

Original Article

Combined versus Individual Effects of Dietary Energy Reduction and Physical Activity on Body Composition in Older Adults with Metabolic Syndrome

Jadwiga Konieczna^{1,2,*}, Victor de la O^{3,4,5}, Miguel Ruiz-Canela^{2,3}, Jordi Salas-Salvadó^{2,6,7}, Vicente Martín-Sánchez^{8,9}, Ramón Estruch^{2,10,11}, Josep Vidal^{12,13,14}, F. Javier Basterra-Gortari^{3,15}, Jesús F. García-Gavilán^{2,6,7}, Joan Pou Bordoý^{1,16}, Diego Martínez-Urbistondo^{2,17}, José Antonio de Paz⁹, Rosa Casas^{2,10,11}, Romina Paula Olbeyra¹³, Héctor Vázquez-Lorente^{2,6,7}, Itziar Abete^{2,18,19}, Javier Díez Espino^{2,3,20}, Miguel Fiol^{1,2}, Albert Goday^{2,21}, Dora Romaguera^{1,2}, J. Alfredo Martínez^{2,4,18,22}

¹Research Group on Nutritional Epidemiology & Cardiovascular Physiopathology (NUTRECOR), Health Research Institute of the Balearic Islands, University Hospital Son Espases, Palma de Mallorca; ²Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN) (Spanish Biomedical Research Center in Physiopathology of Obesity and Nutrition), Institute of Health Carlos III, Madrid; ³Department of Preventive Medicine and Public Health, Navarra Institute for Health Research (IdiSNA), University of Navarra, Pamplona; ⁴Precision Nutrition and Cardiometabolic Health Program, IMDEA Food, CEI UAM+CSIC, Madrid; ⁵Faculty of Health Sciences, International University of La Rioja (UNIR), Logroño; ⁶Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Alimentació, Nutrició Desenvolupament i Salut Mental (ANUTDSM) (Rovira i Virgili University, Department of Biochemistry and Biotechnology, Food, Nutrition, Development and Mental Health), Reus; ⁷Institut d'Investigació Pere Virgili (Pere Virgili Health Research Institute), Reus; ⁸CIBER de Epidemiologia y Salud Pública (CIBERESP) (CIBER of Epidemiology and Public Health), Institute of Health Carlos III, Madrid; ⁹Institute of Biomedicine, University of León, León; ¹⁰Department of Internal Medicine, IDIBAPS, Hospital Clinic, University of Barcelona, Barcelona; ¹¹University of Barcelona Nutrition and Food Safety Research Institute (INSA-UB), Barcelona; ¹²CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM) (CIBER of Diabetes and Associated Metabolic Diseases), Institute of Health Carlos III, Madrid; ¹³Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) (August Pi i Sunyer Biomedical Research Institute), Barcelona; ¹⁴Endocrinology and Nutrition Department, Obesity Unit, Hospital Clinic, Barcelona; ¹⁵Department of Endocrinology and Nutrition, University Hospital of Navarra, Navarra Institute for Health Research (IdiSNA), Public University of Navarra (UPNA), Pamplona; ¹⁶Primary Care Mallorca, Camp Redó Health Centre, Palma de Mallorca; ¹⁷Vascular Medicine Area, Clínica Universidad de Navarra en Madrid (Clinical University of Navarra in Madrid), Madrid; ¹⁸Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, Pamplona; ¹⁹University of Navarra, Nutrition and Health Institute (INS), Pamplona; ²⁰Primary Care Team of Tafalla. Primary Care Management. Navarra Health Service-Osasunbidea, Pamplona; ²¹Unit of Cardiovascular Risk and Nutrition, Hospital del Mar Research Institute (IMIM), Barcelona; ²²Institute of Endocrinology and Nutrition, University of Valladolid, Valladolid, Spain

Background: This study prospectively assessed the combined versus individual effects of reducing energy intake (EI) and increasing physical activity (PA) on body weight and composition in older adults with overweight/obesity and metabolic syndrome. The interaction between both exposures was likewise assessed.

Methods: A subsample of 1,110 participants (aged 55–75 years) from the Prevención con Dieta Mediterránea-Plus (PREDIMED-Plus) trial was followed for 1 year. The combined effects of 1-year changes in EI and PA on reduction of $\geq 5\%$ in baseline body weight and total fat, and on $\geq 5\%$ increments in lean mass were examined using dual-energy X-ray absorptiometry. Multivariate logistic regression models were used to assess the combined association. Multiplicative and additive interactions were tested.

Results: Participants who had reduced EI and increased PA over 1 year were significantly more likely to exhibit $\geq 5\%$ reduction in body weight (odds ratio [OR], 3.24; 95% confidence interval [CI], 1.83 to 5.72) and fat mass (OR, 2.13; 95% CI, 1.23 to 3.69) and $\geq 5\%$ increase in lean mass (OR, 2.46; 95% CI, 1.24 to 4.87) compared to those who had increased EI and reduced PA. A potential for biological, rather than statistical, interaction between PA and EI was found, with synergy index (> 1): 1.08 (95% CI, 0.58 to 1.99) for beneficial changes in body weight, 1.88 (95% CI, 0.41 to 8.65) for fat mass, and 1.44 (95% CI, 0.43 to 4.88) for lean mass.

Conclusion: Encouraging an increase in PA with complementary nutritional education to reduce dietary EI may be more effective in managing body composition in older adults with overweight/obesity and metabolic syndrome than focusing on lifestyle behaviors alone.

Key words: Energy intake, Physical activity, Interaction, Additive interaction, Body composition, Dual-energy X-ray absorptiometry

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*Corresponding author

Jadwiga Konieczna



<https://orcid.org/0000-0002-2947-1338>

Research Group on Nutritional Epidemiology & Cardiovascular Physiopathology (NUTRECOR), Health Research Institute of the Balearic Islands, University Hospital Son Espases, Bldg G, level -1. Ctra. Valldemossa 79, 07120, Palma de Mallorca, Spain
Tel: +34-871-20-5050
E-mail: jadwiga.konieczna@ssib.es

INTRODUCTION

Obesity can occur at any stage of a person's life. It negatively affects whole-body systems and is a tremendous public health challenge throughout the world.¹ This challenge is even more complicated in older adults, as the excessive adipose accumulation that occurs with advancing age is accompanied by the progressive loss of skeletal muscle mass, strength, and function.^{1,2} Hence, health-promotion strategies in older adults should transcend a mere weight-loss goal. Rather, they should specifically target fat mass reduction while maintaining muscle mass to avoid or mitigate health sequelae relating to obesity and sarcopenia.³

Evidence from randomized controlled trials (RCTs) conducted predominantly in young-to-middle-aged populations indicates that calorie restriction and regular exercise or physical activity (PA) may be more effective in combating excessive body weight and associated metabolic abnormalities when prescribed in combination rather than separately.^{4,5} Nonetheless, the nature of this interconnection, especially for body composition changes in elderly populations, remains unexplored.

Although limited in number, some cohort studies among young-to-middle-aged populations found an interactions of either carbohydrate intake or adherence to the Mediterranean Diet (MedDiet) (referred as a proxy for energy intake [EI]) with PA (as a proxy for energy expenditure) on glycemia,⁶ adiposity,⁷ or mortality.⁸ However, these studies, with some exceptions,⁸ did not provide data for a full assessment of the nature of such an interaction (additive or multiplicative), nor did they quantify the synergy between diet and PA. On the other hand, in older individuals, owing to uncertainties regarding the long-term benefits and risks of weight-reduction interventions, moderate calorie restriction combined with exercise and everyday PA has been considered only for older adults who present weight-related health problems in addition to obesity.⁹ A satisfactory understanding of the interaction among lifestyle factors may provide key insights into the nature of their combined effect, helping to establish recommendations for the management of overweight/obesity in older adults and to incorporate them in worldwide clinical practice guidelines.¹⁰

Prior interim analysis in the ongoing Prevención con Dieta Mediterránea-Plus (PREDIMED-Plus) primary cardiovascular preven-

tion RCT¹¹ showed promising results.^{12,13} A 3-year lifestyle intervention based on EI reduction and PA promotion in the context of the MedDiet was compared to the approach of following an *ad libitum* MedDiet only. The former approach was effective in decreasing relative fat and increasing lean mass in older adults with overweight/obesity and metabolic syndrome.¹³ Participants from both groups lost weight, and changes in body composition were more pronounced over the first year of the trial.¹³ Consequently, additional research is warranted to further elucidate the dynamic relationship between diet and PA—considering the energy balance equation—that leads to desired changes in body composition. Given that the PREDIMED-Plus intervention was multifaceted, it was not possible to separate the individual effects of both exposures and compare them with the combined effect while quantifying the possible interaction. Therefore, the goal of this observational study was to estimate the individual and combined effects of reduction in total EI and increase in PA on objectively measured body composition over one year, followed by a comprehensive interaction analysis on additive and multiplicative scales.

METHODS

Study design and population

This observational prospective study was conducted using data collected during the first year of follow-up in the ongoing PREDIMED-Plus study. PREDIMED-Plus is a multicenter, parallel-group nutrition lifestyle intervention trial that is investigating the long-term effects of a 6-year weight-loss multifactorial intervention on the primary prevention of cardiovascular events. Participants in the intervention group of this study received intensive individualized counseling to follow an energy-restricted MedDiet (erMedDiet), with an approximate 30% energy deficit (approximately 600 kcal/day), and to increase PA. In contrast, participants in the control group received the usual care and a non-intensive general recommendation to follow the MedDiet, without EI restriction, PA promotion, or a weight-loss goal. Eligible participants were men (age 55–75 years) and women (age 60–75 years) with overweight or obesity (body mass index ≥ 27 and < 40 kg/m²) and metabolic syndrome. The trial procedures are published elsewhere,^{11–13} and the study protocol is publicly available at www.PREDIMEDplus.

com. The PREDIMED-Plus protocol was approved by the research ethics committees of all recruiting centers: CEIC Universidad de Navarra (053/2013); CEI de las Illes Balears—Conselleria de Salut Direcció General de Salut Pública i Consum (IB 2242/14 PI); CEIC del Hospital Clínic de Barcelona (HCB/2016/0287); CEIC del Hospital Universitari Sant Joan de Reus y IDIAB Jordi Gol (13-07-25/7proj2); CEIC del Hospital Clínic de Barcelona (HCB/2017/0351); and CEI de la Universidad de León (ÉTICA-ULE-014-2015). All participants signed an informed consent form before entering the study. The trial was registered at the International Standard Randomized Controlled Trial (ISRCTN) with code 89898870.

Of the total cohort of PREDIMED-Plus participants ($n = 6,874$), this study consisted of a subsample of participants ($n = 1,556$) who underwent body composition scans with dual-energy X-ray absorptiometry (DXA) in seven out of the 23 recruiting centers that had device access. Participants who had missing values for the variables of interest at baseline and at 1 year were excluded. Outliers were also excluded. To account for EI misreporting, participants with total EI values outside the predefined limits of 500–3,500 kcal/day (women) and 800–4,000 kcal/day (men) were excluded.¹⁴ Finally, the sample of 1,110 participants (49.3% from the intervention group) was included in the analyses (Supplementary Fig. 1).

Exposure assessment

Dietary intake was assessed by trained dietitian–nutritionists using a validated 143-item semi-quantitative food-frequency questionnaire during face-to-face interviews conducted at baseline and at 1-year visits.^{15,16} The average intake of each food and beverage item was calculated by multiplying a typical portion size by the frequency of consumption, which ranged from 0 to > 6 times/day (nine possible responses). Spanish food composition tables¹⁷ were used to derive total EI (kcal/day), nutrients, and alcohol (in g/day).

At baseline and at 1 year, trained interviewers collected information on total leisure time PA using the Registre Gironi del Cor (REGICOR) Short Physical Activity validated questionnaire.¹⁸ The data were collected for frequency and duration of six types of activities performed during a typical month: walking at a slow/normal pace, brisk walking, working in the garden, walking in the countryside, climbing stairs, and exercising or playing sports at home,

outdoors, or in a gym. Each activity had a specific intensity value expressed as a metabolic equivalent of task (MET) value.¹⁹ Total PA was calculated as the summed product of the frequency, duration, and intensity of each activity, divided by 30 days per month (MET min/day).

Changes in EI (kcal/day) and PA (MET min/wk) were calculated as the difference between values measured at 1 year and at baseline. The 1-year changes in the exposures of interest were dichotomized using the cut-off zero, where zero indicated no change or an increase in EI and a decrease in PA, and one indicated a decrease in EI and an increase in PA. Both exposures were combined using a 2×2 contingency table.

Outcome assessment

At baseline and at 1 year, body weight (kg) was measured in duplicate by trained staff according to the study protocol using calibrated scales. At the same time points, body composition was directly quantified using third-generation DXA scanners from General Electric (DXA Lunar Prodigy Primo and Lunar iDXA; GE Healthcare) connected with enCore software. Subject positioning during DXA scanning and daily phantom calibration were performed by trained operators following manufacturer guidelines. Total fat and lean mass were expressed as the percentages of the DXA-derived total body mass (sum of total bone, fat, and muscle mass [g]). These variables were further dichotomized, indicating at least 5% improvements in baseline body weight and body components, i.e., clinically relevant changes over 1 year at follow-up. The threshold of 5% was chosen because it is commonly used in weight-loss strategies associated with beneficial cardiometabolic outcomes.²⁰ We previously used this approach as a proxy for clinically relevant changes in body composition.¹³ To this end, dummy variables were created, where zero indicated a lack of improvement in these parameters (i.e., < 5% reduction from baseline in the body weight and percentage of total fat mass, and < 5% increase in the percentage of total lean mass). A value of one indicated that the parameters were equal or improved from baseline (i.e., a 5% reduction from baseline in the body weight and percentage of total fat mass, and a 5% increase in the percentage of total lean mass).

Covariable assessment

A general questionnaire was administered at baseline to obtain participant information on age, sex, educational level, smoking habits, and type 2 diabetes mellitus status. Type 2 diabetes mellitus at baseline was defined as a previous diagnosis of diabetes, glycosylated hemoglobin $\geq 6.5\%$, use of anti-diabetic medication, or having fasting glucose > 126 mg/dL in both the screening and baseline visits.

Questionnaires previously validated in the Spanish population were used to determine total time spent in sedentary behavior (Nurses' Health Study Questionnaire²¹) and adherence to an erMedDiet (a 17-item screener²²). Data on average daily sleeping time were collected using non-validated open questions. Fatty liver index was calculated according to the formula proposed by Bedogni et al.²³

Statistical analysis

The data were descriptively analyzed to determine the distribution of participant characteristics, which were presented as mean \pm standard deviation (SDs) for continuous variables, or as numbers and percentages (%) for categorical variables, according to the categories of exposures of interest. The statistical difference between the categories of EI and PA was assessed using the independent samples t-test (Student's t-test) or chi-square test (χ^2) for continuous or categorical characteristics, respectively.

The main analyses were conducted using a logistic regression model to determine the individual and combined associations between 1-year changes in EI (increased/reduced [kcal/day]) and PA (reduced/increased [MET min/wk]) on reductions of 5% or more in baseline body weight (kg) and DXA-derived total fat (%), or increments of 5% or more in lean mass (%). Multivariable OR models were adjusted for the study randomization group (control or intervention), sex (men or women), age (years), recruiting center (categorical), as well as baseline variables: smoking habits (current, never, or ex-smoker), prevalence of type 2 diabetes mellitus (yes or no), adherence to an erMedDiet (0–17 points), alcohol intake (g/day), sedentarism, sleep (both in hr/day), number of metabolic syndrome components and fatty liver index (both continuous), total leisure time PA (MET min/wk), total EI (kcal/day), as well as body weight (kg) (for all models), percentage of fat mass (models for $\geq 5\%$ reduction in fat mass as an outcome), and per-

centage of lean mass (models for $\geq 5\%$ increment in lean mass as an outcome). The minimal sufficient adjustment set of covariables was identified in a directed acyclic graph (DAG)²⁴ drawn using DAGitty software (www.dagitty.net)²⁵ (Supplementary Fig. 2).

Interaction is a scenario in which the effect of one factor on a certain outcome varies across the strata of another factor.²⁶ Full assessment of the nature of such an interaction, which could be statistical or biological, requires adequate analysis. According to the methodology proposed by VanderWeele and Knol,²⁷ assessment of single and joint association of the exposures was followed by an interaction analysis on both multiplicative (according to the statistical interaction) and additive (according to the mechanistic or biological interaction) scales. Interaction on the multiplicative scale was conducted with a likelihood ratio test comparing logistic regression models with and without a product term resulting from multiplying EI and PA categories. Interaction on the additive scale was performed by calculating the relative excess risk due to the interaction (RERI). The RERI was calculated using odds ratios (ORs) as follows:²⁷

$$\text{RERI} = \text{OR}_{11} - \text{OR}_{10} - \text{OR}_{01} + 1$$

where ORs were used for attaining at least 5% improvement in baseline body weight and body component values for those who, at 1 year, presented reduced EI and increased PA (OR_{11}), those who presented reduced EI and reduced PA (OR_{10}), and those who showed increased EI and increased PA (OR_{01}). Subjects who did not improve their lifestyle factors were selected as the reference group. According to Knol et al.,²⁸ for correct RERI calculation, preventive factors should be recoded in such a way that the stratum with the lowest risk becomes the reference category. Our analyses were conducted to determine the odds of improvement, not the usual deterioration in health condition or disease. Thus, we recoded EI and PA as protective factors, selecting the reference group as those with the lowest exposition to both factors. We also calculated supplementary additive interaction statistics, such as the synergy index (SI) and the attributable proportion of the joint effect (AP), according to previous recommendations:²⁷

$$\text{SI} = (\text{OR}_{11} - 1) / [(\text{OR}_{10} - 1) + (\text{OR}_{01} - 1)]$$

$$\text{AP} = (\text{OR}_{11} - \text{OR}_{10} - \text{OR}_{01} + 1) / (\text{OR}_{11})$$

RERI > 0, AP > 0, and SI > 1 suggest a positive interaction on the additive scale, or synergism, indicating that the effect of the exposures together exceeds the sum of each of these factors considered separately.²⁷ It must be mentioned that RERI estimates are often statistically non-significant on account of their lack of statistical power; for more precise estimates, a significantly large sample size may be required.^{8,29} This limitation may be overcome, at least partly, by calculating other measures for additivity, such as the AP due to the interaction, and the SI, which does not solely rely on statistical significance and is apparently more stable than RERI.^{30,31}

For sensitivity analysis, the models were repeated after eliminating the participants ($n = 26$) who did not change either EI or PA over a 1-year follow-up. In additional analysis, the models were re-run for a continuous outcome using adjusted linear regression analysis. To visualize the interplay among lifestyle factors, predictive linear models were plotted to present how an annual increase in PA (MET hr/wk) varied by the strata of EI (increased/reduced) with respect to 1-year changes in body weight and composition (continuous variables). To this end, a product term between lifestyle factors was entered in linear regression models, which were controlled for the covariables from the main analysis.

Statistical analyses were performed using Stata version 17 software (StataCorp LLC) and the study dataset from February 23, 2022. Statistical significance was set at $P < 0.05$.

RESULTS

Regarding baseline characteristics (Table 1), the participants who reduced EI over 1 year (mean \pm SD, -447 ± 333 kcal/day) were younger, had higher EI, particularly from polyunsaturated fatty acids (but lower from protein), and consumed more fiber and alcohol compared to the participants who increased EI over 1 year (mean 318 ± 264 kcal/day) (all P -values < 0.05). They also showed worse health-related parameters, including higher diastolic blood pressure, lower high-density lipoprotein cholesterol levels, greater waist circumference, and higher triglyceride glucose and fatty liver indices (all P -values < 0.05). Participants who increased PA over 1 year ($1,668 \pm 1,435$ MET min/wk; 0.69 ± 0.65 hr/day) were less physically active at baseline compared to those who reduced PA over the year ($-1,333 \pm 1,366$ MET min/wk; -0.59 ± 0.66 hr/day)

($P < 0.001$).

Moreover, participants who either reduced EI or increased PA were predominantly from the intervention group (53.8% and 54.1%, respectively). They showed greater improvements in PA (Table 1), as well as in body weight and body composition, as reflected by their reduction in body weight and percentage of fat mass. They also showed an increase in lean mass percentage, compared to those in the opposite EI or PA categories (all P -values < 0.05) (Table 2).

The results detailing the individual and combined associations between 1-year changes in total EI and PA with improvements in body composition from baseline, are shown in Table 3. Overall, greater engagement in total leisure time PA led to more substantial improvements in body weight and composition than reduction in total EI at 1 year. In particular, a reduction in EI (kcal/day) at 1 year was associated with higher odds of achieving at least 5% reduction in body weight (kg) compared to participants who increased EI (OR, 1.70, 95% confidence interval [CI], 1.17 to 2.45). While ORs for improvements in body composition (percentage of fat and lean mass) also increased, they did not reach statistical significance.

Increased PA (MET min/wk) over 1 year was significantly associated with higher odds for achieving at least a 5% reduction in body weight and fat mass from baseline, as well as an increase in lean mass compared to participants who reduced PA (OR, 1.78 [95% CI, 1.25 to 2.53]; OR, 1.62 [95% CI, 1.13 to 2.33]; and OR, 1.74 [95% CI, 1.11 to 2.70], respectively). The odds of these beneficial changes were even greater when reductions in EI were combined with increased PA. As shown in Table 3 and illustrated in Fig. 1, the combined effects of reduced EI and increased PA over 1 year resulted in greater ORs for beneficial changes in body weight (OR, 3.24; 95% CI, 1.83 to 5.72) and body composition (fat mass: OR, 2.13 [95% CI, 1.23 to 3.69]; lean mass: OR, 2.46 [95% CI, 1.24 to 4.87]) than the combination of increased EI and reduced PA.

An interaction analysis suggested that the combined effect of reduced EI and increased PA on beneficial changes in body weight and composition likely involved an interaction beyond additivity, but not multiplicativity. There was no evidence for a multiplicative-scale interaction, as the result of the likelihood ratio test comparing logistic regression models with and without a multiplicative interaction term (EI \times PA) was not statistically significant ($P > 0.05$). However, analysis of an additive interaction suggested potential syner-

Table 1. Baseline characteristics of participants according to categories of changes in total energy intake and physical activity over 1 year (cut-off at zero)

Characteristic	Total participants	Reduced EI (kcal/day)	Increased EI (kcal/day)	<i>P</i>	Reduced PA (MET min/wk)	Increased PA (MET min/wk)	<i>P</i>
Number of participants	1,110	649	461		452	658	
Intervention study group	547 (49)	349 (54)	198 (43)	<0.001	191 (42)	356 (54)	<0.001
Men	599 (54)	364 (56)	235 (50)	0.092	239 (53)	360 (55)	0.547
Age (yr)	65.5±4.9	65.2±4.9	66.0±4.9	0.004	65.5±4.9	65.6±4.9	0.776
BMI (kg/m ²)	32.4±3.3	32.6±3.3	32.2±3.3	0.037	32.3±3.3	32.4±3.3	0.607
Waist circumference (cm)	107±9	108±9	106±9	0.023	107±10	107±9	0.212
Current/ex-smoker	628 (57)	371 (57)	257 (56)	0.639	257 (57)	371 (56)	0.875
Higher education/technician	233 (21)	144 (22)	89 (19)	0.245	87 (19)	146 (22)	0.237
EI (kcal/day)	2,393±523	2,611±481	2,085±416	<0.001	2,406±516	2,384±528	0.490
Change in EI over 1 year (kcal/day)	-129±486	-447±333	318±264	<0.001	-125±468	-132±498	0.801
Protein (% EI/day)	16.6±0.1	16.2±0.1	17.1±0.1	<0.001	16.6±0.1	16.5±0.1	0.816
Carbohydrate (% EI/day)	40.0±0.2	40.2±0.3	39.7±0.3	0.275	40.1±0.3	39.9±0.3	0.724
Fat (% EI/day)	40.3±0.2	40.4±0.2	40.0±0.3	0.274	40.1±0.3	40.3±0.2	0.550
SFA (% EI/day)	10.0±0.1	10.0±0.1	10.0±0.1	0.693	9.9±0.1	10.1±0.1	0.252
MUFA (% EI/day)	21.1±0.1	21.1±0.2	21.0±0.2	0.796	21.1±0.2	21.1±0.2	0.954
PUFA (% EI/day)	6.83±0.06	6.94±0.08	6.68±0.08	0.027	6.82±0.09	6.84±0.08	0.866
Fiber (g/day)	26.0±0.3	27.7±0.3	23.6±0.3	<0.001	26.3±0.4	25.8±0.3	0.311
Alcohol (g/day)	11.5±14.9	12.7±16.5	9.8±12.0	0.001	11.7±15.6	11.3±14.4	0.654
erMedDiet (0–17 points)	8.46±2.60	8.42±2.67	8.52±2.50	0.541	8.62±2.61	8.36±2.59	0.104
PA (MET min/wk)	2,815±2,206	2,767±2,124	2,881±2,314	0.396	3,787±2,433	2,146±1,747	<0.001
PA (hr/day)	1.29±0.98	1.28±0.95	1.31±1.02	0.618	1.71±1.09	1.00±0.77	<0.001
Change in PA over 1 year (MET min/wk)	446±2,038	591±1,958	241±2,131	0.005	-1,333±1,366	1,668±1,435	<0.001
Change in PA over 1 year (hr/day)	0.17±0.91	0.23±0.88	0.09±0.94	0.013	-0.59±0.66	0.69±0.65	<0.001
Sedentarism (hr/day)	5.84±1.82	5.82±1.81	5.87±1.83	0.708	5.75±1.83	5.90±1.81	0.177
Sleep (hr/day)	7.07±1.18	7.04±1.14	7.12±1.23	0.258	7.09±1.16	7.06±1.20	0.732
Type 2 diabetes mellitus	309 (28)	184 (28)	125 (27)	0.651	120 (27)	189 (29)	0.427
Number of MetS components	3.64±0.76	3.65±0.75	3.62±0.77	0.530	3.63±0.73	3.64±0.77	0.995
Systolic blood pressure (mmHg)	142±17	143±17	142±16	0.737	143±16	142±17	0.486
Diastolic blood pressure (mmHg)	81.2±10.1	82.0±10.2	79.9±9.7	0.001	81.3±10.0	81.1±10.1	0.730
Glucose (mg/dL)	113±28	114±28	112±27	0.224	114±29	112±27	0.377
Triglyceride (mg/dL)	147±74	151±79	143±67	0.091	150±82	146±68	0.286
HDL-C (mg/dL)	46.2±11.4	45.6±11.3	47.1±11.4	0.029	46.3±10.9	46.2±11.7	0.861
Cholesterol (mg/dL)	193±35	194±35	192±35	0.375	195±35	192±35	0.153
TyG	8.90±0.51	8.93±0.52	8.87±0.50	0.046	8.92±0.54	8.89±0.49	0.401
FLI	71.1±16.8	78.3±16.0	75.3±17.7	0.003	76.9±17.2	77.2±16.5	0.815

Values are presented as number (%) or mean ± standard deviation. *P*-values were calculated using independent Student's *t*-test or χ^2 test for continuous and categorical variables, respectively. Variables TyG, glucose, and cholesterol (1 missing); blood pressure (4 missing).

EI, energy intake; PA, physical activity; MET, metabolic equivalent of task; BMI, body mass index; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; erMedDiet, energy-restricted Mediterranean diet; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; TyG, triglyceride glucose index; FLI, fatty liver index.

gism between EI and PA, as the RERI coefficients were > 0 and SI > 1 (values indicative of an additive interaction) for beneficial changes in body weight and composition, although the CIs were wide and statistical significance was not achieved (body weight RERI 0.16 [95% CI, -1.12 to 1.44]; SI 1.08 [95% CI, 0.58 to 1.99]; percent-

age of fat mass RERI 0.53 [95% CI, -0.33 to 1.39]; SI 1.88 [95% CI, 0.41 to 8.65]; and percentage of lean mass RERI 0.45 [95% CI, -0.75 to 1.65]; SI 1.44 [95% CI, 0.43 to 4.88]).

Furthermore, 47% of the combined effect on reducing the fat mass percentage could be attributed to the interaction, while 19%

Table 2. Baseline values and 1-year changes in body composition outcomes according to categories of changes in total energy intake and physical activity (cut-off at zero)

Characteristic	Total participants	Reduced EI (kcal/day)	Increased EI (kcal/day)	<i>P</i>	Reduced PA (MET min/wk)	Increased PA (MET min/wk)	<i>P</i>
Number of participants	1,110	649	461		452	658	
Weight (kg)	86.1 ± 12.6	87.1 ± 12.8	84.7 ± 12.3	0.002	85.7 ± 12.7	86.4 ± 12.6	0.355
Change in weight over 1 year (kg)	-1.84 ± 3.88	-2.37 ± 4.04	-1.09 ± 3.50	<0.001	-1.14 ± 3.42	-2.33 ± 4.09	<0.001
5% Reduction in weight (kg) over 1 year	251 (23)	176 (27)	75 (16)	<0.001	78 (17)	173 (26)	<0.001
Fat mass (%)	40.1 ± 6.9	39.9 ± 6.9	40.4 ± 6.7	0.235	40.2 ± 6.8	40.1 ± 6.9	0.822
Change in fat mass (%) over 1 year	-0.61 ± 2.26	-0.82 ± 2.39	-0.31 ± 2.02	<0.001	-0.36 ± 2.07	-0.79 ± 2.36	0.002
5% Reduction in fat mass over 1 year	224 (20)	147 (23)	77 (17)	0.015	71 (16)	153 (23)	0.002
Lean mass (%)	56.8 ± 6.5	57.0 ± 6.6	56.5 ± 6.4	0.254	56.7 ± 6.5	56.8 ± 6.5	0.768
Change in lean mass (%) over 1 year	0.58 ± 2.19	0.77 ± 2.30	0.30 ± 1.98	<0.001	0.34 ± 2.01	0.74 ± 2.28	0.003
5% Increase in lean mass (%) over 1 year	141 (13)	94 (14)	47 (10)	0.034	42 (9)	99 (15)	0.005

Values are presented as mean ± standard deviation or number (%). *P*-values were calculated using independent Student’s *t*-test or χ^2 test for continuous and categorical variables, respectively.

EI, energy intake; PA, physical activity; MET, metabolic equivalent of task.

Table 3. Odds ratios (95% CI) from analysis on individual and combined associations and measures of interaction between categories of changes in total energy intake and physical activity (cut-off at zero) on at least 5% improvements from baseline in body composition over 1 year (categorical outcomes)

Change in EI and PA over 1 year	Change in body composition over 1 year					
	Reduction of 5% in weight (kg)		Reduction of 5% fat mass (%)		Increase of 5% lean mass (%)	
	No. of improvements/total (%)	OR (95% CI)	No. of improvements/total (%)	OR (95% CI)	No. of improvements/total (%)	OR (95% CI)
Individual association						
Increased EI (kcal/day)	75/461 (16.3)	1 (Reference)	77/461 (16.7)	1 (Reference)	47/461 (10.2)	1 (Reference)
Reduced EI (kcal/day)	176/649 (27.1)	1.70 (1.17 to 2.45)*	147/649 (22.7)	1.41 (0.97 to 2.07)	94/649 (14.5)	1.46 (0.92 to 2.31)
Reduced PA (MET min/wk)	74/427 (17.3)	1 (Reference)	69/427 (16.2)	1 (reference)	41/427 (9.6)	1 (Reference)
Increased PA (MET min/wk)	177/683 (25.9)	1.78 (1.25 to 2.53)*	155/683 (22.7)	1.62 (1.13 to 2.33)*	100/683 (14.6)	1.74 (1.11 to 2.70)*
Combined association						
Increased EI & Reduced PA	22/181 (12.2)	(Reference)	26/181 (14.4)	(Reference)	15/181 (8.29)	(Reference)
Reduced EI & Reduced PA	52/246 (21.1)	1.98 (1.10 to 3.56)*	43/246 (17.5)	1.21 (0.68 to 2.16)	26/246 (10.6)	1.37 (0.67 to 2.82)
Increased EI & Increased PA	53/279 (19.0)	2.09 (1.16 to 3.76)*	51/279 (18.3)	1.39 (0.80 to 2.43)	32/279 (11.5)	1.64 (0.81 to 3.29)
Reduced EI & Increased PA	124/404 (30.7)	3.24 (1.83 to 5.72)*	104/404 (25.7)	2.13 (1.23 to 3.69)*	68/404 (16.8)	2.46 (1.24 to 4.87)*
Multiplicative interaction						
Likelihood ratio test	<i>P</i> =0.477		<i>P</i> =0.499		<i>P</i> =0.837	
Additive interaction						
Relative excess risk due to interaction	0.16 (-1.12 to 1.44)		0.53 (-0.33 to 1.39)		0.45 (-0.75 to 1.65)	
Synergy index	1.08 (0.58 to 1.99)		1.88 (0.41 to 8.65)		1.44 (0.43 to 4.88)	
Attributable proportion of the combined association						
Due to interaction (EI × PA) (95% CI)	0.07 (-0.50 to 0.64)		0.47 (-0.34 to 1.28)		0.31 (-0.54 to 1.15)	
Due to reduced EI (95% CI)	0.44 (0.09 to 0.79)*		0.19 (-0.32 to 0.69)		0.26 (-0.26 to 0.77)	
Due to increased PA (95% CI)	0.49 (0.10 to 0.87)*		0.35 (-0.18 to 0.87)		0.44 (-0.13 to 1.01)	

Fully adjusted model for study randomization group (control or intervention), sex (men or women), age (years), and recruiting center (categorical), as well as baseline smoking habits (current, never, or ex-smoker), prevalence of type 2 diabetes mellitus (yes or no), adherence to energy-restricted Mediterranean diet (0–17 points), alcohol intake (g/day), sedentarism, sleep (both in hr/day), number of metabolic syndrome components, fatty liver index (both continuous), total leisure time physical activity (MET min/wk), total energy intake (kcal/day), weight (kg), and outcome variable.

*Statistically significant.

CI, confidence interval; OR, odds ratio; EI, energy intake; PA, physical activity; MET, metabolic equivalent of task.

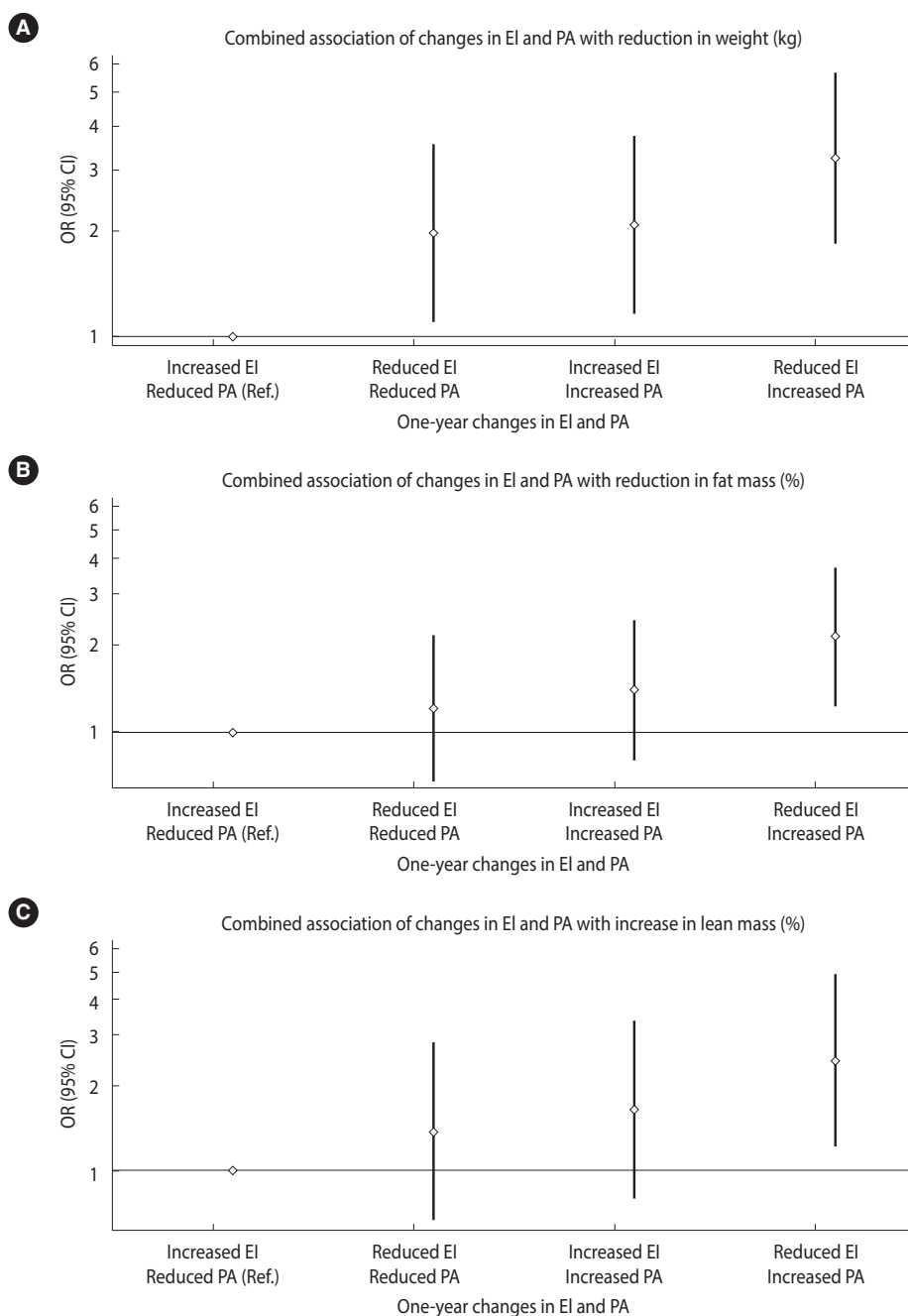


Figure 1. Odds ratios (OR) (95% confidence intervals [CIs]) for associations between categories of changes in total energy intake (EI) and physical activity (PA) (cut-off at zero for both factors) on at least 5% improvements in body composition over 1 year (categorical outcomes): (A) body weight, (B) fat mass (%), and (C) lean mass (%). Logistic regression was used with a fully adjusted model for the study randomization group (control or intervention), sex (men or women), age (years) and recruiting center (categorical), as well as baseline smoking habits (current, never, or ex-smoker), prevalence of type 2 diabetes mellitus (yes or no), adherence to energy-restricted Mediterranean diet (0–17 points), alcohol intake (g/day), sedentarism, sleep (both in hr/day), number of metabolic syndrome components, fatty liver index (both continuous), total leisure time PA (metabolic equivalent of task min/wk), total EI (kcal/day), weight (kg), and outcome variable.

and 35% could be attributed to the independent effects of reduced EI and increased PA, respectively (Table 3). For increases in relative lean mass, 31% of the combined effect could be due to their in-

teraction, 26% due to reduced EI, and 44% due to increased PA. Regarding beneficial reductions in body weight, the greatest proportion of the joint effect was due to increased PA (49%) or re-

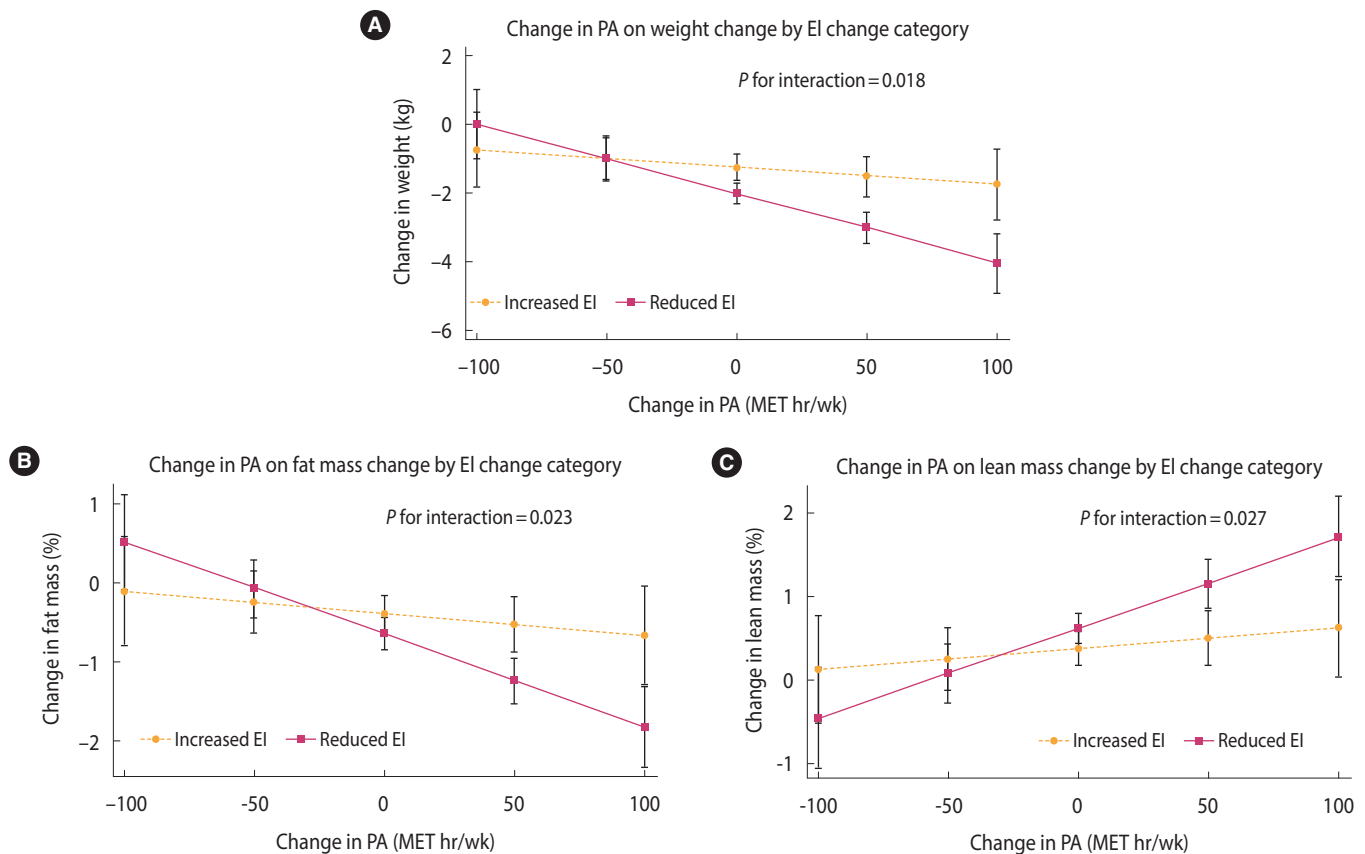


Figure 2. Associations between 1-year changes in physical activity (PA) on changes in (A) body weight, (B) fat mass (%), and (C) lean mass (%) (all continuous variables) by categories of changes in energy intake (EI; cut-off at zero). Linear prediction models and 95% confidence intervals estimated after entering product term between lifestyle factors into linear regression models adjusted for study randomization group (control or intervention), sex (men or women), age (years) and recruiting center (categorical), as well as baseline smoking habits (current, never, or ex-smoker), prevalence of type 2 diabetes (yes or no), adherence to energy-restricted Mediterranean diet (0–17 points), alcohol intake (g/day), sedentarism, sleep (both in h/day), number of metabolic syndrome components, fatty liver index (both continuous), total leisure time PA (metabolic equivalent of task [MET] min/wk), total energy intake (kcal/day), weight (kg), and outcome variable.

duced EI (44%), with only 7% attributed to the interaction between EI and PA. Similar results were obtained after eliminating participants who did not change either EI or PA over the follow-up period (Supplementary Table 1).

In additional analysis, where outcomes were modeled as continuous variables (Supplementary Table 2), it was determined that annual improvements in EI and PA alone were associated with concurrent favorable changes in body weight and composition compared to the opposite categories of EI and PA, respectively (for all outcomes 95% CIs did not cross the null value). Consistent with the main analysis, the greatest benefits for body weight, fat, and lean mass percentages were observed when reductions in EI were combined with increases in PA (95% CIs for all outcomes did not cross the null value). Fig. 2 depicts the interaction between increas-

ing time spent on PA (MET hr/wk) and reducing EI on beneficial changes in body weight and composition (P for interaction < 0.05 for all outcomes).

DISCUSSION

This prospective study was conducted among older adults with overweight/obesity and metabolic syndrome from the PREDIMED-Plus trial. The study focused on the combined versus individual effects of dietary EI reduction and PA increase on beneficial changes in objectively measured body composition, with a notable emphasis on comprehensive interaction analysis. The key finding was that individuals who both increased PA and reduced EI over 1 year showed the greatest likelihood of achieving significant improve-

ments in body weight and composition, including percentage of fat and lean mass, compared to those who did not improve any lifestyle factor or who only made one change (either increased PA or reduced EI). Notably, these improvements likely had public health and clinical relevance, as they were based on the achieving of a minimum 5% beneficial change from baseline, the threshold typically associated with positive cardiometabolic outcomes.²⁰

Our interaction analysis suggested the potential synergistic effect between these two protective lifestyle factors, indicating that the combined effect was greater than the sum of their individual effects, although this interaction was not purely statistical but biological. Individuals who only increased PA showed meaningful improvements in body composition, whereas those who solely reduced EI were more likely to experience reduced body weight without concurrent improvements in body composition. This observation may suggest that engagement in PA has a more significant impact on body composition optimization compared to EI reduction in this population. Further research should more extensively explore these results, considering activity type, frequency, and intensity, and confirm the results using objective PA measures. Notably, the combination of both strategies produced the most substantial and comprehensive improvements in both weight and body composition over 1 year.

Our findings regarding the benefits of combining EI with PA in older adults with obesity align with those of previous studies on the topic.^{1,2,13,32} A recent systematic review and network meta-analysis of RCTs (ranging from 2 to 6 months of duration) concluded that the most effective lifestyle strategy for improving body composition—specifically reducing fat mass while maintaining or increasing muscle mass—in individuals aged 55 to 70 years with obesity, was combining calorie restriction below energy requirements with resistance training or mixed exercising (resistance combined with aerobic exercise) and/or high-protein intake.³³ Moreover, combining calorie restriction with exercise has been shown not only to preserve fat-free mass (i.e., lean mass and bone mass), but also to enhance aerobic capacity and increase strength. These findings underscore the relevance of integrating these lifestyle strategies in older adults, particularly those at risk for frailty and falls.³²

One possible explanation for the effectiveness of combining EI reduction with PA is that the limitations of each strategy may be

partially offset by the other.³² Exercise has been widely recognized to stimulate muscle anabolism, potentially counteracting the declines in skeletal muscle mass, strength, and bone mineral density triggered by dietary-induced weight-loss.^{32,34} Additionally, exercise and other PA appear to promote satiety sensitivity and appetite control in older adults,^{35,36} helping to mitigate the potential increase in appetite as a consequence of an energy deficit.³⁷ On the other hand, the efficacy of PA as a weight-loss strategy in older adults may be limited by reduced functional capacity, which can be offset by calorie expenditure through dietary restriction.¹ Moreover, calorie reduction has been found to reduce oxidative stress markers, which tend to increase in response to exercise.³² A weight-loss intervention combining calorie reduction with exercise has also been shown to exert an additive beneficial effect on glucoregulation, compared to each of the factors alone, in overweight adults aged 45 to 65 years.³⁸ This positive biological interaction between EI reduction and PA increase (although not statistically significant) supports the possibility that combined physiological effects lead to favorable changes in specific body components.

Moreover, the findings of our study suggest a potential positive interaction between EI reduction and PA on body composition, measured on an additive scale. This implies a mechanistic or biological interaction, with potential synergism between these lifestyle factors.^{27,39} The suggested positive interaction alludes to the likelihood that the improvement in body weight and composition that is achieved in subjects who both reduce EI and increase PA is greater than the improvement that would be expected if the individual effects of each factor were summed. In other words, our findings suggest that tailoring lifestyle recommendations to increase PA with complementary nutritional education for reducing EI in older adults with obesity could lead to a more pronounced improvement in body composition. This would include not only the independent effects of each factor, particularly in terms of achieving beneficial changes in fat and lean mass percentages, but also the effects induced by the interaction of the two factors.

Moreover, the proportion of the combined effects attributed to a biological interaction was higher than the proportion attributed to the independent effect of EI reduction and/or PA increase for attaining beneficial changes in fat and lean mass percentages. This observation may be significant for public health and clinical practice,

suggesting that EI reduction and PA increase are most effective when combined, as they interact to yield improvements in specific body components beyond their independent effects. Similarly, other studies have reported the additive interaction between dietary scores and PA on the risk of cardiovascular factors and mortality.^{8,40} While further research is warranted, the predominant indication from both our analysis and previous research is that leveraging the interaction of the two factors can decrease the burden of sarcopenic obesity and its associated complications in older adults. This objective can be achieved through strategies that promote sustainable and complementary lifestyle changes, integrating both dietary and PA components.

This study had some limitations. Owing to its exploratory and observational nature, the discussed causality could not be inferred. Moreover, the study was restricted to older Spanish subjects with overweight/obesity and metabolic syndrome, with half of the cohort participating in a weight-loss program. The generalizability of our findings to the general population was thus restricted. Furthermore, this study was conceptually based on the energy balance model, focusing on EI and PA to explain changes in body weight and composition. However, it did not account for the alternative models that emphasize the role of hormones and/or dietary quality (i.e., the carbohydrate–insulin model). Future research should explore alternative mechanisms to deepen our understanding of body composition changes in older adults. Although total EI and PA were assessed using validated questionnaires, the reliance on self-reporting may have led to measurement errors. Another limitation was the fact that the EI variable was categorized as increased/reduced from the baseline without considering the participant energy requirements. Furthermore, the RERI estimates had wide CIs and failed to reach statistical significance for all study outcomes. Nonetheless, interaction metrics, such as RERI, are often statistically non-significant or underreported owing to their lack of statistical power to detect interactions, which can increase the likelihood of type II errors.^{8,29,30} Consequently, more precise estimates of an interaction analysis may require larger study populations.

It is important to note that all three measures of additive interactions (RERI, AP, and SI) in our study consistently indicated a positive interaction on the additive scale. Lastly, subgroup analyses exploring whether differences in outcomes existed based on age or

sex were not performed owing to a lack of statistical power.

Despite the above limitations, the present study had several strengths, including a prospective design, use of a large sample size, concurrent assessment of changes in diet with directly measured anthropometry and body composition, and control for a variety of covariables.

In conclusion, the findings of this study suggest that dietary energy reduction and PA promotion act synergistically to achieve the most favorable and possibly clinically meaningful changes in body weight and composition in an aging population with overweight/obesity and metabolic syndrome, as the subjects from the PRE-DIMED-Plus study. This finding underscores an important recommendation for public health and clinical practice: prescribing increased PA combined with nutritional education to reduce EI could be more effective in improving the body composition of older adults than focusing on a single lifestyle behavior.

Future studies are warranted to determine the optimal combination of the degree of IE reduction, as well as the amount and intensity of PA, to achieve the greatest benefit for addressing age-related changes in body composition. Further research is also required to replicate these findings in leaner, healthier, and/or younger populations to elucidate the mechanisms underlying the observed synergism between both lifestyle factors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found online at <https://doi.org/10.7570/jomes25027>.

CONFLICTS OF INTEREST

Ramon Estruch reports a relationship outside the submitted work with the following: Grand-Fountain Laboratories, Spain, and Uriach Laboratories, including funding grants; Fundacion Cerveza y Salud, Spain, including speaking and lecture fees; Instituto Cervantes, Albuquerque, NM, USA, including speaking and lecture fees; Instituto Cervantes, Milan, Italy, including speaking and lecture fees; Instituto Cervantes, Tokyo, Japan, including speaking and lecture fees; Wine and Culinary International Forum, including non-financial support; Pernaud Richart, Mexico, including speaking and lecture fees; Fundacion Dieta Mediterranea, Barcelona,

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The other authors of this manuscript declare that they have no known competing financial interests or personal relationships that could have appeared to influence the research reported in this paper.

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AUTHOR CONTRIBUTIONS

Study concept and design: JK, VO, MRC, DR, and JAM; acquisition of data: JK, VO, MRC, JSS, VMS, RE, JV, FJBG, JFGG, JPB, DMU, JAP, RC, RPO, HVL, IA, JDE, MF, AG, DR, and JAM; analysis and interpretation of data: JK, VO, MRC, DR, and JAM; drafting of the manuscript: JK, VO, MRC, DR, and JAM; critical revision of the manuscript: JK, VO, MRC, JSS, VMS, RE, JV, FJBG, JFGG, JPB, DMU, JAP, RC, RPO, HVL, IA, JDE, MF, AG, DR, and JAM; statistical analysis: JK, VO, MRC, DR, and JAM; obtained funding: MRC, JSS, VMS, RE, JV, DR, and JAM; administrative, technical, or material support: JK, JAP, RC, RPO, and IA; and study supervision: JAM.

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