospitalization and death (9). Hence, we hypothesized that in comparison to *ad libitum* MedDiet, an intensive lifestyle intervention for weight loss through improving adherence to an energy-reduced MedDiet pattern and PA recommendations would further reduce COVID-19 incidence in older adults with overweight/obesity. In the absence of existing randomized controlled trials (RCTs), we tested this hypothesis in PREDIMED-Plus participants.

Methods

Setting

The PREDIMED-Plus is an ongoing, multicentre, open-labelled RCT in 6,874 community-dwelling Spanish women

and men, aged 55-75 years at enrolment, with overweight/obesity and metabolic syndrome, but without cardiovascular disease (CVD) (10). The trial aims to assess the effectiveness of an intensive lifestyle intervention using an energy-reduced MedDiet pattern and PA promotion on the primary prevention of CVD in comparison to usual care (*ad libitum* MedDiet) in older adults with high cardiometabolic risks in the Mediterranean region.

Randomization and blinding

The PREDIMED-Plus was approved by institutional review board approvals of the participating centres. The study is registered at the International Standard RCT Registry (ISRCT; <http://www.isrctn.com/ISRCTN89898870>) and the protocol has been published previously (10).

In brief, after screening and ensuring eligibility, 6,874 PREDIMED-Plus participants were randomly allocated using a centrally-controlled, computer-generated random-number system on a 1:1 ratio to either an intervention (IG) or control (CG) group, stratified by sex, age (<65, 65-70, >70) and centre (10). Couples were randomized together as a cluster.

Owing to the nature of the intervention, blinding and masking was not possible. The dietitians at each participating centre were aware of the participant assignment. However, the medical doctors who reviewed participants' medical records and the Clinical Event Ascertainment Committee remained blinded to the allocation and masking of the groups has been retained.

The trial randomization began in 2013, with all trial participants completing the 6-year intervention in 2023. The additional 2-year in-person annual follow-up is currently ongoing, and the trial is scheduled for completion in 2025.

Intervention

Both groups were recommended the MedDiet pattern as implemented in the PREDIMED trial (11). To improve adherence to the MedDiet, participants in both arms received free provision of extra virgin olive oil (1L/month) throughout the trial and were provided instructions about its use and conservation during their group educational sessions (10). CG participants were encouraged to follow a traditional MedDiet based on the PREDIMED study (11) without caloric restrictions or PA recommendations. IG participants were prescribed a traditional MedDiet similar to that of the PREDIMED study, but in contrast to CG whose total energy was *ad libitum*, they were encouraged to reduce their energy intake (eMedDiet). Additionally, IG participants received PA counselling to gradually increase their levels of PA to eventually reach at least 150 min/week of moderate-to-vigorous PA (MVPA) in accordance with the World Health Organization recommendations for adults aged 65 and above. Towards this goal, IG participants were encouraged to walk for a minimum of 45 min/day for 6 days/week, perform static exercises for strength, flexibility and balance at least 3 days/week, and undertake resistance training for 2 days/week for a duration of 30-40min/day. Additionally, participants received behavioural and motivational support strategies including self-monitoring,

Table 1. PREDIMED-Plus participants' baseline characteristics 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 ^a	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 ²	32.2(5.1)	32.2 (5.1)
Waist circumference, cm	107 (13)	107 (13)
Obesity; BMI≥30 kg/m ² , 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 (%) ^b	1,315 (38.5)	1,206 (36.0)
Received at least 1 dose of COVID-19 vaccine, n(%) ²	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) ^c	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)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; COVID-19, coronavirus disease 2019, IQR, interquartile range; MedDiet, Mediterranean diet; MET, metabolic equivalents. Data are n (%) or median (IQR) for categorical and quantitative variables, respectively, unless specified; Notes: a. Possible MedDiet scores range between 0 and 17. Higher MedDiet scores represent higher adherence to Mediterranean diet. b. Data from measurement at the last visit prior to censoring. c. Time in trial prior to COVID-19 was calculated from baseline until 8th March 2020, when community transmission became widespread in Spain. Age, sex, education, intervention group, recruitment centre, baseline PA, anthropometry, prevalence of diabetes, hypertension and hypercholesterolemia had no missing data for this analysis. Baseline smoking status: 28/6,874 (0.4% missing data); marital status: 27/6874 (0.4%) missing data. Missing data for these two variables were replaced with the mode of the variable for the cohort. Alcohol consumption at baseline: 36/6,784 (0.5%) missing data. Missing data was replaced with sex-specific cohort mean consumption (men= 17.47276; women= 4.599879 g/day). Mediterranean diet adherence: 5/6,784 missing (<0.1%) missing data. Missing data was replaced with cohort mean.

goal setting and problem-solving. Participants also underwent individual motivational interviews to facilitate sustainable incorporation of suitable dietary and lifestyle changes to meet individual goals, clinical conditions, preferences and beliefs (10).

Outcome: COVID-19 incidence

COVID-19 event was adjudicated by the independent Trial Clinical Event Ascertainment Committee, based on participant medical records reviewed annually by the participating physicians. According to the study protocol, COVID-19 event (SARS-CoV-2 infection) in the PREDIMED-Plus is 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 confirmed (incident/not-incident) from the emergence of the pandemic until December 31, 2021, were used in this analysis. In this analysis, both confirmed (n=652) and probable (n=1) COVID-19 diagnoses were pooled together as COVID-19 incident cases (n= 653). Others were treated as having COVID-19 non-incident status (n=6,221). Thus COVID-19 status was defined as a dichotomous variable (incident/not-incident).

Covariates

The cohort has baseline data on socio-demography (age, sex, education level, marital status), lifestyle (dietary and physical activity), and clinical status (body mass index (BMI), prevalence of type 2 diabetes, hypercholesterolemia, hypertension) that could confound the relationship between the intervention and COVID-19. The cohort has also documented from the medical records of participants the use of angiotensin-converting enzyme (ACE) inhibitors and whether at least one dose of a COVID-19 vaccine was administered before censoring, enabling additional adjustments for these potential confounders.

Statistical Analysis

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

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

Sensitivity analyses were carried out after excluding participants (n=108) who had deceased before COVID-19 emergence (November 30, 2019) and using a minimal adjustment set identified with a directed acyclic graph (Supplementary Figure S1). We also tested for the interaction of several factors (age, sex, smoking status, prevalence of obesity, diabetes, hypertension and having received at least one dose of COVID-19 vaccine) with the treatment group to evaluate potential moderation effects. For the present study, we used the PREDIMED-Plus database updated until December 2021.

Results

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

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). See Supplementary Figure S1

Discussion

We found in Spanish older adults with overweight/obesity and metabolic syndrome, the effect on COVID-19 risk of an intensive lifestyle intervention encouraging energy-reduced MedDiet and PA for weight loss was not significantly different from that of *ad libitum* MedDiet. It is interesting to juxtapose

these results with previous observational findings in middle-aged adults that showed the benefit of MedDiet (6-8) and our observation that weight loss $\geq 5\%$ significantly reduced COVID-19 risk in this cohort of older adults with overweight/obesity (5).

One potential explanation for our results is that the CG participants in our trial also consumed MedDiet albeit without instruction to restrict energy intake/increase PA. At the Pre-COVID-19 visit, both CG and IG participants in PREDIMED-Plus lost weight (Table 1: (median (IQR) CG: -0.6(6.2) vs IG: -2.9 (6.6) kg) with a between-group difference in weight loss of $< 5\%$. This difference in weight loss between groups while statistically significant, may not be clinically relevant to reduce COVID-19 risk. It is possible that CG participants also lost body weight as a result of improving their eating habits, i.e. through increased adherence to a MedDiet (12). The beneficial effects of MedDiet emphasising specific food groups such as nuts and olive oil on body weight could have attenuated the treatment effect (12). Additionally, improving PA to potentiate negative energy balance for weight loss may be more feasible earlier in life. Moreover, the health benefits of MedDiet have been ascribed to mechanisms beyond weight loss, and primarily to the overall composition of the diet (13), which may explain the lack of significant difference between IG and CG whose interventions were based on MedDiet.

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

We also acknowledge potential limitations. First, asymptomatic infections could have been missed. Since the trial is underway, endpoints on chronic diseases such as diabetes or cancer are not available. This could have added to several other residual confounders relating to susceptibility to infection including the adoption of hygiene and sanitary precautions. COVID-19 is an unexpected event that could not be accounted for in the original statistical analysis plan of the study, and the trial may have been underpowered to identify the small reduction in risks, given the current $< 10\%$ incidence of COVID-19 in the cohort, which, however, was similar to the national incidence rate during the period (14). It should also be noted that this is a secondary analysis relating to COVID-19 risk, an unplanned outcome as ascertained with data censored on 31st, Dec 2021. These results cannot be generalised to other cardiometabolic risks and endpoints. Finally, caution is required when generalising results from an RCT to the general population.

Conclusion

There was no evidence to show that in comparison to an *ad libitum* MedDiet, an intensive lifestyle intervention encouraging energy-reduced MedDiet and PA to promote weight loss had a significantly greater reduction in COVID-19 risk among Spanish older adults with overweight/obesity and metabolic syndrome. These findings require cautious interpretation considering the limitations of this analysis, and our previous results which showed that clinically significant weight loss in this cohort was associated with lower COVID-19 risk. We recommend future evaluations on the effectiveness of weight loss interventions on infection severity, recurrence or hospitalisation in older adults, as these outcomes may be more nutrition-sensitive. Similar evaluations of lifestyle interventions for weight loss are required in younger populations in whom increasing PA may be more feasible.

Trial registration details: Registry name: International Standard Randomized Controlled Trial (ISRCT; <http://www.isrctn.com/ISRCTN89898870>). Registration Number: ISRCTN89898870. Date of registration: 24/07/2014

Conflict of interest statement: Fernandez-Aranda acknowledges consulting fees from Novo Nordisk and Wiley as EIC for the European Eat Dis Rev. He has also received honoraria for lectures and support for travel/meetings from Novo Nordisk. He discloses his honorary participation in the Data Safety Monitoring Board or Advisory Board of Sustain-Consortium-Germany. Emilio Ros has received honoraria for presentations and support for attending meetings/travel from the California Walnut Commission, Alexion and the Spanish Atherosclerosis Society. He has also received consulting fees from Alexion. He participates in the Data Safety Monitoring Board or Advisory Board of the PREDIMED-Plus Clinical Trial. Ramon Estruch has received research grants from Instituto de Salud Carlos III, Madrid, Spain. He has received honoraria for presentations from Fundacion Cerveza y Salud, Spain; Instituto Cervantes, Albuquerque, USA; Instituto Cervantes, Milan, Italy; Instituto Cervantes, Tokyo, Japan; Fundacion Bosch i Gimpera, Spain; Wine and Culinary International Forum; Pernaud Richart; Mexico; Fundacion Dieta Mediterranea, Barcelona, Spain. He has received support for travel or meetings or conference organization from ERAB, Belgium, Brewers of Europe, Belgium, and Sociedad Española de Nutrición (SEN). He has served on the Advisory Board of Cerveza y Salud, Spain. Jordi Salas-Salvadó reported receiving consulting fees from Eroski Foundation. He has also received grants and support for attending meetings/travel from Nut and Dried Fruit Foundation. He is an honorary Member of the International Advisory Board of the Project "Effect of cashew nut supplementation on glycemic status and lipid profile in type 2 diabetes subjects", Member of the Scientific Advisory Committee of the European PEGASO project (Personalized Guidance Services for Optimizing lifestyle management in teenagers through awareness, motivation and engagement) and Member of the Scientific Committee of Danone Institute International. He received personal fees for serving as a Member of the Institute Danone Advisory Board. Sangeetha Shyam has received consulting fees from Abbott Sdn Bhd. Stephanie K. Nishi is a volunteer member of Plant-Based Canada, a non-profit organization. Other authors (Jesús Francisco García-Gavilán, Indira Paz-Graniel, José J Gaforio4 Miguel Ángel Martínez-González, Dolores Corella, J. Alfredo Martínez, Ángel M. Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Francisco J Tinahones, José Lapetra, J. Luís Serra-Majem, Aurora Bueno-Cavanillas, Josep A. Tur, Vicente Martín Sánchez, Xavier Pintó, Pilar Matía-Martín, Josep Vidal, María del Mar Alcarria, Lidia Daimiel, Óscar García Regata, Rafael Perez Araluce, Eva M Asensio, Olga Castañer, Antonio Garcia-Rios, Alejandro Oncina-Cánovas, Cristina Bouzas, M. Angeles Zulet, Elena Rayó, Rosa Casas1,16,17, Sandra Martin-Pelaez, Lucas Tojal-Sierra, Bernal-López MR, Silvia Carlos, Jose V.Sorlí, Albert Goday, Patricia J. Peña-Orihuela, Ana Pastor-Morel, Sonia Eguaras, María Dolors Zomeño, Miguel Delgado-Rodríguez, Nancy Babio, and Montserrat Fitó) declared no potential conflict of interest.

Financial disclosure: This work was supported by a project grant from the Fundación Francisco Soria Melguizo. The project also received support from the Community of Madrid and the European Union, through the European Regional Development Fund (ERDF)-REACT-EU resources of the Madrid Operational Program 2014–2020, in the action line of R+D+i projects in response to COVID-19, FACINGLCOVID -CM. The PREDIMED-Plus trial was supported by the official Spanish Institutions for funding scientific biomedical research, CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Instituto de Salud Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (six coordinated FIS projects led by JS-S and JVi, including the following projects: PI13/00673, PI13/00492, PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090, PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919, PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662, PI16/01873, PI16/01094, PI16/00501,

PI16/00533, PI16/00381, PI16/00366, PI16/01522, PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827, PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957, PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781, PI19/01560, PI19/01332, PI20/01802, PI20/00138, PI20/01532, PI20/00456, PI20/00339, PI20/00557, PI20/00886, PI20/01158, PI21/01617, PI21/01214, PI21/00767, PI21/00465); the Especial Action Project entitled: Implementación y evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus grant to JS-S; the European Research Council (Advanced Research Grant 2014–2019; agreement #340918) granted to MAM-G.; the Recercaixa (number 2013ACUP00194) grant to JS-S; grants from the Consejería de Salud de la Junta de Andalucía (PI0458/2013, PS0358/2016, PI0137/2018); the PROMETEO/2017/017, PROMETEO 21/2021 grants from the Generalitat Valenciana; the SEMERGEN grant. This research was also partially funded by EU-H2020 Grants (Eat2beNICE/ H2020-SFS-2016-2; and the Horizon 2020 PRIME study (Prevention and Remediation of Insulin Multimorbidity in Europe; grant agreement #847879). S.G.S is a recipient of the María Zambrano Fellowship with funding support from the Ministry of Universities and the Recovery, Transformation and Resilience Plan, Spain. The Fellowship is “Funded by the European Union – NextGenerationEU”. S.K.N. is supported by a postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR, MFE-171207). JS-S was partially supported by ICREA under the ICREA Academia program. We thank CERCA Programme/ Generalitat de Catalunya for institutional support. The Institut de Recerca en Nutrició i Seguretat Alimentària (INSA-UB). The University of Barcelona, Barcelona, Spain, is recognized as a Maria de Maeztu Unit of Excellence grant CEX2021-001234-M) funded by MICIN/AEI/FEDER, UE. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions: Conceptualization; Jordi Salas-Salvadó, Montserrat Fitó, Miguel Ángel Martínez-González, Dolores Corella, J. Alfredo Martínez, Ángel M. Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J Tinahones, José Lapetra, J. Luís Serra-Majem, Aurora Bueno-Cavanillas, Josep A. Tur, Vicente Martín Sánchez, Xavier Pintó, Pilar Matía-Martín, Josep Vidal, Clotilde Vázquez, Lidia Daimiel, Emili Ros, Fernando Fernandez-Aranda, Miguel Delgado-Rodríguez, Nancy Babio, Sangeetha Shyam, Stephanie K Nishi. Data curation; Investigation; Jordi Salas-Salvadó, Montserrat Fitó, Miguel Ángel Martínez-González, Dolores Corella, J. Alfredo Martínez, Ángel M. Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J Tinahones, José Lapetra, J. Luís Serra-Majem, Aurora Bueno-Cavanillas, Josep A. Tur, Vicente Martín Sánchez, Xavier Pintó, Pilar Matía-Martín, Josep Vidal, Clotilde Vázquez, Lidia Daimiel, Emili Ros, Fernando Fernandez-Aranda, Miguel Delgado-Rodríguez, María del Mar Alcarria, Eva M Asensio, Cristina Bouzas, M. Angeles Zulet, Elena Rayó, Rosa Casas, Sandra Martín-Pelaez, Lucas Tojal-Sierra, Bernal-López MR, Silvia Carlos, Albert Goday, Patricia J. Peña-Orihuela, Sonia Eguaras, María Dolores Zomeño, Jesús Francisco García-Gavilán, Indira Paz-Graniel, Stephanie K Nishi, Nancy Babio, Sangeetha Shyam. Formal Analysis & Methodology; Sangeetha Shyam, Nancy Babio, Jordi Salas-Salvadó. Funding acquisition; Jordi Salas-Salvadó, Montse Fitó, Miguel Ángel Martínez-González, Dolores Corella, J. Alfredo Martínez, Ángel M. Alonso-Gómez, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J Tinahones, José Lapetra, J. Luís Serra-Majem, Aurora Bueno-Cavanillas, Josep A. Tur, Vicente Martín Sánchez, Xavier Pintó, Pilar Matía-Martín, Josep Vidal, Lidia Daimiel, Emili Ros, Fernando Fernandez-Aranda, and Miguel Delgado-Rodríguez. Project Administration; Resources; Software; Supervision; Jordi Salas-Salvadó & Montserrat Fitó. Writing - original draft; Sangeetha Shyam, Jordi Salas-Salvadó. Writing - review & editing: All authors.

Ethics approval and consent to participate: The studies involving human participants were reviewed and approved by the study was conducted according to the guidelines of the Declaration of Helsinki. The study was approved by the Institutional Review Boards of all participating centres as follows: (Facultad de Medicina de Málaga:CEI Provincial de Málaga-Servicio Andaluz de Salud :O01_feb_PR2 - Predimedplus nodo 1, Centro Salud San Pablo de Sevilla:CEI de los Hospitales Universitarios Virgen Macarena y Virgen del Rocío-Servicio Andaluz de Salud:PI13/00673, Nutrición y Farmacia, Univ. De Navarra:CEIC Universidad de Navarra:053/2013,Hospital Son Espases de Mallorca:CEI de las Illes Balears - Conselleria de Salut Direcció General de Salut Pública i Consum:IB 2242/14 PI, Hospital Clínic de Barcelona:CEIC del Hospital Clínic de Barcelona:HCB/2016/0287,IMIM, Barcelona:CEIC Parc de Salut Mar y IDIAP Jordi Gol:PI13/120,Universitat Rovira i Virgili:CEIC del Hospital Universitari Sant Joan de Reus y IDIAB Jordi Gol:13-07-25/7proj2,Universida de Granada:CEI de la Provincia de Granada- Servicio Andaluz de Salud:MAB/BGP/pg,Fundación Jiménez Díaz:CEIC de la Fundación Jiménez Díaz:EC 26-14/IIS-FJD.Facultad de Mecina, Univ. De Navarra:CEIC Universidad de Navarra:053/2013,Hospital Txagorritxu, Vitoria:CEIC Euskadi:PI2014044,Facultad de Mecina de Valencia:CEIC Corporativo de Atención Primaria de la Comunitat Valenciana :2011-005398-22,Universidad de las Palmas de Gran Canaria:CEI Humana de la Universidad de las Palmas de Gran Canaria:CEIH-2013-07,Hospital Universitari de Bellvitge:CEIC del Hospital de Bellvitge:PR240/13,Universida de Córdoba:CEI de Cordoba-Junta de Salud:3078,IMDEA, Madrid:CEI de la Fundación IMDEA Alimentación:PI-012, Hospital Clínico de Madrid:CEIC Hospital Clínico San

Carlos de Madrid-Piloto-CEIC Servicio Madrileño de salud-General :30/15,Hospital de Málaga:CEI Provincial de Málaga-Servicio Andaluz de Salud .,Universitat de les Illes Balears:CEI de las Illes Balears - Conselleria de Salut Direcció General de Salut Pública i Consum:IB 2251/14 PI,Endocrinología, Hospital Clínic de Barcelona:CEIC del Hospital Clínic de Barcelona:HCB/2017/0351,Universidad Miguel Hernandez de Alicante:CEIC del Hospital General Universitario de Alicante:CEIC PI2017/02, Universidad de Jaén:CEIC de la Investigación Biomédica de Andalucía (CCEIBA),Universidad de León:CEI de la Universidad de León:ÉTICA-ULE-014-2015). The patients/participants provided their written informed consent to participate in this study.

References

- Guo P, Benito Ballesteros A, Yeung SP, Liu R, Saha A, Curtis L, Kaser M, Haggard MP, Cheke LG. COVCOG 1: Factors Predicting Physical, Neurological and Cognitive Symptoms in Long COVID in a Community Sample. A First Publication from the COVID and Cognition Study. *Front Aging Neurosci* 2022;14:804922–804922. DOI: 10.3389/fnagi.2022.804922
- Alberca RW, Oliveira L de M, Branco ACCC, Pereira NZ, Sato MN. Obesity as a risk factor for COVID-19: an overview. *Crit Rev Food Sci Nutr* 2012;61:2262–2276. DOI: 10.1080/10408398.2020.1775546
- Holmes EC. COVID-19—lessons for zoonotic disease. *Science* 2022;375:1114–1115. DOI: 10.1126/science.abn2222
- Lorenzo PM, Sajoux I, Izquierdo AG, Gomez-Arbelaiz D, Zulet MA, Abete I, Castro AI, Baltar J, Portillo MP, Tinahones FJ, Martinez JA, Casanueva FF, Crujeiras AB. Immunomodulatory effect of a very-low-calorie ketogenic diet compared with bariatric surgery and a low-calorie diet in patients with excessive body weight. *Clin Nutr* 2022;41:1566–1577. DOI: 10.1016/j.clnu.2022.05.007
- Shyam S, García Gavilán J, Paz-Graniel I, J. Gaforio J, Martínez-González MÁ, Corella D, Babio N, Salas-Salvado J. Association of adiposity and its changes over time with COVID-19 risk in older adults with overweight/obesity and metabolic syndrome: A longitudinal evaluation in the PREDIMED-Plus Cohort. *BMC Med* 2023;21. DOI: 10.1186/s12916-023-03079-z
- Perez-Araluce R, Martínez-González MA, Fernández-Lázaro CI, Bes-Rastrollo M, Gea A, Carlos S. Mediterranean diet and the risk of COVID-19 in the ‘Seguimiento Universidad de Navarra’ cohort. *Clin Nutr* 2022;41:3061–3068. DOI:10.1016/j.clnu.2021.04.001
- Perez-Araluce R, Martínez-González MÁ, Gea A, Carlos S. Components of the Mediterranean Diet and Risk of COVID-19. *Front Nutr* 2022;8:805533. DOI: 10.3389/fnut.2021.805533
- Sharma S, Di Castelnuovo A, Costanzo S, Persichillo M, Panzera T, Ruggiero E, De Curtis A, Storto M, Cavallo P, Gianfagna F, Donati MB, de Gaetano G, Cerletti C, Iacoviello L, Bonaccio M. Habitual adherence to a traditional Mediterranean diet and risk of SARS-CoV-2 infection and Coronavirus disease 2019 (COVID-19): a longitudinal analysis. *Int J Food Sci Nutr* 2023;74:382–394. DOI: 10.1080/09637486.2023.2212879
- Sallis R, Young DR, Tartof SY, Sallis JF, Sall J, Li Q, Smith GN, Cohen DA. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients. *Br J Sports Med* 2021;55:1099–1105. DOI: 10.1136/bjsports-2021-104080
- Martínez-González MA, Buil-Cosiales P, Corella D, et al. Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial. *Int J Epidemiol* 2019;48:387–388. DOI: 10.1093/ije/dyy225
- Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018;378:e34. DOI: 10.1056/NEJMoa1800389
- Estruch R, Martínez-González MA, Corella D, et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7:e6–e17. DOI: 10.1016/S2213-8587(19)30074-9
- Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E. Benefits of the Mediterranean Diet: Insights From the PREDIMED Study. *Prog Cardiovasc Dis* 2015;58:50–60. DOI: 10.1016/j.pcad.2015.04.003
- Pinedo E. One in 10 Spaniards have had coronavirus, antibody study shows. *Reuters*. Available at: <https://www.reuters.com/article/health-coronavirus-spain-study-idUSKBN28P23M>. Accessed May 2020;2, 2023.

© *Serdí and Springer-Verlag International SAS, part of Springer Nature, 2023*

How to cite this article: S. Shyam, J.F. García-Gavilán, I. Paz-Graniel, et al. Intensive Weight-Loss Lifestyle Intervention Using Mediterranean Diet and COVID-19 Risk in Older Adults: Secondary Analysis of PREDIMED-Plus Trial. *J Nutr Health Aging* 2023;27(12):1162–1167; <https://doi.org/10.1007/s12603-023-2044-4>