

# Relationship between olive oil consumption and ankle-brachial pressure index in a population at high cardiovascular risk

Cristina Sánchez-Quesada<sup>1,2,3,\*</sup>, Estefanía Toledo<sup>4,5,\*</sup>, Guadalupe González-Mata<sup>6</sup>, Maria Isabel Ramos-Ballesta<sup>6</sup>, José Ignacio Peis<sup>7</sup>, Miguel Ángel Martínez-González<sup>4,5,8</sup>, Jordi Salas-Salvadó<sup>4,10,11,12</sup>, Dolores Corella<sup>4,13</sup>, Montserrat Fitó<sup>4,14</sup>, Dora Romaguera<sup>4,15</sup>, Jesús Vioque<sup>9,16</sup>, Ángel M. Alonso-Gómez<sup>4,17</sup>, Julia Wärnberg<sup>4,18</sup>, J. Alfredo Martínez<sup>4,19,20</sup>, Luís Serra-Majem<sup>4,21</sup>, Ramon Estruch<sup>4,22</sup>, Francisco J Tinahones<sup>4,23</sup>, José Lapetra<sup>4,24</sup>, Xavier Pintó<sup>4,25</sup>, Josep A. Tur<sup>4,15,26</sup>, Antonio Garcia-Rios<sup>4,27</sup>, Naomi Cano-Ibáñez<sup>9,28</sup>, Pilar Matia-Martin<sup>29</sup>, Lidia Daimiel<sup>20</sup>, Rubén Sánchez-Rodríguez<sup>30</sup>, Josep Vidal<sup>31,32</sup>, Clotilde Vázquez<sup>4,33</sup>, Emilio Ros<sup>4,34</sup>, Pablo Hernández-Alonso<sup>4,10,12,23</sup>, Rocío Barragan<sup>13</sup>, Julia Muñoz-Martínez<sup>14</sup>, Meritxell López<sup>15</sup>, Sandra González-Palacios<sup>9,16</sup>, Jessica Vaquero-Luna<sup>17</sup>, Edelys Crespo-Oliva<sup>18</sup>, M. Angeles Zulet<sup>4,19</sup>, Vanessa Díaz-González<sup>21</sup>, Rosa Casas<sup>4,22</sup>, José Carlos Fernandez-García<sup>23</sup>, José Manuel Santos-Lozano<sup>4,24</sup>, Ana Galera<sup>4,25</sup>, Tomás Ripoll-Vera<sup>4,15,26,35</sup>, Pilar Buil-Cosiales<sup>4,5,36</sup>, Silvia Canudas<sup>4,10,12</sup>, Raul Martínez-Lacruz<sup>13</sup>, Karla-Alejandra Pérez-Vega<sup>14</sup>, Ángel Rios<sup>15</sup>, Rosario Lloret-Macián<sup>37</sup>, Anai Moreno-Rodriguez<sup>17</sup>, Miguel Ruiz-Canela<sup>4,5</sup>, Nancy Babio<sup>4,10,12</sup>, Maria Dolores Zomeño Fajardo<sup>14,38</sup>, José J. Gaforio<sup>1,2,3,9</sup>.

<sup>1</sup>Center for Advanced Studies in Olive Grove and Olive Oils, University of Jaen, Campus las Lagunillas s/n, 23071, Jaén, Spain.

<sup>2</sup>Immunology Division, Department of Health Sciences, Faculty of Experimental Sciences, University of Jaén, Jaén, Spain;

<sup>3</sup>Agri-food Campus of International Excellence (ceiA3), Córdoba, Spain.

<sup>4</sup>Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain

<sup>5</sup>University of Navarra, Department of Preventive Medicine and Public Health, IdiSNA, Pamplona, Spain

<sup>6</sup>Preventive Medicine and Public Health Division, Department of Health Sciences, Faculty of Experimental Sciences, University of Jaén, Jaén, Spain;

<sup>7</sup>Centro de Salud Bulevar (Servicio Andaluz de Salud, SAS), Jaén, Spain;

<sup>8</sup>Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

<sup>9</sup>CIBER Epidemiología y Salud Pública (CIBER-ESP), Instituto de Salud Carlos III, Madrid, Spain.

<sup>10</sup>Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició, Reus, Spain

<sup>11</sup>University Hospital of Sant Joan de Reus, Nutrition Unit, Reus, Spain

<sup>12</sup>Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain

<sup>13</sup>Department of Preventive Medicine, University of Valencia, Valencia, Spain

<sup>14</sup>Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain.

<sup>15</sup>Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain.

<sup>16</sup>Miguel Hernandez University, ISABIAL-UMH, Alicante, Spain

<sup>17</sup>Bioaraba Health Research Institute; Osakidetza Basque Health Service, Araba University Hospital; University of the Basque Country UPV/EHU; Vitoria-Gasteiz, Spain.

<sup>18</sup>Department of Nursing, School of Health Sciences, Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain

<sup>19</sup>Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain.

<sup>20</sup>Precision Nutrition and Cardiometabolic Health Program. Precision Nutrition and Obesity Program, IMDEA Food, CEI UAM + CSIC, Madrid, Spain

<sup>21</sup>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.

<sup>22</sup>Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain

<sup>23</sup>Virgen de la Victoria Hospital, Department of Endocrinology, Instituto de Investigación Biomédica de Málaga (IBIMA). University of Málaga, Málaga, Spain.

<sup>24</sup>Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain

<sup>25</sup>Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona Spain

<sup>26</sup>Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands, 07122 Palma de Mallorca, Spain

<sup>27</sup>Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain

<sup>28</sup>Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain

<sup>29</sup>Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain

<sup>30</sup>Centro de Salud Siero-Sariego, Asturias.

<sup>31</sup>CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

66 <sup>32</sup>Department of Endocrinology, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain.  
67 <sup>33</sup>Department of Endocrinology and Nutrition, Hospital Fundación Jimenez Díaz. Instituto de Investigaciones  
68 Biomédicas IISFJD. University Autónoma, Madrid, Spain  
69 <sup>34</sup>Lipid Clinic, Department of Endocrinology and Nutrition, Hospital Clínic, IDIBAPS, Barcelona, Spain  
70 <sup>35</sup>Department of Cardiology, Hospital Son Llàtzer, 07198 Palma de Mallorca, Spain  
71 <sup>36</sup>Servicio Navarro de Salud, Pamplona, Spain.  
72 <sup>37</sup>Centro Salud Cabo Huertas, Alicante.  
73 <sup>38</sup>Blanquerna School of Health Sciences, Universitat Ramon Llull, Barcelona, Spain.

74  
75 \* Both authors equally contributed

76  
77 **Corresponding author:**

78 José J. Gaforio

79 Health Sciences Department, Immunology Division

80 Faculty of Experimental Sciences. Campus Las Lagunillas s/n. CP 23071. Jaen (SPAIN)

81 Email: [jgaforio@ujaen.es](mailto:jgaforio@ujaen.es). Phone: +34 953212002

82  
83  
84 **Abstract**

85  
86 *Background and aims:* The aim of this study was to ascertain the association between the  
87 consumption of **different categories of edible olive oils (virgin olive oils and olive oil) total,**  
88 **virgin, olive oil,** and olive pomace oils and ankle-brachial pressure index (ABI) in participants  
89 of the PREDIMED-Plus study, a trial of lifestyle modification for weight and cardiovascular  
90 event reduction in individuals with overweight/obesity harboring the metabolic syndrome.  
91 *Methods:* Cross-sectional analyses of the PREDIMED-Plus trial. Consumption of **any category**  
92 **of olive oil total, virgin, olive oil** and olive pomace oils were assessed through a validated food-  
93 frequency questionnaire. Multivariable linear regression models were fitted to assess  
94 associations between olive oil consumption and ABI. Additionally, an ABI  $\leq 1$  was considered  
95 as the outcome in logistic models with different **types categories** of olive oil **and olive pomace**  
96 **oil** as exposure. *Results:* Among 4,330 participants, the highest quintile of total olive oil  
97 consumption (**sum of all categories of olive oil and olive pomace oil**) was associated with  
98 higher mean values of ABI (beta coefficient: 0.014, 95% confidence interval [CI]: 0.002, 0.027)  
99 (*p* for trend=0.010). Logistic models comparing the consumption of different **types-categories** of  
100 olive oils, **olive pomace oil** and ABI  $\leq 1$  values revealed an inverse association between virgin  
101 olive oils consumption and the likelihood of a low ABI (odds ratio [OR] 0.73, 95% CI [0.56,  
102 0.97]), while consumption of olive pomace oil was positively associated with a low ABI (OR  
103 1.22 95% CI [1.00, 1.48]). *Conclusions:* **In a Mediterranean population at high cardiovascular**  
104 **risk, total olive oil consumption was associated with a higher mean ABI. These results suggest**  
105 **that olive oil consumption may be beneficial for peripheral artery disease prevention, but**  
106 **longitudinal studies are needed.**

107  
108 **Keywords:** Olive oil (OO); virgin olive oils (VOO); ankle-brachial pressure index (ABI);  
109 peripheral artery disease (PAD); PREDIMED-Plus trial; **olive pomace oil.**

110 **Abbreviations:**

111 ABI: ankle-brachial pressure index; PAD: peripheral artery disease; CV: cardiovascular; BMI:  
112 body mass index; MetS: metabolic syndrome; OR: odds ratio; CI: confidence interval.

113  
114 **1. Introduction**

115  
116 The American College of Cardiology/American Heart Association defines peripheral  
117 atherosclerotic vascular diseases as a group of clinical disorders that includes abdominal aortic  
118 aneurysm, renal and mesenteric artery disease, extracranial carotid artery disease, and disease of  
119 the aortoiliac, femoropopliteal, and infrapopliteal arterial segments. It does not address  
120 nonatherosclerotic causes of lower extremity arterial disease, such as vasculitis, fibromuscular  
121 dysplasia, physiological entrapment syndromes, cystic adventitial disease and other entities [1].

Peripheral artery disease (PAD) is the term used by The European Society of Cardiology to describe all the arterial diseases other than coronary arteries or the aorta. ~~This should be clearly distinguished from the term ‘peripheral artery disease’, which is often used for lower extremity artery disease (LEAD). Indeed, other peripheral localizations, including the carotid and vertebral, upper extremities, mesenteric and renal arteries, are also frequently affected, mainly by atherosclerosis, and complete the family of PADs. The guidelines from the European society focus on the atherosclerotic process, which causes stenosis or occlusion of non-cerebral and non-coronary arteries [2]. PAD is only diagnosed in one out of three patients with PAD characteristics, 50% of them have atypical leg symptoms and between 10% and 20% of these patients develop intermittent claudication characterized by discomfort or pain in the limbs while walking [3]. Observational studies have demonstrated that the presence of PAD is a strong independent predictor of coronary and cerebrovascular events [4]. Even with current best medical therapy, the risk of cardiovascular (CV) and all-cause mortality remains almost three times higher in PAD patients than in patients without PAD [4]. Therefore, more effective interventions for PAD prevention are required in high-risk populations.~~

While several methods are used in the diagnosis of PAD, ankle-brachial index (ABI) is recommended as a non-invasive tool for screening and diagnosis [2-5]. ABI is calculated as the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery [3-6]. Usually, the highest ankle systolic pressure is divided by the highest brachial systolic pressure, resulting in an ABI for each leg [2-5]. The ABI is >1.0 in healthy individuals, among whom the blood pressure wave is amplified as it travels distally from the heart, resulting in a higher ankle than brachial systolic blood pressure. The majority of studies use an ABI of 0.90 as the threshold to define PAD, with borderline ABI defined as that between 0.91 and 0.99 [3-6]. ABI has high specificity but suboptimal sensitivity to detect PAD [4-7]. However, an ABI of 1.4 or more has been associated with an increased prevalence of PAD and CV risk, since it can be indicative of frequent arterial medial calcifications [5-8].

Olive oil consumption is reported to have several beneficial effects on CV disease [6-11, 9-13]; however to our knowledge, ~~epidemiological evidences on Mediterranean diet and its implications in PAD risk is limited [12-17] and, there is no evidence on the specific effect of total, virgin, olive oil or olive pomace oils in the prevention of PAD.~~

~~The PREDIMED trial -a controlled trial for the primary prevention of cardiovascular disease based on a nutritional intervention- was the first primary prevention trial which addressed the effect of a Mediterranean diet enriched with extra-virgin olive oil on the incidence of a first cardiovascular event [15]. Participants allocated to the Mediterranean diet group enriched with extra-virgin olive oil showed a significantly lower risk of cardiovascular disease than participants allocated to the control group. In addition, in the PREDIMED trial, participants allocated to the Mediterranean diet enriched with extra-virgin olive oil showed a significantly lower risk of PAD [14].~~

~~Indeed, some properties of isolated minor compounds found in olive oil, such as polyphenols, could contribute to prevent PAD [12].~~

~~This cross-sectional study analyzed the associations between the consumption of different categories of olive oils (total, virgin and olive oil), olive pomace oils and ABI in the PREDIMED-Plus trial.~~

## 2. Patients and Methods

### 2.1. Design and participants

The present study is a cross-sectional assessment conducted within the frame of the PREDIMED-Plus trial. The design and methods of the PREDIMED-Plus trial have been described in detail elsewhere [18] and the protocol is available at [www.predimedplus.com](http://www.predimedplus.com). Briefly, PREDIMED-Plus is an ongoing multicenter, randomized controlled trial conducted in Spain to assess the effect of an intensive weight-loss intervention based on an energy-reduced traditional Mediterranean diet (MedDiet), physical activity promotion, and behavioral support

177 on hard CV events, in comparison to that of a control group receiving usual care intervention  
178 only with energy-unrestricted Mediterranean diet recommendations. This study was registered  
179 with the International Standard Randomized Controlled Trial (ISRCT;  
180 <http://www.isrctn.com/ISRCTN89898870>) with number 89898870 (registration date: July 24,  
181 2014). Written informed consent was obtained from each patient included in the study, the study  
182 protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki and the study  
183 protocol has been priorly approved by the Research Ethics Committees from all recruitment  
184 centers [18]. The eligible participants were adults (aged 55–75 years in men; 60–75 years in  
185 women) with overweight/obesity (body mass index [BMI]  $\geq 27$  and  $< 40$  kg/m<sup>2</sup>, respectively) and  
186 who met at least three criteria for metabolic syndrome (MetS) according to the updated  
187 harmonized criteria of the International Diabetes Federation and the American Heart  
188 Association and National Heart, Lung, and Blood Institute [19]. A total of 6,874 participants  
189 were recruited and randomized from 23 recruitment sites at different universities, hospitals, and  
190 research institutes in Spain. The present analysis included only those participants whose total  
191 energy intakes were within predefined limits (800–4,000 Kcal/day for men, and 500–3,500  
192 Kcal/day for women [20] (n=241 out of limits), participants from recruitment centers with less  
193 than 25% missing data on ABI as a quality control (n=1,913 out of criteria), and participants  
194 with an ABI  $< 1.4$  (n=390 participants with ABI  $\geq 1.4$ ) (Figure 1).

195

## 196 2.2. Exposure Assessment

197 The consumption of total olive oil, in which are included the following types categories: virgin  
198 olive oils (including extra virgin and virgin olive oil), olive oil (described as refined olive oil  
199 and virgin olive oil mixture according to the European Commission Regulation (EC) N°  
200 1019/2002 [21]) and consumption of olive pomace oil was assessed using a validated 143-item  
201 semi-quantitative food-frequency questionnaire [22] administered at baseline. In face-to-face  
202 interviews, the participants were asked about their frequencies of consumption of each food  
203 item during the past year, as well as the usual serving sizes. Nine possibilities of frequency were  
204 offered, ranging from never to  $> 6$  times/day. ~~Total~~ Virgin, olive oil, olive pomace oil and total  
205 olive oil (which include both categories of olive oils and olive pomace oil) consumptions were  
206 adjusted for total energy intake using the residual method and the participants were then  
207 grouped into quintiles according to their total, virgin, or olive oil consumption. Due to the low  
208 consumption and low variability in olive pomace oil consumption, the participants were  
209 classified into tertiles according to their olive pomace oil consumption. Smoke variable was  
210 introduced as positive control to assess well known associations with PAD.

211

## 212 2.3. Outcome Assessment

213 At baseline, trained staff measured ABI in accordance with the PREDIMED-Plus operation  
214 protocol as the lowest value of two different measurements in each leg of the participant. For  
215 the present analyses, we averaged the ABI values of both legs. A sphygmomanometer cuff is  
216 placed just above the ankle and a Doppler instrument is used to measure the pressure of the  
217 posterior and anterior tibial (dorsalis pedis) arteries of each foot. In addition to ABI as a  
218 continuous variable, we also used a dichotomous outcome defined as an ABI lower or equal to  
219 1. On the other side of the spectrum, since ABI  $\geq 1.4$  can be indicative of frequent arterial  
220 medial calcifications [5], we excluded patients with ABI  $\geq 1.4$ .

221

## 222 2.4. Covariate Assessment

223 Information on socio-demographic variables (e.g., sex, age, marital status, and educational  
224 level) and lifestyle-related characteristics (e.g., smoking status, physical activity, or adherence  
225 to the Mediterranean diet) were obtained from the baseline questionnaire. Weight and height  
226 were measured in duplicate with calibrated scales and a wall-mounted stadiometer, respectively.  
227 BMI was calculated as the weight in kilograms divided by the height in meters squared.  
228 Leisure-time physical activity was assessed using the short form of the Minnesota Leisure Time  
229 Physical Activity Questionnaire validated in Spain [23, 24]. Leisure-time activities were  
230 computed by assigning a metabolic equivalent score to each activity [25], multiplied by the time  
231 spent for each activity and summing all activities. Adherence to an energy-restricted

232 Mediterranean diet was evaluated with a 17-item questionnaire [26] which we modified with the  
233 exclusion of the extra-virgin olive oil component to avoid collinearity (score range 0-16). Self-  
234 reported comorbidities (hypertension and type 2 diabetes) were collected from each participant.  
235

## 236 2.5. Statistical Analysis

237

238 Baseline variables across quintiles of total olive oil consumption were described as means and  
239 standard deviations for continuous traits and as percentages for qualitative traits. We estimated  
240 the Pearson's correlation coefficient between different categories of olive oil consumption and  
241 between continuous traits considered as potential confounders.

242 Multivariable linear regression models were fitted to assess the association between energy-  
243 adjusted consumption of total, virgin, olive oil (quintiles) and olive pomace oil (tertiles)  
244 consumption and ABI index. Beta coefficients and their 95% confidence intervals (CI) were  
245 calculated with the lowest quintile as the reference category.

246 To control for potential confounding factors, the results were adjusted for age (continuous), sex,  
247 and recruitment center in multivariable Model 1. Multivariable Model 2 was additionally  
248 adjusted for BMI (tertiles) and multivariable Model 3 was additionally adjusted for waist  
249 circumference (continuous); self-reported prevalent diabetes (yes/no); self-reported  
250 hypertension (yes/no); score appraising adherence to an energy-reduced Mediterranean diet  
251 (score 0–17); physical activity (metabolic equivalents [METs]-min/ week) (quintiles);  
252 educational level (primary school or less, secondary school, university); use of blood pressure-  
253 lowering drugs (yes/no); use of lipid-lowering medication (yes/no); use of diuretics (yes/no);  
254 use of insulin or oral antidiabetic agents (yes/no); dietary vitamin D intake (tertile); folic acid  
255 intake (continuous); family history of coronary heart disease (CHD) (yes/no); smoking (never,  
256 current, former  $\geq 5$  years, former  $< 5$  years); and total energy intake (continuous).

257 Tests of linear trend across increasing quintiles of exposures were conducted by assigning the  
258 quintile-specific median to each participant and treating the resulting variable as continuous  
259 trait.

260 Finally, to assess the robustness of the multivariable linear regressions, we performed sensitivity  
261 analysis for Q5 vs. Q1 of total olive oil consumption with different energy limits (percentiles 1  
262 and 99), including participants with  $ABI \geq 1.4$ , or participants from all recruitment centers. We  
263 also assessed the association after stratifying by sex (men and women), BMI ( $< 30$  kg/m<sup>2</sup> or  $\geq 30$   
264 kg/m<sup>2</sup>), age ( $\leq 65$  or  $> 65$  years), baseline adherence to the Mediterranean diet ( $\leq 7$  points vs  $\geq 8$   
265 points), and baseline diabetes.

266 Additional logistic regression models were fitted to assess the odds ratios (ORs) (95% CI) for  
267 an  $ABI \leq 1$ , as a dichotomous outcome, according to energy-adjusted consumption of total,  
268 virgin, and olive oil (quintiles) and olive pomace oil (tertiles). The ORs and their 95% CIs were  
269 calculated considering the lowest quintile as the reference category. A sensitivity analysis with  
270 ORs for an  $ABI \leq 0.9$  is presented in Table 2 of Supplementary files.

271 To control for potential confounding factors in logistic regression models, the results were  
272 adjusted for the same confounding factors as the multiple linear regression models. We also  
273 conducted tests of linear trend across increasing quintiles of exposure. Smoke variable was  
274 introduced as positive control to assess a well-known association with PAD.

275 Finally, we assessed correlations between total, virgin, olive oil and olive pomace oil  
276 consumption in the PREDIMED-Plus trial.  
277

## 278 3. Results

279

280 This study included 4,330 out of 6,874 participants recruited in the PREDIMED-Plus trial,  
281 according to previously defined exclusion criteria (Figure 1). The mean age of study subjects  
282 was 65 and 47.9% were women. Table 1 shows the baseline characteristics of the participants  
283 included according to energy-adjusted quintiles of total olive oil consumption. Participants in  
284 the highest category of total olive oil consumption had a higher total energy intake, higher  
285 adherence to the Mediterranean diet, higher fat intake (especially monounsaturated fatty acids),

286 lower consumption of meat, fish, and dairy products and a decrease in fruit, vegetables, cereals  
287 and legumes, respect to lowest category of total olive oil intake.

288 The results of correlation analyses between total, virgin, olive oil and olive pomace oil  
289 consumption are shown in Table 2. We observed a significant inverse correlation between  
290 virgin and olive oils consumption (-0.41). Correlations between all continuous traits considered  
291 as potential confounders are shown in Table 1 of Supplementary files.

292 The associations between energy-adjusted consumption of total, virgin, olive oil and olive  
293 pomace oil and ABI are shown in Table 3. The ABI was 0.014 points (95% CI: 0.002, 0.027)  
294 higher among participants in the highest category of total olive oil consumption compared to  
295 participants in the lowest consumption quintile in the fully-adjusted model (*p* for trend 0.010).  
296 Associations between specific categories types of olive oil, olive pomace oil and ABI were not  
297 statistically significant.

298 Table 4 shows the ORs (95% CI) between types categories of total, virgin, olive oil and olive  
299 pomace oil consumption and a low or borderline ABI (defined as  $ABI \leq 1$ ). Participants in Q5 of  
300 virgin olive oils intake showed a significantly lower odds of borderline ABI (0.73, 95% CI 0.56,  
301 0.97; *p* for trend 0.031), whereas participants in Q5 of olive oil (OR 1.43, 95% CI 1.07, 1.90; *p*  
302 for trend 0.114) or olive pomace oil (OR 1.22, 95% CI 1.00, 1.48; *p* for trend 0.050) showed a  
303 significantly higher odds of borderline ABI compared to participants in the Q1. When  $ABI \leq 0.9$   
304 was analyzed in a logistic model (Table 2-Supplementary data) any category or total olive oil  
305 intake were statistically significant.

306 In order to assess the robustness of our findings, we performed sensitivity analyses of the  
307 differences in mean ABI across categories of olive oil and olive pomace oil consumption from  
308 all recruitment centers included but removing those with missing values of ABI in the right or  
309 the left leg (Table 3-Supplementary files). We also conducted sensitivity analysis for total  
310 olive oil consumption (comparing extreme quintiles), after applying different energy limits  
311 (percentiles 1 and 99), from all recruitment centers and other analysis including participants  
312 with  $ABI \geq 1.4$ . We also conducted stratified analyses by sex (men and women), BMI ( $< 30$   
313  $kg/m^2$  or  $\geq 30$   $kg/m^2$ ), age ( $\leq 65$  or  $> 65$  years), baseline adherence to the Mediterranean diet ( $\leq 7$   
314 points vs  $\geq 8$  points), and baseline diabetes (Figure 2). These analyses supported the robustness  
315 of our main results.

316 We also analyzed the association between smoking habit and the ABI or an  $ABI \leq 1$  as a positive  
317 control. When compared to never smokers ( $n=1873$ ), smokers who quit  $> 5$  years ago  
318 ( $n=1586$ ) showed an ABI difference of -0.008 (-0.017, 0.000), smokers who quit  $< 5$  years  
319 ago ( $n=96$ ) an ABI difference of -0.030 (-0.054, -0.005) and current smokers ( $n=755$ ) an ABI  
320 difference of -0.032 (-0.043, -0.021) in multivariable adjusted models. Compared to never  
321 smokers, the OR of an  $ABI \leq 1$  was 1.32 (1.08, 1.61) for smokers who quit  $> 5$  years ago, 1.50  
322 (0.88, 2.57) for smokers who quit  $< 5$  years ago and 2.09 (1.66, 2.64) for current smokers in  
323 the multivariable adjusted models.

324

#### 325 4. Discussion

326

327 The results of this cross-sectional analysis of the PREDIMED-Plus trial showed a direct  
328 association between total olive oil consumption (including olive pomace oil) and ABI. In  
329 addition, virgin olive oils consumption was inversely associated with borderline ABI whereas  
330 olive oil and olive pomace oil consumption were directly associated with borderline ABI.  
331 ABI is a non-invasive, simple, and reliable diagnostic method used as a simple method to screen  
332 for PAD and to evaluate CV prognosis in the general population [27]. The range of normal ABI  
333 values is between 0.90 and 1.4. In fact, an ABI below 0.90 represents an independent marker of  
334 CV risk [28]. This threshold of  $\leq 0.90$  is based on studies reporting  $> 90\%$  sensitivity and  
335 specificity to detect PAD compared to angiography [29, 30]. Otherwise, with an  $ABI \geq 1.0$  used  
336 as a threshold for detecting PAD, sensitivities as high as 100% have been reported [28, 30].

337 Thus, ABI should be carefully interpreted according to *a priori* probability of PAD and values  
338 between 0.91 and 1.00 should be considered borderline [3]. In this study, our evaluation of the  
339 probability of an  $ABI \leq 1$  included all participants considered to be borderline. Total and virgin

340 olive oils consumption appeared to be inversely associated with the risk of an ABI  $\leq 1$  (OR 0.86  
341 and OR 0.73, respectively). However, olive pomace oil and olive oil consumption appeared to  
342 be associated with a higher odd of borderline ABI (OR 1.22, 95% CI 1.00, 1.48 and OR 1.43,  
343 95% CI 1.07, 1.90, respectively).

344 There is no clear association between the role of nutrition in preventing PAD [31]; although the  
345 Mediterranean diet may reduce the risk of PAD [32-34], more trials with an experimental design  
346 to confirm this protective effect are required. Regarding the consumption of extra-virgin olive  
347 oil –the main fat source of the Mediterranean diet– has been associated with beneficial effects  
348 on PAD [6, 34] and ~~the this~~ association may be related to several components of virgin olive  
349 oils. Indeed, the InCHIANTI study reported that increasing HDL cholesterol levels could exert  
350 some protective effect against PAD [33]. Considering that virgin olive oils increase HDL  
351 cholesterol levels in humans, as reported by the VOHF study [8], it could indirectly prevent  
352 PAD. Pedret *et al.* recently described the activity of the phenolic fraction of virgin olive oils in  
353 the HDL proteome because it may lead to the up-regulation of proteins related to cholesterol  
354 homeostasis, protection against oxidation, and blood coagulation [8]. The authors also reported  
355 the down-regulation of acute-phase response, lipid transport, and immune response [8]. Some  
356 studies have described the effects of virgin olive oils or its components in preventing CV  
357 disease [7-10], which could also be related to the potential protective effect of olive oil  
358 consumption against PAD.

359 Overall, our results suggest that a higher total olive oil consumption was associated with better  
360 values for the ABI but there was no significant association with borderline ABI used as a  
361 dichotomous variable ( $ABI \leq 1$ ). When we further addressed if consumption of specific olive oil  
362 categories was associated with ABI, we found significant association with virgin olive oils and  
363 olive pomace oil. Higher virgin olive oil consumption was significantly associated with a lower  
364 odds of borderline ABI, whereas olive oil consumption and olive pomace oil consumption were  
365 associated with a higher odds of borderline ABI compared to the lowest consumption category,  
366 with a statistically significant finding for olive pomace oil. It could be hypothesized that  
367 replacing more processed categories of olive oil and olive pomace oils by virgin olive oils may  
368 help improve the ABI. The observed results across the different olive oil categories could be  
369 due to minor compounds present in virgin olive oil, which are practically absent in refined olive  
370 oil and olive pomace oil [32, 33]. Given that the lipid profile is mainly the same in all categories  
371 of olive oils and olive pomace oil, this idea becomes coherent. In fact, minor compounds of  
372 virgin olive oils have been described to be responsible for different beneficial properties against  
373 several diseases, including CV disease prevention [7, 9, 34-36]. Contrarily, olive pomace oil  
374 loses the majority of minor compounds and some chemical contaminants could be present in it  
375 as a result of manufacturing processes [37]. Some of these contaminants have been described as  
376 harmful compounds [38]. Nevertheless, we have to notice that differences between categories  
377 of olive oils and olive pomace oils may be due not only to their composition, but also to their  
378 differential culinary use. It is known that the fatty acid profile of olive pomace oil is similar to  
379 the fatty acid profile of virgin olive oils, but it is generally used for frying foods, including  
380 ultraprocessed foods, which have been reported to increase CV risk [39]. These hypotheses  
381 could explain the differences observed between extreme quintiles and tertiles of consumption in  
382 virgin olive oils as compared to olive pomace oil or refined olive oil in their association with the  
383 ABI index; however, prospective studies are needed to corroborate these associations.  
384 ~~Currently, virgin olive oils are suggested to be beneficial against CV risk [38-40] and, thus, they~~  
385 ~~could be more useful to prevent an  $ABI < 1$  than other types of olive oils. Ultimately, they may~~  
386 ~~eventually be beneficial against PAD. Nevertheless, there is a need for more experimental studies~~  
387 ~~to directly relate olive oil consumption to the prevention of PAD and to differentiate between~~  
388 ~~the consumption of olive oil types and the risk of PAD.~~

389 This study has several strengths, including the large sample size, inclusion of both men and  
390 women in the trial, adjustment for a wide array of potential confounders, and the use of  
391 validated tools to assess information. However, ~~its~~ we acknowledge some limitations such as  
392 ~~include~~ its cross-sectional design, which does not allow the establishment of any causal  
393 association between olive oil consumption and ABI. In addition, the age of the participants was  
394 limited to 55–75 years and all of our participants had metabolic syndrome; therefore,

395 generalization of the results to other age groups may be limited. Furthermore, as this is not a  
396 prospective study, results should be treated carefully and potential causal inferences need to be  
397 confirmed by future prospective studies. Also, olive oil consumption was addressed only once.  
398 The food-frequency questionnaire covered one year of exposure over the previous year. The  
399 implicit assumption is that past year consumption tends to be correlated with lifetime  
400 consumption. However, we admit that appraising a longer exposure to olive oil may be  
401 important to fully disentangle the association between olive oil consumption and ABI or PAD.  
402 Finally, we were not able to distinguish between the minor components of the different  
403 categories of olive oils and olive pomace oils. Concentration of minor components does not  
404 only depend on olive oil category but also on other characteristics such as its origin, olive  
405 variety or ripeness of the olives from which olive oil was extracted [40].  
406 In conclusion, the main findings of the current study suggest a direct association between total  
407 olive oil consumption and a better ABI. Moreover, consumption of virgin olive oils could be  
408 useful to promote a better ABI instead other olive oils categories or olive pomace oils.  
409 ~~Moreover, consumption of virgin olive oils may be associated with a lower probability of~~  
410 ~~having a borderline ABI, while olive pomace oil consumption was associated with a higher~~  
411 ~~probability of having an ABI < 1.~~ Nevertheless, longitudinal studies are needed to confirm these  
412 results and to definitively establish the role of total olive oil consumption, and different types  
413 categories of olive oil and olive pomace oils consumption in the development of PAD.

414

## 415 5. Conflicts of Interest

416 Jordi Salas-Salvadó reports serving on the board of the International Nut and Dried Fruit  
417 Council, the Danone International Institute, and the Eroski Foundation and receiving grant  
418 support from these entities through his institution. He also reports serving on the Executive  
419 Committee of the Instituto Danone Spain. He has also received the olive oil and nuts used in  
420 PREDIMED and PREDIMED-plus studies from the Patrimonio Comunal Olivarero, Spain; La  
421 Morella Nuts, Spain; and Borges S.A., Spain. He reports receiving consulting fees or travel  
422 expenses from Danone; the California Walnut Commission, the Eroski Foundation, the Instituto  
423 Danone - Spain, Nuts for Life, the Australian Nut Industry Council, Nestlé, Abbot Laboratories,  
424 and Font Vella Lanjarón.

425 Dr Estruch reported receiving grants from Instituto de Salud Carlos III and olive oil for the trial  
426 from Fundacion Patrimonio Comunal Olivarero during the conduct of the study and personal  
427 fees from Brewers of Europe, Fundación Cerveza y Salud, Interprofesional del Aceite de Oliva,  
428 Instituto Cervantes, Instituto Cervantes, Pernaud Richar, Fundación Dieta Mediterránea, Wine  
429 and Culinary International Forum; nonfinancial support from Sociedad Española de Nutrición  
430 and Fundación Bosch y Gimpera; and grants from Uriach Laboratories outside the submitted  
431 work.

432

## 433 6. Financial support

434

435 The PREDIMED-Plus trial was supported by the official funding agency for biomedical  
436 research of the Spanish government, ISCIII, through the Fondo de Investigación para la Salud  
437 (FIS), which is co-funded by the European Regional Development Fund (five coordinated FIS  
438 projects led by J.S.-S. and J.Vid., including the following projects: PI13/00673, PI13/00492,  
439 PI13/00272, PI13/01123, PI13/00462, PI13/00233, PI13/02184, PI13/00728, PI13/01090,  
440 PI13/01056, PI14/01722, PI14/00636, PI14/00618, PI14/00696, PI14/01206, PI14/01919,  
441 PI14/00853, PI14/01374, PI14/00972, PI14/00728, PI14/01471, PI16/00473, PI16/00662,  
442 PI16/01873, PI16/01094, PI16/00501, PI16/00533, PI16/00381, PI16/00366, PI16/01522,  
443 PI16/01120, PI17/00764, PI17/01183, PI17/00855, PI17/01347, PI17/00525, PI17/01827,  
444 PI17/00532, PI17/00215, PI17/01441, PI17/00508, PI17/01732, PI17/00926, PI19/00957,  
445 PI19/00386, PI19/00309, PI19/01032, PI19/00576, PI19/00017, PI19/01226, PI19/00781,  
446 PI19/01560, and PI19/01332), the Especial Action Project entitled: Implementación y  
447 evaluación de una intervención intensiva sobre la actividad física Cohorte PREDIMED-Plus  
448 grant to J.S.-S., the European Research Council (Advanced Research Grant 2013–2018,  
449 340918) to M.Á.M.-G., the Recercaixa Grant to J.S.-S. (2013ACUP00194), a grant from the

450 Generalitat Valenciana (APOSTD/2019/136 to RB), grants from the Consejería de Salud de la  
451 Junta de Andalucía (PI0458/2013, PS0358/2016, and PI0137/2018), a grant from the Generalitat  
452 Valenciana (PROMETEO/2017/017), a SEMERGEN Grant, EU-COST Action CA16112, a  
453 grant of support to research groups no. 35/2011 from the Balearic Islands Government, Grants  
454 from Balearic Islands Health Research Institute (IDISBA), funds from the European Regional  
455 Development Fund (CIBEROBN CB06/03 and CB12/03) and from the European Commission  
456 (EAT2BENICE\_H2020\_SFS2016). PH-A is supported by a postdoctoral fellowship (Juan de la  
457 Cierva-Formación, FJCI-2017-32205). GG-M is supported by a grant of Diputación de Jaén.  
458 The funding sponsors had no role in the design of the study, in the collection, analyses, or  
459 interpretation of the data; in the writing of the manuscript, and in the decision to publish the  
460 results.

461

## 462 **7. Authors contributions**

463

464 CS-Q and ET conducted the statistical analyses and drafted the article. ET, JJG and MAM-G  
465 made substantial contributions to the conception and design of the work. All authors contributed  
466 substantially in the acquisition of data or analysis and interpretation of data. All authors revised  
467 the article critically for important intellectual content. All authors approved the final version to  
468 be published.

469

470

471

## 471 **8. Acknowledgments**

472 The authors especially thank the PREDIMED-Plus participants for their enthusiastic  
473 collaboration, the PREDIMED-Plus personnel for outstanding support, and the personnel of all  
474 associated primary care centres for their exceptional effort. CIBEROBN, CIBERESP and  
475 CIBERDEM are initiatives of Instituto de Salud Carlos III, Spain.

476

477

## 478 **9. References**

479

480 1. Gerhard-Herman, MD.; Gornik, H.L.; Barrett, C.; Barshes, N.R.; Corriere, M.A.; Drachman, DE.;  
481 Fleisher, L.A.; Fowkes, FGR.; Hamburg, N.M. Kinlay, S.; et al. 2016 AHA/ACC Guideline on the  
482 Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary.  
483 *Circulation*, 2017, 135, e-686-e725.

484

485 2. ~~5~~ European Stroke Organisation, Tendera, M.; Aboyans, V.; Bartelink, ML.; Baumgartner, I.;  
486 Clement, D. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document  
487 covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower  
488 extremity arteries: The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the  
489 European Society of Cardiology (ESC). *Eur Heart J* 2011, 32, 2851-2906.

490

491 3. ~~6~~ Aboyans, V.; Criqui, M.H.; Abraham, P.; Allison, M.A.; Creager, MA.; Diehm, C. Measurement and  
492 interpretation of the ankle-brachial index: A scientific statement from the American Heart Association.  
493 *Circulation*, 2012, 126, 2890 -2909.

494

495 4. ~~7~~ Dachun, X.; Jue, L.; Liling, Z.; Yawei, X.; Dayi, H.; Pagoto, S.L. Sensitivity and specificity of the  
496 ankle-brachial index to diagnose peripheral artery disease: A structured review. *Vasc Med* 2010, 15, 361-  
497 369.

498

499 5. ~~8~~ Potier, L.; Abi Khalil, C.; Mohammedi, K.; Roussel, R. Use and utility of ankle brachial index in  
500 patients with diabetes. *Eur J Vasc Endovasc Surg*. 2011, 41(1), 110-116.

501

502 6. ~~9~~ Ramirez-Tortosa, M.C.; Urbano, G.; López-Jurado, M.; Nestares, T.; Gomez, M.C.; Mir, A.; Ros,  
503 E.; Mataix, J.; Gil, A. Extra-virgin olive oil increases the resistance of LDL to oxidation more than  
504 refined olive oil in free-living men with peripheral vascular disease. *J Nutr*. 1999, 129(12), 2177-2183.

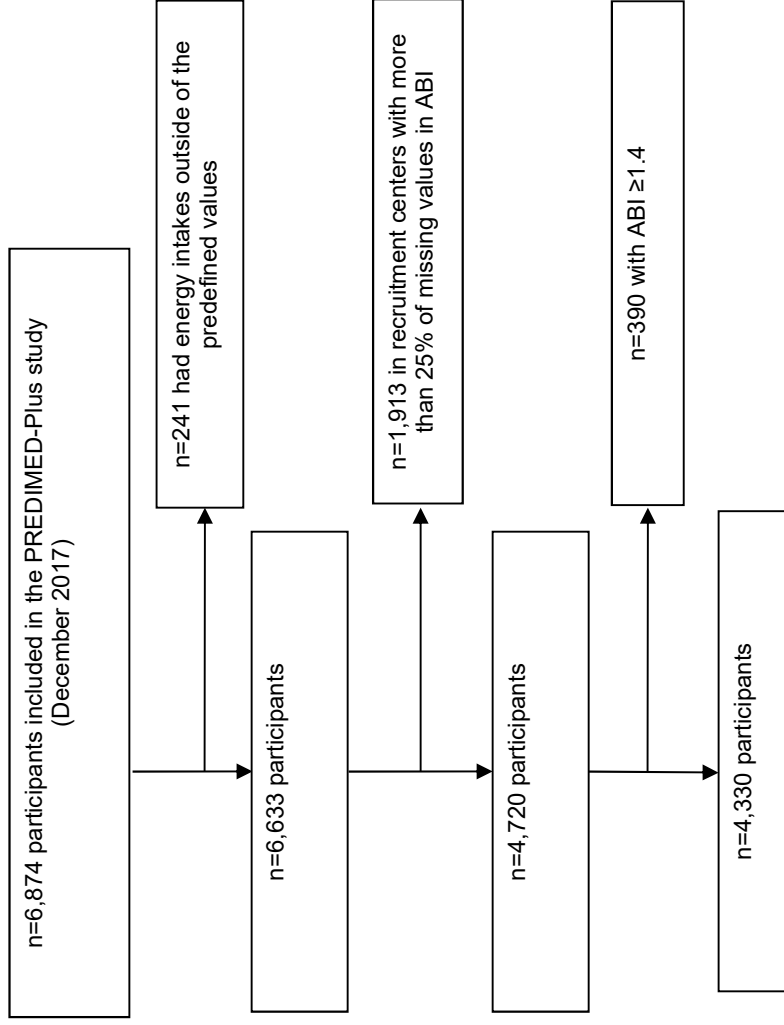
505

- 506 7. ~~40~~. Covas, M.; Nyssönen, K.; Poulsen, HE.; Kaikkonen, J.; Zunft, H-JF.; Kiesewetter, H. The effect  
507 of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann Intern Med.* 2006, 145,  
508 333-341.
- 509
- 510 8. ~~44~~. Pedret, A.; Catalán, U.; Fernández-Castillejo, S.; Farràs, M.; Valls, RM.; Rubió, L.; Canela, N.;  
511 Aragonés, G.; Romeu, M.; Castañer, O.; de la Torre, R.; Covas, M.; Fitó, M.; Motilva, M.J.; Solà, R.  
512 Impact of Virgin Olive Oil and Phenol-Enriched Virgin Olive Oils on the HDL Proteome in  
513 Hypercholesterolemic Subjects: A Double Blind, Randomized, Controlled, Cross-Over Clinical Trial  
514 (VOHF Study). *PLoS One.* 2015, 10(6), e0129160.
- 515
- 516 9. ~~42~~. Widmer, R.J.; Freund, M.A.; Flammer, A.J.; Sexton, J.; Lennon, R.; Romani, A.; Mulinacci, N.;  
517 Vincer, F.F.; Lerman, L.O.; Lerman, A. Beneficial effects of polyphenol-rich Olive Oil in patients with  
518 early atherosclerosis. *Eur J Nutr.* 2013, 52(3): 1223-1231.
- 519
- 520 10. ~~43~~. Gaforio JJ, Visioli F, Alarcón-de-la-Lastra C, Castañer O, Delgado-Rodríguez M, Fitó M,  
521 Hernández AF, Huertas JR, Martínez-González MA, Menendez JA, Osada J, Papadaki A, Parrón T,  
522 Pereira JE, Rosillo MA, Sánchez-Quesada C, Schwingshackl L, Toledo E, Tsatsakis AM. Virgin Olive  
523 Oil and Health: Summary of the III International Conference on Virgin Olive Oil and Health Consensus  
524 Report, JAEN (Spain) 2018. *Nutrients.* 2019, 11(9), E2039.
- 525
- 526 11. Guasch-Ferré, M.; Liu, G.; Li, Y.; Sampson, L.; Manson, JE.; Salas-Salvadó, J.; Martínez-González,  
527 MA.; Stampfer, MJ.; Willett, WC.; Sun, Q.; Hu, FB. Olive Oil Consumption and Cardiovascular Risk in  
528 U.S. Adults. *J Am Coll Cardiol,* 2020, 75(15), 1729-1739.
- 529
- 530 12. ~~27~~. Ruiz-Canela, M.; Martínez-González, M.A. Lifestyle and Dietary Risk Factors for Peripheral  
531 Artery Disease. *Circulation Journal,* 2014, 78, 553-559.
- 532
- 533 13. ~~28~~. Antonelli-Incalzi, R.; Pedone, C.; McDermott, M.M.; Bandinelli, S.; Miniati, B.; Molino Lova, R.;  
534 Lauretani, F.; Ferruccio, L. Association between nutrient intake and peripheral artery disease: Results  
535 from the InCHIANTI study. *Atherosclerosis.* 2006, 186(1), 200-206.
- 536
- 537 14. ~~29~~. Ruiz-Canela, M.; Estruch, R.; Corella, D.; Salas-Salvadó, J.; Martínez-González, MA. Association  
538 of Mediterranean Diet With Peripheral Artery Disease: The PREDIMED Randomized Trial. *JAMA,*  
539 2014, 311, 4, 415-416.
- 540
- 541 15. ~~40~~. Estruch R.; Ros E.; Salas-Salvadó J.; Covas MI.; Corella D.; Arós F.; Gómez-Gracia E.; Ruiz-  
542 Gutiérrez V.; Fiol M.; Lapetra J.; *et al.* Primary Prevention of Cardiovascular Disease with a  
543 Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med.* 2018, 378, 25,  
544 e34.
- 545
- 546 16. ~~39~~. Guasch-Ferré M.; Hu FB.; Martínez-González MA.; Fitó M.; Bulló M.; Estruch R.; Ros E.;  
547 Corella D.; Recondo J.; Gómez-Gracia E.; *et al.* Olive oil intake and risk of cardiovascular disease and  
548 mortality in the PREDIMED Study. *BMC Med.* 2014,12:78.
- 549
- 550 17. Ruiz-Canela M. and Martínez-González M.A. Olive oil in the primary prevention of cardiovascular  
551 disease. *Maturitas.* 2011, 68, 3, 245-250.
- 552
- 553 18. ~~44~~. Martínez-González, MA.; Buil-Cosiales, P.; Corella, D.; Bulló, M.; Fitó, M.; Vioque, J.;  
554 Romaguera, D.; Martínez JA.; Wärnberg, J.; López-Miranda, J. *et al.* Cohort Profile: Design and methods  
555 of the PREDIMED-Plus randomized trial. *Int J Epidemiol.* 2018, doi: 10.1093/ije/dyy225.
- 556
- 557 19. ~~45~~. Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart,  
558 J.C.; James, W.P.; Loria, C.M.; Smith, S.C., Jr. Harmonizing the metabolic syndrome: A joint interim  
559 statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National  
560 Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International  
561 Circulation 2009, 120, 1640-1645.
- 562 20. ~~46~~. Willett, W. *Nutritional Epidemiology.* 3rd ed.: Oxford University Press; 2012.

- 563 21. **17.** Commission Implementing Regulation (EU) N° 29/2012 of 13 January 2012 on marketing  
564 standards for olive oil. <https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32012R0029>.  
565 Accessed on February 5th, 2020.
- 566 22. **18.** Fernández-Ballart, J.D.; Piñol, J.L.; Zazpe, I.; Corella, D.; Carrasco, P.; Toledo, E.; Perez-Bauer,  
567 M.; Martínez-González, M.A.; Salas-Salvadó, J.; Martí-Moreno, J.M. Relative validity of a semi-  
568 quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *Br. J. Nutr.*  
569 2010, 103, 1808-1816.
- 570 23. **19.** Elosua, R.; Garcia, M.; Aguilar, A.; Molina, L.; Covas, M.I.; Marrugat, J. Validation of the  
571 Minnesota Leisure Time Physical Activity Questionnaire in Spanish Women. Investigators of the  
572 MARATHOM Group. *Med. Sci. Sports Exerc.* 2000, 32, 1431-1437.  
573
- 574 24. **20.** Elosua, R.; Marrugat, J.; Molina, L.; Pons, S.; Pujol, E. Validation of the Minnesota Leisure Time  
575 Physical Activity Questionnaire in Spanish men. The MARATHOM Investigators. *Am. J. Epidemiol.*  
576 1994, 139, 1197-1209.  
577
- 578 25. **21.** Ainsworth, B.E.; Haskell, W.L.; Herrmann, S.D.; Meckes, N.; Bassett, D.R.; Tudor-Locke, C.;  
579 Greer, J.L.; Vezina, J.; Whitt-Glover, M.C.; Leon, A.S. 2011 compendium of physical activities: A  
580 second update of codes and MET values. *Med. Sci. Sports Exerc.* 2011, 43, 1575-1581.  
581
- 582 26. **22.** Galilea-Zabalza, I.; Buil-Cosiales, P.; Salas-Salvadó, J.; Toledo, E.; Ortega-Azorín, C.; Díez-  
583 Espino, J.; Vázquez-Ruiz, Z.; Zomeño, MD.; Vioque, J.; Martínez, JA.; *et al.* Mediterranean diet and  
584 quality of life: Baseline cross-sectional analysis of the PREDIMED-PLUS trial. *Plos One.* 2018, 13, 6,  
585 e0198974.  
586
- 587 27. **23.** Rac-Albu, M.; Iliuta, L.; Guberna, S.M.; Sinescu, C.; The Role of Ankle-Brachial Index for  
588 Predicting Peripheral Arterial Disease. *MAEDICA* 2014, 9(3), 295-302.  
589
- 590 28. **24.** Carter, S.A. Indirect systolic pressures and pulse waves in arterial occlusive diseases of the lower  
591 extremities. *Circulation.* 1968, 37, 624-637.  
592
- 593 29. **25.** Yao, S.T.; Hobbs, J.T.; Irvine, W.T. Ankle systolic pressure measurements in arterial disease  
594 affecting the lower extremities. *Br J Surg.* 1969, 56, 676-679.  
595
- 596 30. **26.** Baxter, GM.; Polak, J.F. Lower limb colour flow imaging: a comparison with ankle: brachial  
597 measurements and angiography. *Clin Radiol.* 1993, 47, 91-95.  
598
- 599 **31. Delaney CL.; Smale, MK.; Miller, MD. Nutritional Considerations for Peripheral Arterial Disease: A**  
600 **Narrative Review. *Nutrients.* 2019, 11(6):1219.**  
601
- 602 32. Cert, A.; Moreda, W.; Perez-Camino, M.C. Chromatographic analysis of minor constituents in  
603 vegetable oils. *J. Chromatogr. A*, 2000, 881, 1-2, 131-148.  
604
- 605 33. Ambrosewicz-Walacik, M.; Tańska, M.; Rotkiewicz, D. Comparison of the quality of two classes of  
606 olive oil: Extra virgin and refined oil. *Polish Journal of Natural Science.* 2012, 27(2), 229-241.  
607
- 608 34. Lou-Bonafonte, J.M.; Arnal, C.; Navarro, M.A.; Osada, J. Efficacy of Bioactive Compounds from  
609 Extra Virgin Olive Oil to Modulate Atherosclerosis Development. *Mol. Nutr. Food Res.* 2012, 56, 1043-  
610 1057.  
611
- 612 35. Storniolo, C.E.; Rosello-Catafau, J.; Pinto, X.; Mitjavila, M.T.; Moreno, J.J. Polyphenol Fraction of  
613 Extra Virgin Olive Oil Protects Against Endothelial Dysfunction Induced by High Glucose and Free Fatty  
614 Acids through Modulation of Nitric Oxide and Endothelin-1. *Redox Biol.* 2014, 2, 971-977.  
615
- 616 36. Bullon, P.; Quiles, J.L.; Morillo, J.M.; Rubini, C.; Goteri, G.; Granados-Principal, S.; Battino, M.;  
617 Ramirez-Tortosa, M. Gingival Vascular Damage in Atherosclerotic Rabbits: Hydroxytyrosol and  
618 Squalene Benefits. *Food Chem. Toxicol.* 2009, 47, 2327-2331.  
619

- 620 37. Guillén MD.; Sopelana P.; Palencia G. Polycyclic Aromatic Hydrocarbons and Olive Pomace Oil. J  
621 Agric Food Chem, 2004, 52, 2123-2132.  
622
- 623 38. Kim KH.; Jahan SA.; Kabir E.; Brown RJ. A review of airborne polycyclic aromatic hydrocarbons  
624 (PAHs) and their human health effects. Environ Int. 2013, 60, 71-80.  
625
- 626 39. Srour B.; Fezeu LK.; Kesse-Guyot E.; Allès B.; Méjean C.; Andrianasolo RM.; Chazelas E.;  
627 Deschasaux M.; Hercberg S.; Galan P.; *et al.* Ultra-processed food intake and risk of cardiovascular  
628 disease: prospective cohort study (NutriNet-Santé). BMJ. 2019, 365, 11451.  
629
- 630 40. Allouche, Y.; Jimenez, A.; Uceda, M.; Aguilera, M.P.; Gaforio, J.J.; Beltran, G. Triterpenic content and  
631 chemometric analysis of virgin olive oils from forty olive cultivars. J. Agric. Food Chem., 2009, 57, 9,  
632 3604-3610.

**Figure 1.** Flow chart of participants recruited in the PREDIMED-Plus project.



ABI = ankle-brachial pressure index. Total energy intakes were within predefined limits (800–4,000 Kcal/day for men, and 500–3,500 Kcal/day for women).

**Table 1.** Baseline characteristics of 4,330 participants in the PREDIMED-Plus study according to quintiles of total olive oil consumption.

	Quintiles of total olive oil consumption				
	Q1	Q2	Q3	Q4	Q5
<b>N</b>	866	866	866	866	866
<b>Median total olive oil consumption (g/day)<sup>a</sup></b>	30.9 (6.2)	41.4 (3.4)	56.1 (2.7)	62.2 (1.5)	72.0 (8.0)
<b>Age (years)</b>	65 (5)	66 (5)	65 (5)	65 (5)	65 (5)
<b>Women (%)</b>	50.5	53.8	50.0	39.7	45.6
<b>Waist circumference (cm)</b>	109 (10)	108 (9)	107 (9)	107 (9)	108 (10)
<b>Height (cm)</b>	163.2 (9.2)	161.9 (9.4)	162.8 (9.3)	164.1 (9.2)	162.8 (9.3)
<b>BMI (kg/m<sup>2</sup>)</b>	32.8 (3.5)	32.7 (3.4)	32.4 (3.4)	32.1 (3.3)	32.8 (3.5)
<b>Systolic blood pressure (mm Hg)</b>	136.3 (16.3)	137.2 (16.9)	139.1 (15.1)	139.8 (15.5)	139.7 (16.5)
<b>Diastolic blood pressure (mm Hg)</b>	81.9 (9.3)	81.8 (9.9)	83.0 (8.8)	82.6 (8.7)	82.1 (9.3)
<b>Leisure-time physical activity (METs-min/week)</b>	2451 (2345)	2628 (2369)	2536 (2404)	2695 (2258)	2605 (2458)
<b>Smoking (%)</b>					
Former smoker	39.4	40.3	43.0	47.0	46.3
Current smoker	12.6	12.4	12.9	14.1	13.5
<b>Educational level</b>					
Primary or less	53.9	51.8	49.3	44.8	46.4
Secondary	26.2	28.1	27.6	30.5	27.7
University	18.8	18.9	22.3	24.1	24.9
<b>Family history of CHD<sup>b</sup> (%)</b>	43.0	42.6	42.1	38.7	43.2
<b>Self-reported diabetes (%)</b>	25.9	26.0	21.8	22.5	27.3
<b>Self-reported hypertension (%)</b>	93.3	92.8	93.4	92.1	92.3
<b>Self-reported medication use</b>					
Diuretics (%)	0.4	0.5	0.4	0.2	0.4
Insulin and other glucose-lowering agents (%)	45.4	46.5	34.2	37.5	47.3

<b>Lipid lowering medication (%)</b>	52.2	52.4	48.7	47.1	50.5
<b>Blood pressure-lowering drugs (%)</b>	79.0	78.9	77.8	75.8	78.1
<b>Adherence to energy-reduced Mediterranean diet (0-16 score)</b>	7.5 (2.5)	7.9 (2.6)	7.8 (2.6)	7.9 (2.6)	8.2 (2.6)
<b>Total energy intake (kcal/day)</b>	2489 (579)	2007 (509)	2775 (463)	2275 (237)	2316 (602)
<b><i>Macronutrient intake</i></b>					
<b>Carbohydrate intake (% energy)</b>	45.1 (6.7)	42.5 (6.4)	40.7 (5.5)	37.9 (5.3)	35.2 (5.5)
<b>Protein intake (% energy)</b>	17.1 (2.9)	17.8 (3.0)	15.9 (2.4)	16.2 (2.4)	15.5 (2.4)
<b>Fat intake (% energy)</b>	34.9 (5.9)	36.9 (5.2)	40.0 (4.7)	42.4 (4.7)	46.2 (5)
<b>Monounsaturated fatty acids (% energy)</b>	16.3 (3.7)	18.5 (3.0)	20.9 (2.8)	23.1 (3.0)	26.0 (3.3)
<b>Polyunsaturated fatty acids (% energy)</b>	6.4 (2.2)	6.0 (1.9)	6.3 (1.7)	6.5 (1.6)	6.8 (1.5)
<b>Saturated fatty acids (% energy)</b>	9.8 (2.4)	9.6 (2.1)	10.0 (1.8)	10.0 (1.8)	10.3 (1.8)
<b>Alcohol intake (g/day)</b>	11.1 (15.6)	8.4 (12.8)	14.1 (17.4)	11.5 (14.0)	10.8 (14.6)
<b>Fruit consumption (g/day)</b>	394 (225)	333 (204)	392 (207)	344 (174)	341 (187)
<b>Vegetable consumption (g/day)</b>	340 (156)	316 (136)	335 (137)	303 (115)	305 (130)
<b>Cereal consumption (g/day)</b>	162 (82)	129 (70)	185 (86)	142 (63)	128 (67)
<b>Legume consumption (g/day)</b>	23.8 (13.1)	19.8 (10.7)	21.7 (11.9)	18.8 (8.3)	19.6 (10.9)
<b>Meat product consumption (g/day)</b>	149 (66)	132 (55)	165 (60)	144 (48)	135 (53)
<b>Fish product consumption (g/day)</b>	100.1 (52.8)	88.8 (45.2)	108.5 (45.7)	98.9 (43.0)	98.1 (45.3)
<b>Dairy product consumption (g/day)</b>	405 (220)	328 (202)	380 (217)	303 (169)	293 (181)
<b><i>Micronutrient intake</i></b>					
<b>Vitamin D intake (mg/day)</b>	6.3 (3.4)	5.4 (3.3)	6.7 (3.5)	6.0 (3.3)	6.1 (3.4)
<b>Folic acid intake (mg/day)</b>	384 (113)	327 (98)	382 (95)	328 (75)	320 (99)

Values are expressed as mean (SD), unless otherwise stated

METs: metabolic equivalents

CHD: coronary heart disease

<sup>a</sup> Energy-adjusted consumption

<sup>b</sup> Information from parents and siblings

**Table 2.** Correlations between ~~total~~ virgin, olive oil and olive pomace oil consumption in the PREDIMED-Plus trial. (\*)  $p < 0.05$ .

	Virgin olive oil consumption	Olive oil consumption	Olive pomace oil consumption
Virgin olive oil consumption		-0.41*	-0.03
Olive oil consumption			-0.14*

**Table 3.** Differences in ankle-brachial indexes across categories of energy-adjusted total, virgin, olive oil, olive pomace oil consumption in the PREDIMED-Plus trial. n=4,330

<i>Quintiles of total olive oil consumption</i>		<i>Q1</i>	<i>Q2</i>	<i>Q3</i>	<i>Q4</i>	<i>Q5</i>	<i>p for trend</i>
Median total olive oil consumption (g/day)		31	41	56	62	72	
	<i>N</i>	866	866	866	866	866	
Multivariable Model 1		0 (ref)	0.002 (-0.009, 0.013)	0.010 (-0.002, 0.022)	0.010 (-0.002, 0.022)	0.014 (0.001, 0.026)	0.011
Multivariable Model 2		0 (ref)	0.002 (-0.010, 0.013)	0.010 (-0.002, 0.022)	0.010 (-0.002, 0.022)	0.014 (0.001, 0.026)	0.011
Multivariable Model 3		0 (ref)	0.002 (-0.010, 0.014)	0.010 (-0.002, 0.022)	0.010 (-0.003, 0.022)	0.014 (0.002, 0.027)	0.010
<i>Quintiles of virgin olive oil consumption</i>		<i>Q1</i>	<i>Q2</i>	<i>Q3</i>	<i>Q4</i>	<i>Q5</i>	
Median virgin olive oil consumption (g/day)		15	35	44	61	68	
	<i>N</i>	866	866	866	866	866	
Multivariable Model 1		0 (ref)	-0.003 (-0.014, 0.008)	0.001 (-0.011, 0.013)	0.003 (-0.010, 0.015)	0.010 (-0.003, 0.022)	0.114
Multivariable Model 2		0 (ref)	-0.003 (-0.014, 0.008)	0.001 (-0.011, 0.013)	0.003 (-0.009, 0.015)	0.010 (-0.003, 0.022)	0.110
Multivariable Model 3		0 (ref)	-0.002 (-0.014, 0.009)	0.002 (-0.010, 0.014)	0.002 (-0.010, 0.014)	0.010 (-0.002, 0.022)	0.127
<i>Quintiles of olive oil consumption</i>		<i>Q1</i>	<i>Q2</i>	<i>Q3</i>	<i>Q4</i>	<i>Q5</i>	
Median olive oil consumption (g/day)		3	4	4	5	30	
	<i>N</i>	866	866	866	866	866	
Multivariable Model 1		0 (ref)	0.002 (-0.009, 0.013)	-0.004 (-0.015, 0.007)	-0.004 (-0.015, 0.008)	0.0003 (-0.011, 0.012)	0.743
Multivariable Model 2		0 (ref)	0.002 (-0.009, 0.013)	-0.004 (-0.015, 0.007)	-0.004 (-0.015, 0.008)	0.0003 (-0.011, 0.012)	0.743
Multivariable Model 3		0 (ref)	-0.002 (-0.015, 0.010)	-0.010 (-0.025, 0.005)	-0.011 (-0.029, 0.006)	-0.003 (-0.017, 0.010)	0.698
<i>Tertiles of olive pomace oil consumption</i>		<i>T1</i>	<i>T2</i>	<i>T3</i>			
Median olive pomace oil consumption (g/day)		0.003	0.02	0.03			
	<i>N</i>	1,444	1,443	1,443			
Multivariable Model 1		0 (ref)	-0.003 (-0.012, 0.007)	0.0003 (-0.008, 0.009)			0.960
Multivariable Model 2		0 (ref)	-0.003 (-0.012, 0.007)	0.0003 (-0.008, 0.009)			0.959
Multivariable Model 3		0 (ref)	-0.003 (-0.012, 0.007)	0.0002 (-0.009, 0.009)			0.980

Results from multivariable linear regression models. Q, quintile; T, tertile.

**Multivariable Model 1:** adjusted for age (continuous), recruitment center, and sex.

**Multivariable Model 2:** Model 1 additionally adjusted for BMI (tertiles).

**Multivariable Model 3:** Model 2 additionally adjusted for waist circumference (continuous); self-reported prevalent diabetes (yes/no); self-reported hypertension (yes/no); adherence to a Mediterranean diet (score 0–16); physical activity (metabolic equivalents-min/ week) (quintiles); educational level (primary school, secondary school, university); blood pressure-lowering drug use (yes/no); lipid-lowering medication use

(yes/no); diuretics use (yes/no); insulin and oral antidiabetic agents use (yes/no); vitamin D intake (tertile); folic acid intake (continuous); family history of coronary heart disease (yes/no); smoking (never, current, former >5 years, former <5 years); and total energy intake (continuous).

**Table 4.** Odds ratios (95% CI) for ankle-brachial index (ABI)  $\leq 1$  across categories of energy-adjusted total, virgin, olive oil, virgin, olive oil, olive pomace oil consumption in the PREDIMED-Plus trial.

		Odds Ratio (95% CI)					<i>p</i> for trend
		Q1	Q2	Q3	Q4	Q5	
<b>Quintiles of total olive oil consumption</b>							
Range of total olive oil consumption (g/day)		(< 36.63)	(36.63, 49.32)	(49.32, 59.53)	(59.53, 64.93)	(64.93, 119.89)	
	N	866	866	866	866	866	
	Multivariable Model 1	1 (ref)	1.04 (0.82, 1.33)	0.97 (0.75, 1.26)	1.00 (0.77, 1.29)	0.86 (0.66, 1.12)	0.258
	Multivariable Model 2	1 (ref)	1.04 (0.82, 1.33)	0.98 (0.76, 1.26)	1.00 (0.77, 1.30)	0.86 (0.66, 1.12)	0.253
	Multivariable Model 3	1 (ref)	1.04 (0.81, 1.34)	0.99 (0.76, 1.29)	1.01 (0.77, 1.32)	0.86 (0.65, 1.13)	0.278
<b>Quintiles of virgin olive oil consumption</b>							
Range of virgin olive oil consumption (g/day)		(< 25.91)	(25.91, 38.68)	(38.68, 57.68)	(57.68, 63.49)	(63.49, 92.62)	
	N	866	866	866	866	866	
	Multivariable Model 1	1 (ref)	0.93 (0.74, 1.18)	0.95 (0.74, 1.21)	0.83 (0.64, 1.08)	0.74 (0.56, 0.96)	0.022
	Multivariable Model 2	1 (ref)	0.94 (0.74, 1.19)	0.96 (0.75, 1.22)	0.83 (0.64, 1.08)	0.74 (0.56, 0.96)	0.022
	Multivariable Model 3	1 (ref)	0.92, (0.72, 1.17)	0.94 (0.73, 1.20)	0.84 (0.65, 1.10)	0.73 (0.56, 0.97)	0.031
<b>Quintiles of olive oil consumption</b>							
Range of olive oil consumption (g/day)		(< 3.15)	(3.15, 3.90)	(3.90, 4.63)	(4.63, 15.52)	(15.52, 74.66)	
	N	866	866	866	866	866	
	Multivariable Model 1	1 (ref)	0.98 (0.76, 1.26)	1.21 (0.95, 1.56)	1.16 (0.90, 1.50)	1.28 (0.99, 1.65)	0.084
	Multivariable Model 2	1 (ref)	0.98 (0.76, 1.26)	1.21 (0.95, 1.56)	1.15 (0.89, 1.49)	1.27 (0.99, 1.64)	0.090
	Multivariable Model 3	1 (ref)	1.10 (0.83, 1.46)	1.46 (1.06, 2.03)	1.45 (1.00, 2.10)	1.43 (1.07, 1.90)	0.114
<b>Teriles of olive pomace oil consumption</b>							
Range of olive pomace oil consumption (g/day)		(< 0.01)	(0.01, 0.02)	(0.02, 49.99)			
	N	1,444	1,443	1,443			
	Multivariable Model 1	1 (ref)	1.18 (0.96, 1.46)	1.22 (1.00, 1.47)			0.045
	Multivariable Model 2	1 (ref)	1.18 (0.96, 1.45)	1.21 (1.00, 1.47)			0.047
	Multivariable Model 3	1 (ref)	1.18 (0.96, 1.46)	1.22 (1.00, 1.48)			0.050

Results from logistic models. Q, quintile; T, tertile.

**Logistic Model 1:** adjusted for age (continuous), recruitment center, and sex.

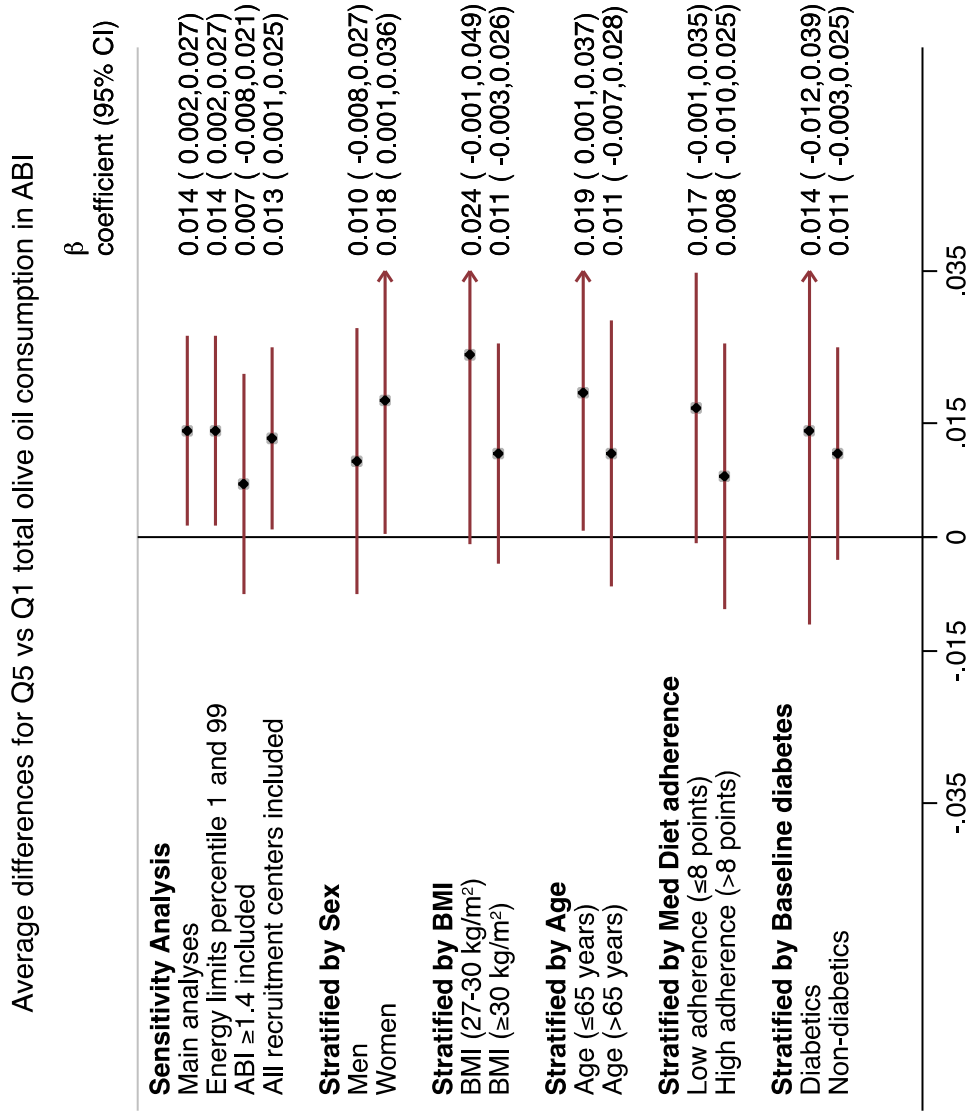
**Logistic Model 2:** Model 1 additionally adjusted for body mass index (tertiles).

**Logistic Model 3:** Model 2 additionally adjusted for waist circumference (continuous); self-reported prevalent diabetes (yes/no); self-reported hypertension (yes/no); adherence to a Mediterranean diet (score 0–16); physical activity (metabolic equivalents-min/ week) (quintiles);

educational level (primary school, secondary school, university); blood pressure-lowering drug use (yes/no); lipid-lowering medication use (yes/no); diuretics use (yes/no); insulin and oral antidiabetic agents use (yes/no); vitamin D intake (tertile); folic acid intake (continuous); family history of coronary heart disease (yes/no); smoking (never, current, former >5 years, former <5 years); and total energy intake (continuous).

<sup>a</sup> Model 3 adjusted without smoking variable.

**Figure 2.** Sensitivity analyses. Average differences for Q5 vs. Q1 total olive oil consumption in ABI.



ABI, ankle-brachial index; BMI, body mass index; Med Diet, Mediterranean diet; Q, quintile.

**Supplementary files.**

**Supplementary Table 1.** Correlations between confounding variables in the PREDIMED-Plus trial. (\*)  $p < 0.05$ .

	Age	Body-Mass index	Waist circumference	Adherence to a Meddiet	Physical activity	Vitamin D intake	Folic acid intake
Body- Mass index	-0.02						
Waist circumference	-0.10*	0.62*					
Adherence to a Meddiet	0.12*	-0.06*	-0.14*				
Physical activity	0.04*	-0.15*	-0.10*	0.14*			
Vitamin D intake	0.01	-0.03	-0.01	0.22*	0.11*		
Folic acid intake	0.09*	-0.01	-0.05*	0.36*	0.14*	0.21*	
Total energy intake	-0.12*	-0.02	0.13*	-0.12*	0.05*	-0.00	-0.04*

Meddiet: Mediterranean diet.

**Supplementary Table 2.** Sensitivity analysis. Odds ratios (95% CI) for ankle-brachial index (ABI)  $\leq 0.9$  across categories of energy-adjusted total, virgin, olive oil and olive pomace oil consumption in the PREDIMED-Plus trial.

		Odds Ratio (95% CI)					<i>p</i> for trend
<i>Quintiles of total olive oil consumption</i>		Q1	Q2	Q3	Q4	Q5	
Range of total olive oil consumption (g/day)		(< 36.63)	(36.63, 49.32)	(49.32, 59.53)	(59.53, 64.93)	(64.93, 119.89)	
Multivariable Model 1		1 (ref)	1.52 (0.92, 2.51)	1.52 (0.90, 2.54)	1.02 (0.59, 1.77)	1.22 (0.72, 2.09)	0.979
Multivariable Model 2		1 (ref)	1.52 (0.92, 2.51)	1.53 (0.91, 2.56)	1.03 (0.59, 1.79)	1.21 (0.70, 2.06)	0.954
Multivariable Model 3		1 (ref)	1.45 (0.85, 2.46)	1.52 (0.89, 2.58)	1.02 (0.58, 1.79)	1.16 (0.67, 2.02)	0.940
<i>Quintiles of virgin olive oil consumption</i>		Q1	Q2	Q3	Q4	Q5	
Range of virgin olive oil consumption (g/day)		(< 25.91)	(25.91, 38.68)	(38.68, 57.68)	(57.68, 63.49)	(63.49, 92.62)	
Multivariable Model 1		1 (ref)	0.95 (0.60, 1.50)	0.96 (0.60, 1.52)	0.84 (0.51, 1.38)	0.69 (0.41, 1.15)	0.172
Multivariable Model 2		1 (ref)	0.95 (0.60, 1.51)	0.98 (0.62, 1.56)	0.85 (0.52, 1.40)	0.68 (0.41, 1.14)	0.169
Multivariable Model 3		1 (ref)	0.96 (0.60, 1.54)	0.96 (0.60, 1.54)	0.91 (0.55, 1.51)	0.69 (0.41, 1.18)	0.244
<i>Quintiles of olive oil consumption</i>		Q1	Q2	Q3	Q4	Q5	
Range of olive oil consumption (g/day)		(< 3.15)	(3.15, 3.90)	(3.90, 4.63)	(4.63, 15.52)	(15.52, 74.66)	
Multivariable Model 1		1 (ref)	0.71 (0.42, 1.19)	1.04 (0.65, 1.67)	0.86 (0.51, 1.43)	1.16 (0.72, 1.85)	0.168
Multivariable Model 2		1 (ref)	0.70 (0.42, 1.18)	1.04 (0.65, 1.67)	0.84 (0.50, 1.40)	1.13 (0.71, 1.81)	0.187
Multivariable Model 3		1 (ref)	0.68 (0.39, 1.21)	1.00 (0.54, 1.86)	0.81 (0.39, 1.70)	1.08 (0.62, 1.86)	0.265
<i>Tertiles of olive pomace oil consumption</i>		T1	T2	T3			
Range of olive pomace oil consumption (g/day)		(< 0.01)	(0.01, 0.02)	(0.02, 49.99)			
Multivariable Model 1		1 (ref)	0.90 (0.60, 1.34)	1.11 (0.77, 1.59)			0.590
Multivariable Model 2		1 (ref)	0.89 (0.59, 1.33)	1.10 (0.76, 1.57)			0.622
Multivariable Model 3		1 (ref)	0.85 (0.56, 1.29)	1.07 (0.74, 1.55)			0.723

Results from logistic models. Q, quintile; T, tertile.

**Logistic Model 1:** adjusted for age (continuous), recruitment center, and sex.

**Logistic Model 2:** Model 1 additionally adjusted for body mass index (tertiles).

**Logistic Model 3:** Model 2 additionally adjusted for waist circumference (continuous); self-reported prevalent diabetes (yes/no); self-reported hypertension (yes/no); adherence to a Mediterranean diet (score 0–16); physical activity (metabolic equivalents-min/ week) (quintiles); educational level (primary school, secondary school, university); blood pressure-lowering drug use (yes/no); lipid-lowering medication use (yes/no); diuretics use (yes/no); insulin and oral antidiabetic agents use (yes/no); vitamin D intake (tertile); folic acid intake (continuous); family history of coronary heart disease (yes/no); smoking (never, current, former >5 years, former <5 years); and total energy intake (continuous).

**Supplementary Table 3.** Differences in ankle-brachial index (ABI) across categories of energy-adjusted total, virgin, olive oil and olive pomace oil consumption in the PREDIMED-Plus trial. (n=4729, with all recruitment centers included but without missing ABI values in the right or left leg).

<i>Quintiles of total olive oil consumption</i>	Q1	Q2	Q3	Q4	Q5	<i>p for trend</i>
Median total olive oil consumption (g/day)	30	40	54	61	69	
Multivariable Model 1	0 (ref)	-2.84 e-06 (-0.011, 0.011)	0.006 (-0.005, 0.018)	0.009 (-0.003, 0.020)	0.012 (0.00006, 0.024)	0.018
Multivariable Model 2	0 (ref)	0.00004 (-0.011, 0.011)	0.006 (-0.005, 0.018)	0.009 (-0.003, 0.020)	0.012 (0.00002, 0.024)	0.019
Multivariable Model 3	0 (ref)	0.0005 (-0.011, 0.012)	0.007 (-0.005, 0.018)	0.009 (-0.003, 0.021)	0.013 (0.001, 0.025)	0.011
<i>Quintiles of virgin olive oil consumption</i>	Q1	Q2	Q3	Q4	Q5	
Median virgin olive oil consumption (g/day)	14	33	40	60	66	
Multivariable Model 1	0 (ref)	-0.002 (-0.013, 0.009)	0.003 (-0.011, 0.012)	0.002 (-0.010, 0.013)	0.009 (-0.003, 0.021)	0.168
Multivariable Model 2	0 (ref)	-0.002 (-0.013, 0.009)	0.003 (-0.011, 0.012)	0.002 (-0.010, 0.013)	0.009 (-0.003, 0.021)	0.166
Multivariable Model 3	0 (ref)	-0.002 (-0.013, 0.009)	0.001 (-0.010, 0.013)	0.0009 (-0.011, 0.013)	0.010 (-0.002, 0.022)	0.155
<i>Quintiles of olive oil consumption</i>	Q1	Q2	Q3	Q4	Q5	
Median olive oil consumption (g/day)	2	4	5	7	30	
Multivariable Model 1	0 (ref)	0.003 (-0.008, 0.014)	-0.003 (-0.014, 0.008)	-0.003 (-0.014, 0.009)	0.002 (-0.011, 0.011)	0.870
Multivariable Model 2	0 (ref)	0.003 (-0.008, 0.013)	-0.003 (-0.014, 0.008)	-0.003 (-0.014, 0.008)	0.0002 (-0.011, 0.012)	0.859
Multivariable Model 3	0 (ref)	-0.0002 (-0.012, 0.012)	-0.006 (-0.020, 0.008)	-0.007 (-0.023, 0.009)	-0.002 (-0.014, 0.011)	0.759
<i>Tertiles of olive pomace oil consumption</i>	T1	T2	T3			
Median olive pomace oil consumption (g/day)	0.01	0.02	0.02			
Multivariable Model 1	0 (ref)	0.002 (-0.007, 0.011)	0.002 (-0.006, 0.011)			0.587
Multivariable Model 2	0 (ref)	0.002 (-0.007, 0.011)	0.002 (-0.006, 0.011)			0.591
Multivariable Model 3	0 (ref)	0.002 (-0.007, 0.011)	0.002 (-0.006, 0.011)			0.584

Results from multivariable linear regression models. Q, quintile; T, tertile.

**Multivariable Model 1:** adjusted for age (continuous), recruitment center and sex.

**Multivariable Model 2:** Model 1 additionally adjusted for body mass index (tertiles).

**Multivariable Model 3:** Model 2 additionally adjusted for waist circumference (continuous); self-reported prevalent diabetes (yes/no); self-reported hypertension (yes/no); adherence to a Mediterranean diet (score 0–16); physical activity (metabolic equivalents-min/ week) (quintiles); educational level (primary school, secondary school, university studies); blood pressure-lowering drugs use (yes/no); lipid-lowering medication use (yes/no); diuretics use (yes/no); insulin and oral antidiabetic agents use (yes/no); vitamin D intake (tertile); folic acid intake (continuous); family history of coronary heart disease (yes/no); smoking (never, current, former >5 years, former <5 years); and total energy intake (continuous).