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Supplementary appendix

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Supplement to: 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* 2016; published online June 6. [http://dx.doi.org/10.1016/S2213-8587\(16\)30085-7](http://dx.doi.org/10.1016/S2213-8587(16)30085-7).

Supplementary appendix

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Supplement to: Ramon Estruch, MD; Prof. Miguel Angel Martínez-González, MD; Prof. Dolores Corella, D Pharm; Prof. Jordi Salas-Salvadó, MD; Montserrat Fitó, MD; Gemma Chiva-Blanch, PhD; Miquel Fiol, MD; Enrique Gómez-Gracia, MD; Fernando Arós, MD; José Lapetra, MD; Prof. Lluís Serra-Majem, MD; Xavier Pintó, MD; Pilar Buil-Cosiales, MD; José V. Sorlí, MD; Miguel A Muñoz, MD; Josep Basora-Gallisá, MD; Rosa María Lamuela-Raventós, D Pharm; Mercè Serra-Mir, RD, and Emilio Ros, MD, on behalf of the PREDIMED Study Investigators. High-fat Mediterranean diet, body weight and waist circumference: Long-term evidence from the PREDIMED randomized trial.

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Appendix 1

LIST OF PREDIMED INVESTIGATORS

Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona, Spain: A. Pérez-Heras, C. Viñas, R. Casas, A. Medina-Renom, J.M. Baena, M. García, M. Oller, J. Amat, I. Duaso, Y. García, C. Iglesias, C. Simón, L. Quinzavos, L. Parra, M. Liroz, J. Benavent, J. Clos, I. Pla, M. Amorós, M.T. Bonet, M.T. Martín, M.S. Sánchez, J. Altirriba, E. Manzano, A. Altés, M. Cofán, C. Valls-Pedret, A. Sala-Vila, and M. Doménech.

Rovira i Virgili University, Reus, Spain: M. Bulló, N. Babio, J. Basora, R. González, C. Molina, A. Díaz-López, F. Márquez, P. Martínez, N. Ibarrola, M. Sorlí, J. García Roselló, A. Castro, F. Martín, N. Tort, A. Isach, M. Guasch-Ferre, N. Becerra-Tomás, J.J. Cabré, G. Mestres, F. Paris, M. Llauradó, N. Rosique-Esteban, R. Pedret, J. Basells, J. Vizcaino, R. Segarra, J. Frigola, J. Costa-Vizcaino, A. Salas-Huetos, J. Boj, D. Montañes and J. Fernández-Ballart.

University of Valencia, Valencia, Spain: P. Carrasco, C. Ortega-Azorín, E.M. Asensio, R. Osma, R. Barragán, F. Francés, M. Guillén, J.I. González, C. Sáiz, O. Portolés, F.J. Giménez, O. Coltell, R. Fernández-Carrión, P. Guillem-Sáiz, I. González-Monje, L. Quiles, V. Pascual, C. Riera, M.A. Pages, D. Godoy, A. Carratalá-Calvo, S. Sánchez-Navarro, and C. Valero-Barceló.

Hospital del Mar Research Institute, Barcelona, Spain: S. Tello, J. Vila, R. de la Torre, D. Muñoz-Aguayo, R. Elosua, J. Marrugat, H. Schröder, N. Molina, E. Maestre, A. Rovira, O. Castañer, and M. Farré.

University of Navarra and Osasunbidea (Servicio Navarro de Salud), Primary Care Centres, Pamplona, Spain: E. Toledo, M. Ruiz-Canela, B. Sanjulián, A. Sánchez-Tainta, S. Egúaras, A. Martí, P. Buil-Cosiales, M. SerranoMartínez, J. Diez-Espino, A. García-Arellano, E.H. Martínez-Lapiscina, E. Goñi, Z. Vázquez, N. Berrade, V. Extremera-Urabayen, C. Arroyo-Azpa, L. García-Pérez, J. Villanueva-Telleria, F. Cortés-Ugalde, T. Sagredo-Arce, M.D. Vigata-López, M.T. Arceiz Campo, A. Urtasun-Samper, M.V. Gueto Rubio, and B. Churio-Beraza.

University Hospital of Álava, Vitoria, Spain: F. Arós, I. Salaverria, T. del Hierro, J. Algorta, S. Francisco, A. Alonso-Gómez, E. Sanz, J. Rekondo, M.C. Belló, and A. Loma-Osorio.

University of Málaga, Málaga, Spain: E. Gómez-Gracia, J. Wörnberg, R. Benítez Pont, M. Bianchi Alba, R. Gómez-Huelgas, J. Martínez-González, V. Velasco García, J. de Diego Salas, A. Baca Osorio, J. Gil Zarzosa, J.J. Sánchez Luque, and E. Vargas López.

Instituto de la Grasa, Consejo Superior de Investigaciones Científicas, Sevilla, Spain: V. Ruiz-Gutiérrez, J. Sánchez Perona, E. Montero Romero, M. García-García, and E. Jurado-Ruiz.
Instituto de Investigación Sanitaria de Palma (IdISPa), Palma de Mallorca, Spain. M. Fiol, D. Romaguera, M. García-Valdúeza, M. Moñino, S. Munuera, M. Vivó, F. Bestard, J.A. Munar, L. Coll, A. Proenza, R. Prieto, G. Frontera, F. Fiol, M. Ginard, A, and Jover, J. García,

Department of Family Medicine, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain: JM. Santos-Lozano, M. Ortega-Calvo, L. Mellado, FJ. García-Corte, P. Román, P. Iglesias, Y. Corchado, L. Miró-Moriano, C. Domínguez-Espinaco, JM. Lozano-Rodríguez, and S. Vaquero-Díaz.

School of Pharmacy, University of Barcelona, Barcelona, Spain: M.C. López- Sabater, A.I. Castellote-Bargalló, P. Quifer-Rada and A. Tresserra-Rimbau.

Instituto Universitario de Investigaciones Biomédicas y Sanitarias (I.U.I.B.S.) de la Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain: J. Álvarez-Pérez, E.M. Díaz-Benítez, A. Sánchez-Villegas, L.T. Casañas-Quintana, J. Pérez-Cabrera, C. Ruano-Rodríguez, I. Bautista-Castaño, F. Sarmiento de la Fe, J.A. García Pastor, B.V. Díaz-González, J.M. Castillo Anzalas, R.E. Sosa-Also, J. Medina-Ponce.

Hospital Universitari de Bellvitge-IDIBELL, Hospitalet de Llobregat, Barcelona, Spain: E. de la Cruz, M. Fanlo-Maresma, A. Galera, F. Trias, I. Sarasa, E. Corbella and X. Corbella.

Primary Care Division, Catalan Institute of Health, Barcelona, Spain: C. Cabezas, E. Vinyoles, M.A. Rovira, L. García, G. Flores, J.M. Verdú, P. Baby, A. Ramos, L. Mengual, P. Roura, M.C. Yuste, A. Guarner, A. Rovira, M.I. Santamaría, M. Mata, C. de Juan, and A. Brau.

Other investigators of the PREDIMED network: J.A. Tur (University of Balearic Islands), M.P. Portillo (University of Basque Country), and G. Sáez (University of Valencia).

Clinical End Point Committee — F. Arós (chair), M. Aldamiz-Echevarría, A.M. Alonso-Gómez, J. Berjón, L. Forga, J. Gállego, A. García-Layana, A. Larrauri, J. Portu-Zapirain, and J. Timiraus-Fernández.

Appendix 2

CHANGES TO METHODS AFTER COMMENCEMENT OF THE TRIAL

Participants in the control group also received dietary training at the baseline visit and completed the 14-item dietary screener used to assess baseline adherence to the Mediterranean diet. Thereafter, during the first 3 years of the trial, they received a leaflet explaining the low-fat diet on a yearly basis. However, the realization that the more infrequent visit schedule and less intense support for the control group might be limitations of the trial prompted us to amend the protocol in October 2006. Thereafter, participants assigned to the control diet received personalized advice and were invited to group sessions with the same frequency and intensity as those in the Mediterranean-diet groups, with use of a separate 9-item dietary screener (See online Research Protocol).

Appendix 3

STATISTICAL ANALYSES: SAMPLE SIZE AND CRITERIA TO STOP DE TRIAL

We initially estimated that a sample of 9000 participants would be required to provide statistical power of 80% to detect a relative risk reduction of incident cardiovascular diseases of 20% in each Mediterranean-diet group versus the control-diet group during a 4-year follow-up period, assuming an event rate of 12% in the control group^{1,2}. In April 2008, on the advice of the Data and Safety Monitoring Board and on the basis of lower-than-expected rates of end-point events, the sample size was recalculated as 7400 participants, with the assumption of a 6-year follow-up period and underlying event rates of 8.8% and 6.6% in the control and intervention groups, respectively. Yearly interim analyses began after a median of 2 years of follow-up. With the use of O'Brien–Fleming stopping boundaries, the P values for stopping the trial at each yearly interim analysis were 5×10^{-6} , 0.001, 0.009, and 0.02 for benefit and 9×10^{-5} , 0.005, 0.02, and 0.05 for adverse effects³. The stopping boundary for the benefit of the Mediterranean diets with respect to the primary end point (cardiovascular disease) was crossed at the fourth interim evaluation; on July 22, 2011, the Data and Safety Monitoring Board recommended stopping the trial on the basis of end points documented through December 1, 2010.

¹ Martínez-González MA, Corella D, Salas-Salvadó J, et al. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol* 2012;41:377-85.

- ² ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;288:2998-3007.
- ³ O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.

Appendix 4

eTable 1. Mean baseline values and changes in the consumption of key foods in the three arms of the study. Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean Diet intervention (versus the control diet group).

Food items (serving sizes)	Mean baseline			Within-group mean changes			Between-group changes (differences vs.control)			
	MeDiet ^a with extravirgin olive oil (n = 2364)	MeDiet with mixed nuts (n = 2108)	Control group (n = 1941)	MeDiet ^a with extravirgin olive oil (n = 2364)	MeDiet with mixed nuts (n = 2108)	Control group (n = 1941)	MeDiet with extravirgin olive oil vs. Control group		MeDiet with mixed nuts vs. Control group	
	Mean (standard deviation)			Mean (95% CI)			Mean (95% CI)	P value	Mean (95% CI)	P value
Virgin olive oil (10 g) (s/d ^b)	2.1 ± 2.3	2.2 ± 2.3	2.0 ± 2.3	2.93 (2.82, 3.04)	0.99 (0.88, 1.11)	0.27 (0.16, 0.38)	2.66 (2.47, 2.86)	< 0.001	0.72 (0.53, 0.92)	< 0.001
Refined-mixed olive oil (10 g) (s/d)	1.8 ± 2.0	1.6 ± 2.0	1.7 ± 2.0	-1.71 (-1.80, -1.62)	-0.57 (-0.67, -0.47)	-0.44 (-0.55, -0.34)	-1.27 (-1.10, -1.43)	< 0.001	-0.13 (-0.30, 0.05)	0.24
Total nuts (25 g) (s/d)	0.4 ± 0.5	0.5 ± 0.6	0.4 ± 0.5	0.001 (-0.03, 0.03)	0.71 (0.67, 0.75)	-0.13 (-0.16, -0.11)	0.13 (0.09, 0.18)	< 0.001	0.84 (0.78, 0.90)	< 0.001
Vegetables (125 g) (s/d)	2.8 ± 1.2	2.7 ± 1.2	2.6 ± 1.1	-0.08 (-0.13, -0.01)	-0.01 (-0.06, 0.05)	-0.09 (-0.14, -0.03)	0.014 (-0.08, 0.11)	0.98	0.08 (-0.01, 0.18)	0.12
Cereals (60 g) (s/d)	3.8 ± 1.8	3.8 ± 1.6	3.7 ± 1.7	-0.34 (-0.42, -0.26)	-0.37 (-0.45, -0.29)	-0.35 (-0.44, -0.26)	0.01 (-0.13, 0.15)	0.99	-0.02 (-0.16, 0.13)	0.99
Legumes (40 g) (s/d)	0.5 ± 0.3	0.5 ± 0.4	0.5 ± 0.3	0.06 (0.04, 0.07)	0.06 (0.04, 0.08)	0.002 (-0.01, 0.02)	0.06 (0.03, 0.08)	< 0.001	0.06 (0.003, 0.08)	< 0.001
Fruits (125 g) (s/d)	3.0 ± 1.7	3.0 ± 1.6	2.8 ± 1.6	0.21 (0.13, 0.28)	0.25 (0.17, 0.33)	0.15 (0.07, 0.23)	0.05 (-0.09, 0.19)	0.75	0.10 (-0.04, 0.24)	0.25
Fish or seafood (125) (s/d)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4	0.01 (-0.01, 0.03)	0.02 (0.001, 0.04)	-0.03 (-0.05, -0.01)	0.04 (0.01, 0.07)	0.01	0.05 (0.02, 0.08)	0.001
Meat or meat products (150 g) (s/d)	0.9 ± 0.4	0.9 ± 0.4	0.8 ± 0.4	-0.11 (-0.12, -0.09)	-0.11 (-0.13, -0.10)	-0.10 (-0.11, -0.08)	-0.01 (-0.04, 0.02)	0.72	-0.01 (-0.01, 0.04)	0.53
Pastries, cakes or sweets (50 g) (s/d)	0.4 ± 0.5	0.4 ± 0.6	0.4 ± 0.5	-0.07 (-0.10, -0.05)	-0.09 (-0.12, -0.06)	-0.06 (-0.09, -0.03)	-0.01 (-0.06, 0.03)	0.86	-0.03 (-0.08, 0.02)	0.41
Dairy products (200 g) (s/d)	1.9 ± 1.1	1.9 ± 1.1	1.9 ± 1.1	-0.07 (-0.12, -0.02)	-0.05 (-0.09, 0.003)	-0.08 (-0.13, -0.04)	0.02 (-0.07, 0.10)	0.96	0.03 (-0.05, 0.12)	0.61
Alcohol (g/d)	8.6 ± 14.5	9.2 ± 15.0	7.4 ± 12.9	-1.40 (-1.86, -0.95)	-1.40 (-1.92, -0.89)	-0.88 (-1.31, -0.45)	-0.52 (-1.28, 0.24)	0.27	-0.52 (-1.33, 0.29)	0.34

NOTE: Of participants in the MeDiet with extra virgin olive oil, MeDiet with mixed nuts, and control groups, 42, 57 and 25 participants, respectively, were excluded from calculations of food intake because energy intake was outside prespecified ranges. Dietary assessment was conducted using a food frequency questionnaire (136 items) previously validated for the Spanish population.

^a MeDiet Mediterranean diet; ^bs/d: serving/day.

Appendix 5

eTable 2. Intake of Energy, Nutrients and Supplemental Foods at Baseline and the end of the Trial by Study Group.

	MeDiet with extravirgin Olive Oil		MeDiet with Mixed Nuts		Control group	
	(n = 2364)		(n = 2108)		(n = 1941)	
	Baseline	End of trial	Baseline	End of trial	Baseline	End of trial
	<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>	
Energy (kcal)	2,257 ± 550	2,172 ± 475	2,276 ± 527	2,229 ± 477	2,186 ± 535	1960 ± 497
Total protein (% E ^a)	16.7 ± 2.8	16.2 ± 2.4	16.6 ± 2.7	16.4 ± 2.5	16.6 ± 2.8	17.1 ± 3.0
Total CH ^b (% E)	41.7 ± 7.2	40.4 ± 5.9	41.4 ± 7.0	39.7 ± 6.3	42.2 ± 7.1	43.7 ± 7.0
Fiber (g/d)	25.7 ± 9.1	25.4 ± 7.5	25.7 ± 8.6	27.0 ± 8.0	24.7 ± 8.4	23.7 ± 7.7
Total fat (% E)	39.2 ± 6.9	41.2 ± 5.4	39.4 ± 6.5	41.5 ± 6.1	39.0 ± 7.0	37.0 ± 7.0
SFA ^c (% E)	10.0 ± 2.2	9.4 ± 2	10.0 ± 2.1	9.3 ± 2.0	10.0 ± 2.3	9.1 ± 2.1
MUFA ^d (% E)	19.6 ± 4.6	22.1 ± 3.7	19.6 ± 4.3	20.9 ± 4.1	19.3 ± 4.7	18.8 ± 4.6
PUFA ^e (% E)	6.1 ± 2.1	6.1 ± 1.4	6.4 ± 2.0	7.7 ± 1.8	6.2 ± 2.1	5.5 ± 1.7
MUFA/ SFA (% E)	2.0 ± 0.5	2.4 ± 0.5	2.0 ± 0.5	2.3 ± 0.5	2.0 ± 0.5	2.1 ± 0.5
Linoleic acid, (g/d)	12.9 ± 6.0	12.2 ± 4.6	13.6 ± 6.1	16.0 ± 5.5	12.6 ± 6.0	10.0 ± 4.8
α- linolenic acid, (g/d)	1.4 ± 0.7	1.3 ± 0.7	1.5 ± 0.7	1.9 ± 0.7	1.3 ± 0.6	1.1 ± 0.5
Marine n-3 fatty acids (g/d)	0.8 ± 0.5	0.9 ± 0.5	0.8 ± 0.5	0.8 ± 0.5	0.8 ± 0.5	0.7 ± 0.4
Olive oil (% E)	16.3 ± 7.1	22.0 ± 6.0	15.9 ± 6.7	17.6 ± 6.4	15.8 ± 7.4	16.4 ± 6.8
Nuts (% E)	2.5 ± 3.4	2.6 ± 3.1	3.3 ± 3.7	8.2 ± 4.5	2.4 ± 3.2	1.6 ± 2.5
Cholesterol (mg/d)	363.4 ± 131.1	338.5 ± 100.7	366.6 ± 117.1	338.2 ± 99.2	356.4 ± 122.4	324.1 ± 105.7

NOTE: In the Mediterranean diet with extravirgin olive oil, Mediterranean diet with nuts, and control diet groups, 42, 57 and 25 participants, respectively, were excluded from calculations of food intake because their total energy intake was outside the prespecified ranges; ^aE, energy intake; ^bCH, carbohydrates; ^cSFA, saturated fatty acids; ^dMUFA, monounsaturated fatty acids; ^ePUFA, polyunsaturated fatty acids.

Appendix 6.

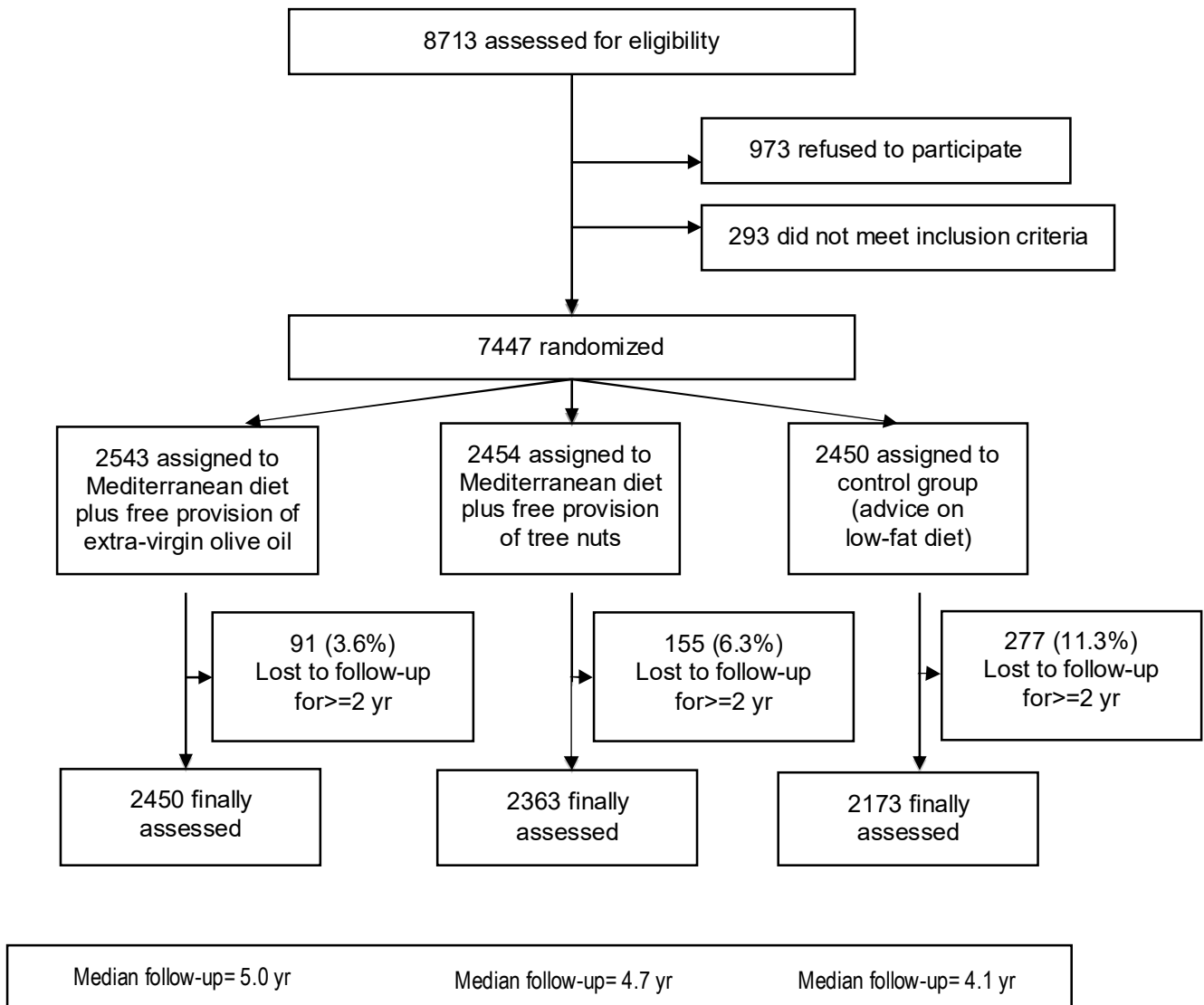
e Table 3. Mean changes in energy and nutrient intake in the three treatment arms. Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean diet intervention (versus the control group).

	Within-group mean changes					Between-group changes (differences vs. control)						
	MeDiet ^a with extravirgin Olive Oil (n = 2364)		MeDiet with mixed nuts (n = 2108)		Control group (n = 1941)		MeDiet with extravirgin olive oil vs. Control group		MeDiet with mixed nuts vs. Control group		P value	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)		
Energy (kcal)	-85	(-109, -60)	-47	(-73, -20)	-227	(-253, -200)	141	(97, 185)	<0.001	180	(134, 225)	<0.001
Total protein (% E) ^b	-0.44	(-0.57, -0.32)	-0.12	(-0.24, 0.01)	0.51	(0.37, 0.66)	-0.98	(-1.19, -0.73)	<0.001	-0.62	(-0.96, -0.40)	<0.001
Total CH ^c (% E)	-1.29	(-1.61, -0.98)	-1.65	(-1.98, -1.32)	1.50	(1.16, 1.85)	-2.79	(-3.37, -2.23)	<0.001	-3.15	(-3.74, -2.58)	<0.001
Fiber (g/d)	-0.29	(-0.71, 0.12)	1.36	(0.93, 1.79)	-0.93	(-1.35, -0.51)	0.64	(-0.08, 1.36)	0.10	2.29	(1.56, 3.03)	<0.001
Total fat (% E)	2.03	(1.72, 2.35)	2.10	(1.74, 2.40)	-1.96	(-2.32, -1.59)	3.99	(3.41, 4.57)	<0.001	4.03	(3.44, 4.62)	<0.001
SFA ^d (% E)	-0.56	(-0.65, -0.46)	-0.67	(-0.77, -0.57)	-0.79	(-0.90, -0.70)	0.24	(0.06, 0.41)	0.004	0.12	(-0.06, 0.30)	0.30
MUFA ^e (% E)	2.52	(2.30, 2.74)	1.32	(1.11, 1.55)	-0.53	(-0.78, -0.28)	3.05	(2.65, 3.46)	<0.001	1.89	(1.45, 2.26)	<0.001
PUFA ^f (% E)	-0.03	(-0.13, 0.06)	1.31	(1.20, 1.41)	-0.65	(-0.75, -0.55)	0.62	(0.45, 0.79)	<0.001	1.96	(1.77, 2.14)	<0.001
MUFA/ SFA (% E)	0.40	(0.38, 0.43)	0.29	(0.26, 0.31)	0.11	(0.08, 0.13)	0.29	(0.25, 0.34)	<0.001	0.18	(0.14, 0.22)	<0.001
Linoleic acid, (g/d)	-0.65	(-0.92, -0.37)	2.45	(2.13, 2.79)	-2.59	(-2.88, -2.30)	1.94	(1.45, 2.43)	<0.001	5.05	(4.51, 5.58)	<0.001
α-linolenic acid, (g/d)	-0.05	(-0.09, -0.02)	0.43	(0.40, 0.48)	-0.25	(-0.29, -0.22)	0.20	(0.14, 0.26)	<0.001	0.69	(0.63, 0.76)	<0.001
Marine n-3 fatty acids (g/d)	0.04	(0.01, 0.06)	0.04	(0.02, 0.07)	-0.07	(-0.10, -0.05)	0.11	(0.07, 0.16)	<0.001	0.12	(0.08, 0.16)	<0.001
Olive oil (% E)	5.63	(5.27, 6.00)	1.74	(1.39, 2.10)	0.67	(0.27, 1.06)	4.97	(4.31, 5.62)	<0.001	1.08	(0.43, 1.72)	<0.001
Nuts (% E)	0.11	(-0.06, 0.28)	4.95	(4.70, 5.20)	-0.71	(-0.87, -0.55)	0.82	(0.53, 1.10)	<0.001	5.65	(5.30, 6.01)	<0.001
Cholesterol (mg/d)	-24.9	(-30.5, -19.2)	-28.4	(-33.9, -22.9)	-32.3	(-38.1, -26.6)	7.48	(-2.34, 17.30)	0.19	3.97	(-5.69, 13.62)	0.70

NOTE: In the MeDiet with extravirgin olive oil, MeDiet with nuts, and low-fat diet groups, 42, 57 and 25 participants, respectively, were excluded from calculations of energy and nutrient intake because their total energy intake was out of the predefined range. ^aMeDiet Mediterranean diet; ^bE, energy intake; ^cCH, carbohydrates; ^dSFA, saturated fatty acids; ^eMUFA, monounsaturated fatty acids; ^fPUFA, polyunsaturated fatty acids.

Appendix 7

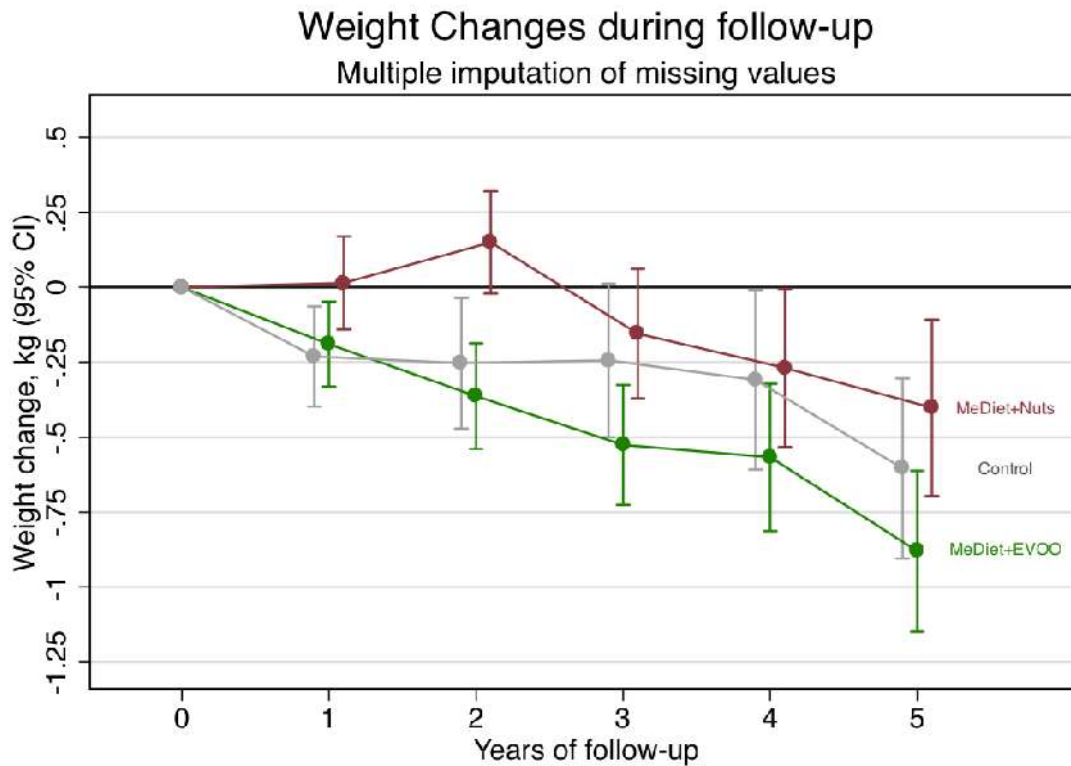
eFig. 1. The PREDIMED study 2003-2010: CONSORT flow diagram.



Intention to treat analysis

Appendix 8

eFigure 2. Average weight changes (95% confidence intervals) of PREDIMED participants during follow-up according to intervention group (with multiple imputation of missing values).



A multivariable normal procedure with 20 sets of imputations was used in Stata 12.0. Imputations were obtained by simulating from a Bayesian posterior predictive distribution of the missing data (or its approximation) under a multivariable normal prior distribution. When a pattern of missing values is arbitrary, iterative methods are used by Stata to fill in missing values. We selected the multivariate normal method that uses multivariate normal data augmentation to impute missing values of continuous imputation variables. Predictors for the imputations were: sex, age, center, smoking, baseline weight and waist circumference, baseline dyslipidemia, baseline hypertension, leisure-time physical activity (at baseline and after 1-y follow-up), educational level, total energy intake (at baseline and after 1-y follow-up), alcohol consumption, baseline body mass index and group allocation. Data sets of the imputed data were analyzed by multivariable adjusted GEE models including the interaction term between time and dietary intervention as indicated in Methods.