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

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A R T I C L E I N F O

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A B S T R A C T

Background and aims: The aim of this study was to ascertain the association between the consumption of different categories of edible olive oils (virgin olive oils and olive oil) and olive pomace oil and ankle-brachial pressure index (ABI) in participants in the PREDIMED-Plus study, a trial of lifestyle modification for weight and cardiovascular event reduction in individuals with overweight/obesity harboring the metabolic syndrome.
Methods: We performed a cross-sectional analysis of the PREDIMED-Plus trial. Consumption of any category of olive oil and olive pomace oil was assessed through a validated food-frequency questionnaire. Multivariable linear regression models were fitted to assess associations between olive oil consumption and ABI. Additionally, ABI ≤1 was considered as the outcome in logistic models with different categories of olive oil and olive pomace oil as exposure.
Results: Among 4330 participants, the highest quintile of total olive oil consumption (sum of all categories of olive oil and olive pomace oil) was associated with higher mean values of ABI (beta coefficient: 0.014, 95% confidence interval [CI]: 0.002, 0.027) (*p* for trend = 0.010). Logistic models comparing the consumption of different categories of olive oils, olive pomace oil and ABI ≤1 values revealed an inverse association between virgin olive oils consumption and the likelihood of a low ABI (odds ratio [OR] 0.73, 95% CI [0.56, 0.97]), while consumption of olive pomace oil was positively associated with a low ABI (OR 1.22 95% CI [1.00, 1.48]).
Conclusions: In a Mediterranean population at high cardiovascular risk, total olive oil consumption was associated with a higher mean ABI. These results suggest that olive oil consumption may be beneficial for peripheral artery disease prevention, but longitudinal studies are needed.

1. Introduction

The American College of Cardiology/American Heart Association defines peripheral atherosclerotic vascular diseases as a group of clinical disorders that includes abdominal aortic aneurysm, renal and mesenteric artery disease, extracranial carotid artery disease, and disease of the aortoiliac, femoropopliteal, and infrapopliteal arterial segments. It does not address nonatherosclerotic causes of lower extremity arterial disease, such as vasculitis, fibromuscular 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.

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]. ABI is calculated as the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery [3]. Usually, the highest ankle systolic pressure is divided by the highest brachial systolic pressure, resulting in an ABI for each leg [2]. 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 between 0.91 and 0.99 [3]. ABI has high specificity but suboptimal sensitivity to detect PAD [4]. 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].

Olive oil consumption is reported to have several beneficial effects on CV disease [6–11]; however to our knowledge, epidemiological evidence 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 oil 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 to address 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].

This cross-sectional study analyzed the associations between the consumption of different categories of olive oils (total, virgin and olive oil), olive pomace oil 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. 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 on hard CV events, in comparison to that of a control group receiving usual care intervention only with energy-unrestricted Mediterranean diet recommendations. This study was registered with the International Standard Randomized Controlled Trial (ISRCT; http://www.isrctn.

[1] These authors equally contributed to the work.

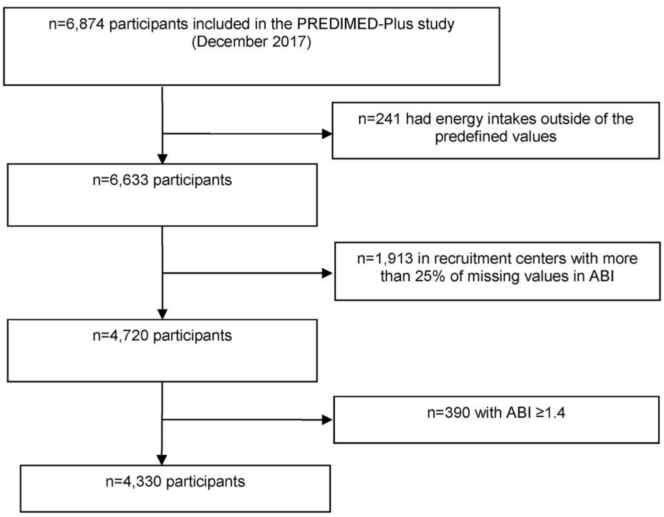

Fig. 1. Flow chart of participants recruited in the PREDIMED-Plus project. ABI = ankle-brachial pressure index. Total energy intakes were within predefined limits (800–4000 Kcal/day for men, and 500–3500 Kcal/day for women).

com/ISRCTN89898870) with number 89898870 (registration date: July 24, 2014). Written informed consent was obtained from each patient included in the study, the study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki and the study protocol has been approved by the Research Ethics Committees from all recruitment centers [18]. The eligible participants were adults (aged 55–75 years in men; 60–75 years in women) with overweight/obesity (body mass index [BMI] ≥27 and < 40 kg/m^2, respectively] and who met at least three criteria for metabolic syndrome (MetS) according to the updated harmonized criteria of the International Diabetes Federation and the American Heart Association and National Heart, Lung, and Blood Institute [19]. A total of 6874 participants were recruited and randomized from 23 recruitment sites at different universities, hospitals, and research institutes in Spain. The present analysis included only those participants whose total energy intakes were within predefined limits (800–4000 Kcal/day for men, and 500–3500 Kcal/day for women [20] (n = 241 out of limits), participants from recruitment centers with less than 25% missing data on ABI as a quality control (n = 1913 out of criteria), and participants with an ABI <1.4 (n = 390 participants with ABI ≥1.4) (Fig. 1).

2.2. *Exposure assessment*

The consumption of total olive oil, in which are included the following categories: virgin olive oils (including extra virgin and virgin olive oil), olive oil (described as refined olive oil and virgin olive oil mixture according to the European Commission Regulation (EC) Nº 1019/2002 [21]) and consumption of olive pomace oil was assessed using a validated 143-item semi-quantitative food-frequency questionnaire [22] administered at baseline. In face-to-face interviews, the participants were asked about their frequencies of consumption of each food item during the past year, as well as the usual serving sizes. Nine possibilities of frequency were offered, ranging from never to >6 times/day. Virgin, olive oil, olive pomace oil and total olive oil (which include both categories of olive oils and olive pomace oil) consumptions were adjusted for total energy intake using the residual method, and the participants were then grouped into quintiles according to their total, virgin, or olive oil consumption. Due to the low consumption and low variability in olive pomace oil consumption, the participants were classified into tertiles according to their olive pomace oil consumption. Smoke variable was introduced as positive control to assess well known associations with PAD.

2.3. *Outcome assessment*

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

2.4. *Covariate assessment*

Information on socio-demographic variables (e.g., sex, age, marital status, and educational level) and lifestyle-related characteristics (e.g., smoking status, physical activity, or adherence to the Mediterranean diet) was obtained from the baseline questionnaire. Weight and height were measured in duplicate with calibrated scales and a wall-mounted stadiometer, respectively. BMI was calculated as the weight in kilograms divided by the height in meters squared.

Leisure-time physical activity was assessed using the short form of the Minnesota Leisure Time Physical Activity Questionnaire validated in Spain [23,24]. Leisure-time activities were computed by assigning a metabolic equivalent score to each activity [25], multiplied by the time spent for each activity and summing all activities. Adherence to an energy-restricted Mediterranean diet was evaluated with a 17-item questionnaire [26], which we modified with the exclusion of the extra-virgin olive oil component to avoid collinearity (score range 0–16). Self-reported comorbidities (hypertension and type 2 diabetes) were collected from each participant.

2.5. *Statistical analysis*

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

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

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

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

Finally, to assess the robustness of the multivariable linear regressions, we performed sensitivity analysis for Q5 *vs*. Q1 of total olive

Table 1
Baseline characteristics of 4330 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
N	866	866	866	866	866
Median total olive oil consumption (g/day)[a]	30.9 (6.2)	41.4 (3.4)	56.1 (2.7)	62.2 (1.5)	72.0 (8.0)
Age (years)	65 (5)	66 (5)	65 (5)	65 (5)	65 (5)
Women (%)	50.5	53.8	50.0	39.7	45.6
Waist circumference (cm)	109 (10)	108 (9)	107 (9)	107 (9)	108 (10)
Height (cm)	163.2 (9.2)	161.9 (9.4)	162.8 (9.3)	164.1 (9.2)	162.8 (9.3)
BMI (kg/m^2)	32.8 (3.5)	32.7 (3.4)	32.4 (3.4)	32.1 (3.3)	32.8 (3.5)
Systolic blood pressure (mm Hg)	136.3 (16.3)	137.2 (16.9)	139.1 (15.1)	139.8 (15.5)	139.7 (16.5)
Diastolic blood pressure (mm Hg)	81.9 (9.3)	81.8 (9.9)	83.0 (8.8)	82.6 (8.7)	82.1 (9.3)
Leisure-time physical activity (METs-min/week)	2451 (2345)	2628 (2369)	2536 (2404)	2695 (2258)	2605 (2458)
Smoking (%)					
Former smoker	39.4	40.3	43.0	47.0	46.3
Current smoker	12.6	12.4	12.9	14.1	13.5
Educational level					
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
Family history of CHD[b] (%)	43.0	42.6	42.1	38.7	43.2
Self-reported diabetes (%)	25.9	26.0	21.8	22.5	27.3
Self-reported hypertension (%)	93.3	92.8	93.4	92.1	92.3
Self-reported medication use					
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
Lipid lowering medication (%)	52.2	52.4	48.7	47.1	50.5
Blood pressure-lowering drugs (%)	79.0	78.9	77.8	75.8	78.1
Adherence to energy-reduced Mediterranean diet (0–16 score)	7.5 (2.5)	7.9 (2.6)	7.8 (2.6)	7.9 (2.6)	8.2 (2.6)
Total energy intake (kcal/day)	2489 (579)	2007 (509)	2775 (463)	2275 (237)	2316 (602)
Macronutrient intake					
Carbohydrate intake (% energy)	45.1 (6.7)	42.5 (6.4)	40.7 (5.5)	37.9 (5.3)	35.2 (5.5)
Protein intake (% energy)	17.1 (2.9)	17.8 (3.0)	15.9 (2.4)	16.2 (2.4)	15.5 (2.4)
Fat intake (% energy)	34.9 (5.9)	36.9 (5.2)	40.0 (4.7)	42.4 (4.7)	46.2 (5)
Monounsaturated fatty acids (% energy)	16.3 (3.7)	18.5 (3.0)	20.9 (2.8)	23.1 (3.0)	26.0 (3.3)
Polyunsaturated fatty acids (% energy)	6.4 (2.2)	6.0 (1.9)	6.3 (1.7)	6.5 (1.6)	6.8 (1.5)
Saturated fatty acids (% energy)	9.8 (2.4)	9.6 (2.1)	10.0 (1.8)	10.0 (1.8)	10.3 (1.8)
Alcohol intake (g/day)	11.1 (15.6)	8.4 (12.8)	14.1 (17.4)	11.5 (14.0)	10.8 (14.6)
Fruit consumption (g/day)	394 (225)	333 (204)	392 (207)	344 (174)	341 (187)
Vegetable consumption (g/day)	340 (156)	316 (136)	335 (137)	303 (115)	305 (130)
Cereal consumption (g/day)	162 (82)	129 (70)	185 (86)	142 (63)	128 (67)
Legume consumption (g/day)	23.8 (13.1)	19.8 (10.7)	21.7 (11.9)	18.8 (8.3)	19.6 (10.9)
Meat product consumption (g/day)	149 (66)	132 (55)	165 (60)	144 (48)	135 (53)
Fish product consumption (g/day)	100.1 (52.8)	88.8 (45.2)	108.5 (45.7)	98.9 (43.0)	98.1 (45.3)
Dairy product consumption (g/day)	405 (220)	328 (202)	380 (217)	303 (169)	293 (181)
Micronutrient intake					
Vitamin D intake (mg/day)	6.3 (3.4)	5.4 (3.3)	6.7 (3.5)	6.0 (3.3)	6.1 (3.4)
Folic acid intake (mg/day)	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.
[a] Energy-adjusted consumption.
[b] Information from parents and siblings.

Table 2
Correlations between virgin, olive oil and olive pomace oil consumption in the PREDIMED-Plus trial.

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

(*) $p < 0.05$

oil consumption with different energy limits (percentiles 1 and 99), including participants with ABI ≥1.4, or participants from all recruitment centers. We also assessed the association after stratifying by sex (men and women), BMI (<30 kg/m^2 or ≥30 kg/m^2), age (≤65 or >65 years), baseline adherence to the Mediterranean diet (≤7 points vs ≥ 8 points), and baseline diabetes.

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

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

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

3. Results

This study included 4330 out of 6874 participants recruited in the PREDIMED-Plus trial, according to previously defined exclusion criteria (Fig. 1). The mean age of study subjects was 65 and 47.9% were women. Table 1 shows the baseline characteristics of the participants included according to energy-adjusted quintiles of total olive oil consumption. Participants in the highest category of total olive oil consumption had a higher total energy intake, higher adherence to the Mediterranean diet, higher fat intake (especially monounsaturated fatty acids), lower consumption of meat, fish, and dairy products and a decrease in fruit, vegetables, cereals and legumes, respect to lowest category of total olive oil intake.

The results of correlation analyses between total, virgin, olive oil and olive pomace oil consumption are shown in Table 2. We observed a significant inverse correlation between virgin and olive oils consumption (−0.41). Correlations between all continuous traits considered as

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 = 4330.

Quintiles of total olive oil consumption	Q1	Q2	Q3	Q4	Q5	***p* for trend**
Median total olive oil consumption (g/day)	**31**	**41**	**56**	**62**	**72**	
N	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
Quintiles of virgin olive oil consumption	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
Median virgin olive oil consumption (g/day)	15	35	44	61	68	
N	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
Quintiles of olive oil consumption	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
Median olive oil consumption (g/day)	3	4	4	5	30	
N	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
Tertiles of olive pomace oil consumption	**T1**	**T2**	**T3**			
Median olive pomace oil consumption (g/day)	0.003	0.02	0.03			
N	1444	1443	1443			
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 lineal 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).

potential confounders are shown in Supplementary Table 1.

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

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

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

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

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

	Odds Ratio (95% CI)					
Quintiles of total olive oil consumption	Q1	Q2	Q3	Q4	Q5	*p* for trend
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
Quintiles of virgin olive oil consumption	**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)	
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*
Quintiles of olive oil consumption	**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)	
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
Tertiles of olive pomace oil consumption	**T1**	**T2**	**T3**			
Range of olive pomace oil consumption (g/day)	(<0.01)	(0.01, 0.02)	(0.02, 49.99)			
N	1444	1443	1443			
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).
Model 3 adjusted without smoking variable.

4. Discussion

The results of this cross-sectional analysis of the PREDIMED-Plus trial showed a direct association between total olive oil consumption (including olive pomace oil) and ABI. In addition, virgin olive oils consumption was inversely associated with borderline ABI whereas olive oil and olive pomace oil consumption were directly associated with borderline ABI.

ABI is a non-invasive, simple, and reliable diagnostic method used as a simple method to screen for PAD and to evaluate CV prognosis in the general population [27]. The range of normal ABI values is between 0.90 and 1.4. In fact, an ABI below 0.90 represents an independent marker of CV risk [28]. This threshold of ≤0.90 is based on studies reporting >90% sensitivity and specificity to detect PAD compared to angiography [29,30]. Otherwise, with an ABI ≥1.0 used as a threshold for detecting PAD, sensitivities as high as 100% have been reported [28,30]. Thus, ABI should be carefully interpreted according to *a priori* probability of PAD and values between 0.91 and 1.00 should be considered borderline [3]. In this study, our evaluation of the probability of an ABI ≤1 included all participants considered to be borderline. Total and virgin olive oils consumption appeared to be inversely associated with the risk of an ABI ≤1 (OR 0.86 and OR 0.73, respectively). However, olive pomace oil and olive oil consumption appeared to be associated with a higher odd of borderline ABI (OR 1.22, 95% CI 1.00, 1.48 and OR 1.43, 95% CI 1.07, 1.90, respectively).

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

Overall, our results suggest that a higher total olive oil consumption was associated with better values for ABI but there was no significant association with borderline ABI used as a dichotomous variable (ABI≤1). When we further addressed if consumption of specific olive oil categories was associated with ABI, we found significant association with virgin olive oils and olive pomace oil (Fig. 3). Higher virgin olive oil consumption was significantly associated with a lower odds of borderline ABI, whereas olive oil consumption and olive pomace oil consumption were associated with a higher odds of borderline ABI compared to the lowest consumption category, with a statistically

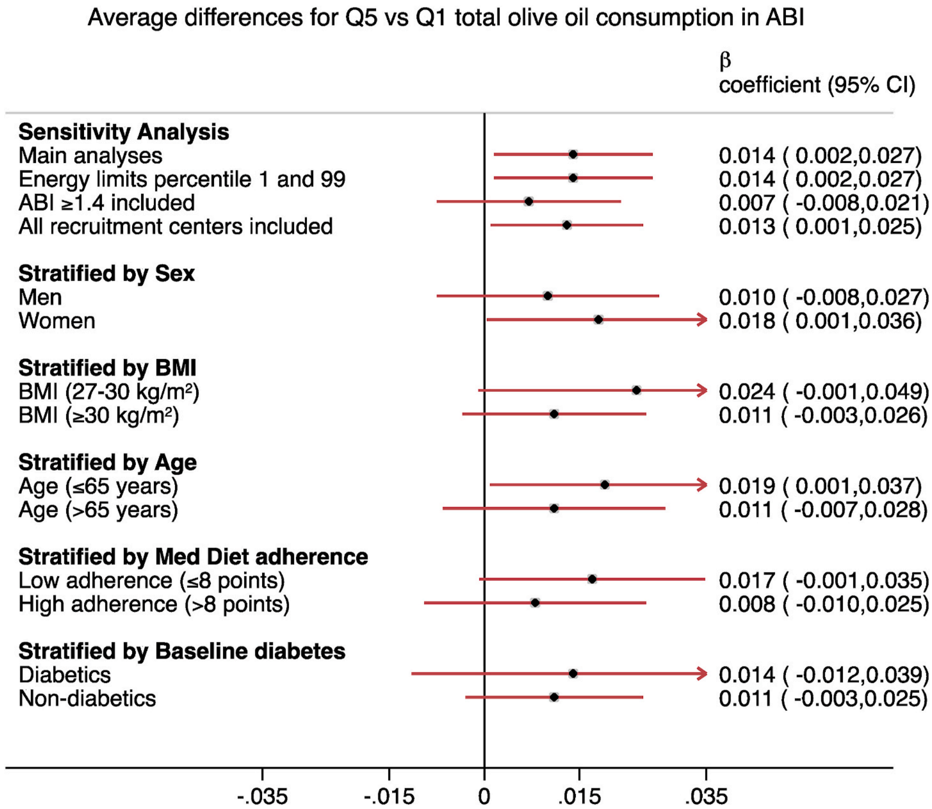

Fig. 2. Sensitivity analyses.
Average differences for Q5 *vs.* Q1 total olive oil consumption in ABI.
ABI, ankle-brachial index; BMI, body mass index; Med Diet, Mediterranean diet; Q, quintile.

significant finding for olive pomace oil. It could be hypothesized that replacing more processed categories of olive oil and olive pomace oil by virgin olive oils may help improve ABI. The observed results across the different olive oil categories could be due to minor compounds present in virgin olive oil, which are practically absent in refined olive oil and olive pomace oil [32,33]. Given that the lipid profile is mainly the same in all categories of olive oils and olive pomace oil, this idea becomes coherent. In fact, minor compounds of virgin olive oils have been described to be responsible for different beneficial properties against several diseases, including CV disease prevention [7,9,34–36]. Contrarily, olive pomace oil loses the majority of minor compounds and some chemical contaminants could be present in it as a result of manufacturing processes [37]. Some of these contaminants have been described as harmful compounds [38]. Nevertheless, we have to notice that differences between categories of olive oils and olive pomace oil may be due not only to their composition, but also to their differential culinary use. It is known that the fatty acid profile of olive pomace oil is similar to the fatty acid profile of virgin olive oils, but it is generally used for frying foods, including ultraprocessed foods, which have been reported to increase CV risk [39]. Indeed, several authors have been described the impact of short supply chain (food from local and regional origin) in metabolic syndrome patients of a Mediterranean population, which was better that long supply chain food (food from big retail distribution, coming from intensive producers of mass food) [40,41]. These hypotheses could explain the differences observed between extreme quintiles and tertiles of consumption in virgin olive oils as compared to olive pomace oil or refined olive oil in their association with the ABI index; however, prospective studies are needed to corroborate these associations.

This study has several strengths, including the large sample size, inclusion of both men and women in the trial, adjustment for a wide array of potential confounders, and the use of validated tools to assess information. However, we acknowledge some limitations such as its cross-sectional design, which does not allow the establishment of any causal association between olive oil consumption and ABI. In addition, the age of the participants was limited to 55–75 years and all of our participants had metabolic syndrome; therefore, generalization of the results to other age groups may be limited. Furthermore, as this is not a prospective study, results should be treated carefully and potential causal inferences need to be confirmed by future prospective studies. Also, olive oil consumption was addressed only once. The food-frequency questionnaire covered one year of exposure over the previous year. The implicit assumption is that past year consumption tends to be correlated with lifetime consumption. However, we admit that appraising a longer exposure to olive oil may be important to fully disentangle the association between olive oil consumption and ABI or PAD. Finally, we were not able to distinguish between the minor components of the different categories of olive oils and olive pomace oils. Concentration of minor components does not only depend on olive oil category but also on other characteristics such as its origin, olive variety or ripeness of the olives from which olive oil was extracted [42].

In conclusion, the main findings of the current study suggest a direct association between total olive oil consumption and a better ABI. Moreover, consumption of virgin olive oils could be useful to promote a better ABI instead of other olive oils categories or olive pomace oil. Nevertheless, longitudinal studies are needed to confirm these results and to definitively establish the role of total olive oil consumption, different categories of olive oil and olive pomace oil consumption in the development of PAD.

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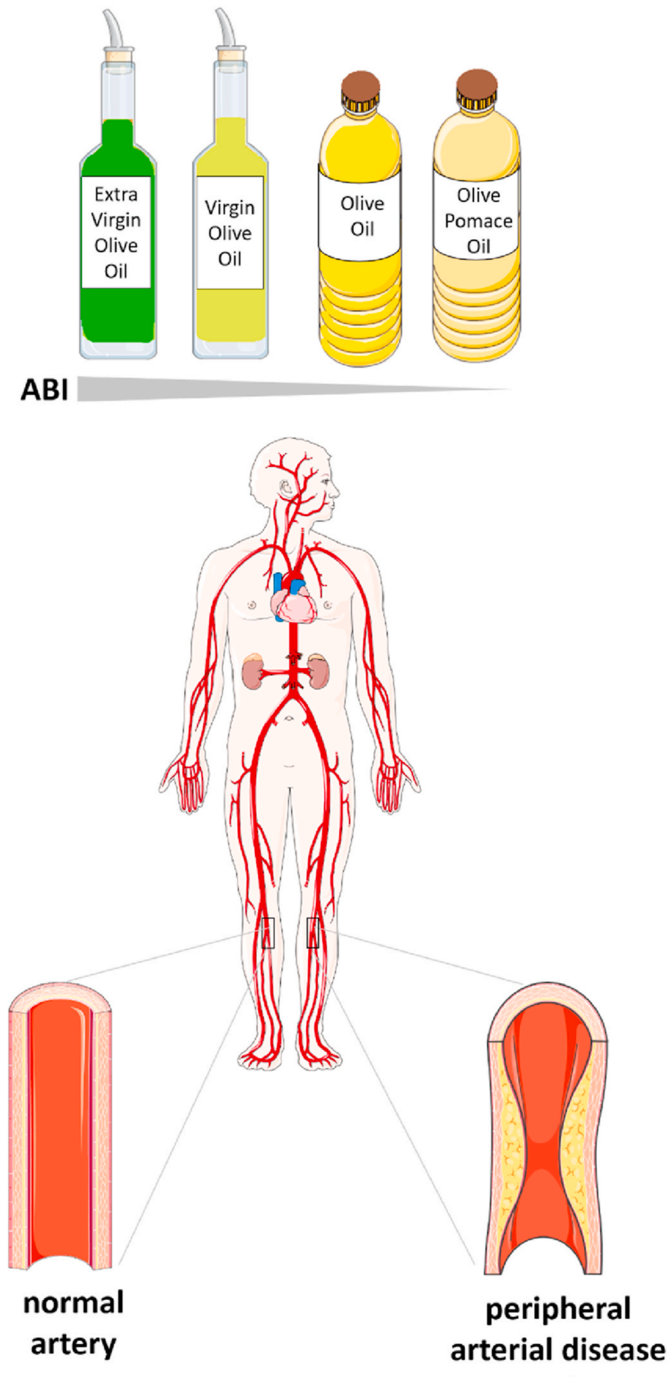

Fig. 3. Ankle-brachial index (ABI) after total, virgin, olive oil and olive pomace oil consumption in the PREDIMED-Plus trial.

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CRediT authorship contribution statement

Cristina Sánchez-Quesada: Formal analysis, Writing - original draft, Funding acquisition, Data curation. **Estefanía Toledo:** Formal analysis, Writing - original draft, Conceptualization, Funding acquisition, Data curation. **Guadalupe González-Mata:** Funding acquisition, Data curation. **Maria Isabel Ramos-Ballesta:** Funding acquisition, Data curation. **José Ignacio Peis:** Funding acquisition, Data curation. **Miguel Ángel Martínez-González:** Funding acquisition, Data curation, Conceptualization, substantial contributions to the conception and design of the work, All authors contributed substantially in the acquisition of data or analysis and interpretation of data, All authors revised the article critically for important intellectual content. **Jordi Salas-Salvadó:** Funding acquisition, Data curation. **Dolores Corella:** Funding acquisition, Data curation. **Montserrat Fitó:** Funding acquisition, Data curation. **Dora Romaguera:** Funding acquisition, Data curation. **Jesús Vioque:** Funding acquisition, Data curation. **Ángel M. Alonso-Gómez:** Funding acquisition, Data curation. **Julia Wärnberg:** Funding acquisition, Data curation. **J. Alfredo Martínez:** Funding acquisition, Data curation. **Luís Serra-Majem:** Funding acquisition, Data curation. **Ramon Estruch:** Funding acquisition, Data curation. **Francisco J. Tinahones:** Funding acquisition, Data curation. **José Lapetra:** Funding acquisition, Data curation. **Xavier Pintó:** Funding acquisition, Data curation. **Josep A. Tur:** Funding acquisition, Data curation. **Antonio Garcia-Rios:** Funding acquisition, Data curation. **Naomi Cano-Ibáñez:** Funding acquisition, Data curation. **Pilar Matía-Martín:** Funding acquisition, Data curation. **Lidia Daimiel:** Funding acquisition, Data curation. **Rubén Sánchez-Rodríguez:** Funding acquisition, Data curation. **Josep Vidal:** Funding acquisition, Data curation. **Clotilde Vázquez:** Funding acquisition, Data curation. **Emilio Ros:** Funding acquisition, Data curation. **Pablo Hernández-Alonso:** Funding acquisition, Data . **Rocío Barragan:** Funding acquisition, Data curation. **Julia Muñoz-Martínez:** Funding acquisition, Data curation. **Meritxell López:** Funding acquisition, Data curation. **Sandra González-Palacios:** Funding acquisition, Data curation. **Jessica Vaquero-Luna:** Funding acquisition, Data curation. **Edelys Crespo-Oliva:** Funding acquisition, Data curation. **M. Angeles Zulet:** Funding acquisition, Data curation. **Vanessa Díaz-González:** All authors contributed substantially in the acquisition of data or analysis and interpretation of data, All authors revised the article critically for important intellectual content. **Rosa Casas:** Funding acquisition, Data curation. **José Carlos Fernandez-Garcia:** Funding acquisition, Data curation. **José Manuel Santos-Lozano:** Funding acquisition, Data curation. **Ana Galera:** Funding acquisition, Data curation. **Tomás Ripoll-Vera:** Funding acquisition, Data curation. **Pilar Buil-Cosiales:** Funding acquisition, Data curation. **Silvia Canudas:** Funding acquisition, Data curation. **Raul Martinez-Lacruz:** Funding acquisition, Data curation. **Karla-Alejandra Pérez-Vega:** Funding acquisition, Data curation. **Ángel Rios:** Funding acquisition, Data curation. **Rosario Lloret-Macián:** Funding acquisition, Data curation. **Anai Moreno-Rodriguez:** Funding acquisition, Data curation. **Miguel Ruiz-Canela:** Funding acquisition, Data curation. **Nancy Babio:** Funding acquisition, Data curation, All authors contributed substantially in the acquisition of data or analysis and interpretation of data, All authors revised the article critically for important intellectual content. **Maria Dolores Zomeño Fajardo:** Funding acquisition, Data curation. **José J. Gaforio:** Funding acquisition, Data curation, Formal analysis, Conceptualization, All authors contributed substantially in the acquisition of data or analysis and interpretation of data, substantial contributions to the conception and design of the work, All authors revised the article critically for important intellectual content.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2020.10.008.

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