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Original article

Increase from low to moderate, but not high, caffeinated coffee consumption is associated with favorable changes in body fat

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SUMMARY

Background & aims: Higher consumption of coffee and caffeine has been linked to less weight gain and lower body mass index in prospective cohort studies. The aim of the study was to longitudinally assess the association of changes in coffee and caffeine intake with changes in fat tissue, in particular, visceral adipose tissue (VAT) using dual x-ray absorptiometry (DXA).

Methods: In the setting of a large, randomized trial of Mediterranean diet and physical activity intervention, we evaluated 1483 participants with metabolic syndrome (MetS). Repeated measurements of coffee consumption from validated food frequency questionnaires (FFQ) and DXA measurements of adipose tissue were collected at baseline, 6 months, 12 months and 3 years of follow-up. DXA-derived measurements of total and regional adipose tissue expressed as % of total body weight were transformed into sex-specific z-scores. Linear multilevel mixed-effect models were used to investigate the relationship between changes in coffee consumption and corresponding concurrent changes in fat tissue during a 3-year follow-up.

Results: After adjustment for intervention group, and other potential confounders, an increase in caffeinated coffee consumption from no or infrequent consumption (≤3 cups/month) to moderate consumption (1–7 cups/week) was associated with reductions in total body fat (Δ z-score: −0.06; 95%

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CI: −0.11 to −0.02), trunk fat (Δ z-score: −0.07; 95% CI: −0.12 to −0.02), and VAT (Δ z-score: −0.07; 95% CI: −0.13 to −0.01). Neither changes from no or infrequent consumption to high levels of caffeinated coffee consumption (>1 cup/day) nor any changes in decaffeinated coffee consumption showed significant associations with changes in DXA measures.

Conclusions: Moderate changes in the consumption of caffeinated coffee, but not changes to high consumption, were associated with reductions in total body fat, trunk fat and VAT in a Mediterranean cohort with MetS. Decaffeinated coffee was not linked to adiposity indicators. Moderate consumption of caffeinated coffee may be part of a weight management strategy.

Trial registration: The trial was registered at the International Standard Randomized Controlled Trial (ISRCTN: http://www.isrctn.com/ISRCTN89898870) with number 89898870 and registration date of 24 July 2014, retrospectively registered.

1. Introduction

Rising prevalence of overweight and obesity worldwide represents a major challenge for public health. Overweight and obesity increase the risk of many chronic diseases, such as cardiovascular disease (CVD), type 2 diabetes (T2D), some types of cancer or depression [1]. Anthropometric measures like body mass index (BMI) and waist circumference (WC) are good proxies for adiposity, but do not specifically capture fat tissue or its distribution, which highly influences the actual risk for metabolic disorders. In fact, a high BMI can reflect a wide range of body compositions with diverse health effects [2,3]. For instance, visceral adipose tissue (VAT) has a stronger association with CVD, T2D and all-cause mortality than general obesity [4,5]. Dual-energy x-ray absorptiometry (DXA) overcomes the limitations of anthropometric measures, because it precisely determines and localizes fat tissue and therefore provides more reliable cardiometabolic risk assessments of obesity [6–8].

Regular consumption of coffee has been inversely associated with the risk for T2D, CVD, certain cancers and all-cause mortality in several large prospective cohorts, with a high degree of consistency in these associations [9]. Some of these health benefits might be mediated by the effect of coffee on energy metabolism, suggesting an anti-obesity effect, in part due to direct metabolic actions of caffeine [10,11]. The NHANES study suggested an inverse association between coffee consumption and fat tissue measured by DXA, but their cross-sectional findings can only be considered preliminary until prospective studies may overcome the inherent limitations of that design [12]. In the absence of randomized clinical trials, prospective observational studies conducted in large samples with repeated measurements can provide the best evidence by evaluating changes in coffee consumption as the most relevant exposure and changes in body fat composition as the primary outcome.

The aims of this study were twofold. First, we assessed the association between changes in caffeinated and decaffeinated coffee consumption with concurrent changes in DXA-derived adiposity measures. Second, we evaluated the association of changes in caffeine intake with fat tissue using a similar approach.

2. Material and methods

2.1. Study design

The prospective analyses of our study rely on data collected during the first 3 years of the PREDIMED-Plus (PREvención con DIeta MEDiterránea Plus) study, a 6-year, randomized clinical trial still on-going. The trial is conducted in 23 Spanish centers. The study started in September 2013 at the vanguard center in Navarra, and during 2014–2015 in the other centers. The recruitment was completed in the last center at the end of 2016.

The PREDIMED-Plus trial compares the effect of an intensive lifestyle intervention aiming at weight loss through an energy-restricted Mediterranean diet (erMedDiet), promotion of physical activity (PA) and behavioral support on the primary prevention of CVDs with a control group receiving traditional healthcare and non-intensive recommendations on the Mediterranean diet (MedDiet) without any advice on either energy restriction or PA or the objective to lose weight. A detailed description of the study design and methods has been previously published [13,14].

The study's protocol was approved by the Research Ethic Committees from all recruiting centers according to the ethical standards of the Declaration of Helsinki. The trial was registered at the International Standard Randomized Controlled Trial (ISRCTN: http://www.isrctn.com/ISRCTN89898870). All participants provided written informed consent.

2.2. Study population

Participants in the PREDIMED-Plus trial were recruited according to the following selection criteria: senior men (aged 55–75 years) and women (aged 60–75 years) were enrolled if they were overweight or obese (BMI $\geq$27 and < 40 kg/m^2) and met at least three out of five criteria for the metabolic syndrome (MetS) according to the updated harmonized International Diabetes Federation and the American Heart Association (abdominal obesity, high blood pressure, fasting glucose and triglyceride, as well as low HDL-cholesterol levels) [15]. Among criteria for the MetS, abdominal obesity, determined as high WC (>88 cm for women and >102 cm for men), showed highest prevalence being found in 96.1% of participants. Most of participants (97.5%) were of Caucasian origin.

This study analyzed data from a subsample of participants who underwent whole body dual-energy X-ray absorptiometry (DXA) scans providing precise body composition assessment in 7 out of the 23 study centers (2 study centers in Pamplona, 2 in Barcelona, and other 3 centers, one in Palma de Mallorca, one in Reus and one in León). Among a total of 1556 participants with DXA data at baseline, we excluded 73 from analyses because of missing information on VAT and subcutaneous adipose tissue (SAT) (n = 31), dietary habits (n = 1), sedentary behavior (n = 2) and smoking (n = 4). Moreover, 35 participants were not included as their diets showed total energy intakes outside of the limits defined by cut-offs proposed by Willett (n = 35; <500 or >3500 kcal for women, <800 or >4000 kcal for men) [16]. Finally, a total of 1483 participants entered the analyses. Selection of participants for analyses and available follow-up data are shown in Supplementary Fig. 1.

2.3. Dietary and Physical Activity assessment

At baseline, six months, and yearly, participants provided information on their current lifestyle and dietary habits. During face-to-face interviews with trained dietitians, they responded to a 143-item semi-quantitative Food Frequency Questionnaire (FFQ). This FFQ has been previously validated and re-evaluated in Spain [17,18]. Quantitative intake of each food item was described with 9 possible responses indicating the frequency of a typical portion consumed (ranging from never to > 6 times/day). Our calculations of specific nutrient intakes (sodium (mg/day), saturated, unsaturated (% of total fat) and trans (mg/day) fatty acids (FA)), total energy intake (kcal/day), fiber, alcohol, and specific food groups, such as fruits and vegetables (g/day), were conducted by a team of specifically trained dietitians using Spanish food composition tables [19], among other sources. Dietary sodium intake (mg/day) included sodium already in foods and sodium from salt added to the meal. Coffee habits were evaluated differentiating between caffeinated coffee and decaffeinated one. The FFQ captured coffee intake according to the number of cups of coffee (50 mL/cup) consumed: never or practically never, 1–3 times/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–6/day, >6/day. Major caffeine sources were caffeinated coffee, decaffeinated coffee, tea, chocolate and energy drinks and their content were calculated using Spanish food composition tables [19,20]. Among all items of the FFQ, caffeine and coffee ranked among the most reproducible ones, showing a correlation coefficient of $r = 0.80$ for caffeine and $r = 0.91$ for coffee in the validation study [21]. In addition, at each visit, adherence to the energy-reduced MedDiet was assessed by a validated 17-item screener, which is a modified version of the previously validated 14-item questionnaire and it provides additional information on food habits [22,23].

Study participants reported their physical activity (PA) using a validated questionnaire (REGICOR) [24]. Afterwards, MET values were calculated using formulas from the 2011 Compendium of Physical Activities, previously used to assess both total leisure-time PA (METs. min/week) [25,26]. Sedentary behaviors were reported using a Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study [27].

2.4. Other variables assessment

At baseline, participants answered questions on socio-demographics (sex, age, education level), medical conditions and medication use (antidiabetic, antihypertensive, cholesterol lowering), educational level, tobacco habits, family status and prevalence of self-reported, T2D, depression and criteria of the MetS.

At each yearly visit, trained staff took anthropometric measures of the participants. Height and weight were measured in participants wearing light clothes and without shoes in duplicate (the average value was used for analysis) by using a wall-mounted stadiometer and calibrated scales, respectively. BMI was calculated as weight (kg)/height (m) squared. WC (cm) was measured between the lowest rib and the iliac crest using an anthropometric tape.

2.5. Adiposity assessment

Study outcomes were adipose tissues quantified by DXA at baseline and after 6, 12 months and three years of follow-up. Whole body scans provided specific information on body composition, differentiating between three main body components (fat, lean and bone mass) and their localization (arms, legs, trunk, android and gynoid region). Measurements of fat tissue distinguished between total body fat, trunk fat, VAT, SAT and android-to-gynoid fat ratio, capturing regional differences which allowed to relate changes in adipose tissue with their cardiometabolic relevance [7,28]. Trained operators had third-generation DXA scanners from General Electric (DXA Lunar Prodigy Primo and Lunar iDXA; GE Healthcare, Madison, WI) connected with the enCore™ software at their disposal to carry out the body scans. VAT within android region was quantified by a reanalysis of the android region scans using the validated CoreScan™ software developed by GE Healthcare [29]. SAT (g) within android region was calculated by subtracting VAT from android fat mass, as previously described [30]. Protocols of DXA scans, including subject positioning and daily phantom calibration, were in accordance with manufacturer guidelines. Android-to-gynoid fat ratio was calculated by simple division of fat mass (g) from the respective regions. Total body fat was expressed in % of DXA-derived total body mass (sum of total bone, fat and muscle mass (g)).

2.6. Statistical analysis

Continuous variables describing the participants' socio-demographic, dietary and behavioral characteristics at baseline were presented with their sex- and age-adjusted means ± standard deviations (SDs) according to categories of coffee consumption (≤3 cups/month = infrequent, 1–7 cups/week = moderate, >1 cup/day = high; 1 cup = 50 mL). Categories were made for caffeinated, decaffeinated, total coffee and tertiles of caffeine intake. Categorical variables were described with the number of participants and percentages. Cohort descriptions were made according to the four independent variables of interest (total coffee consumption; caffeinated coffee; decaffeinated coffee and caffeine intake). Differences in age-, and sex-adjusted variables by coffee consumption categories were assessed using one-way analysis of variance (ANOVA) and chi-square tests (χ^2) (for continuous and categorical variables, respectively), and Kruskal Wallis for the 17-item score describing adherence to MedDiet.[22]

Repeated measures of all adiposity indicators, expressed as percent of total body weight, were normalized into a sex-specific z-scores (mean = 0, SD = 1), and they were used in statistical analyses accounting for the sexual dimorphism in body fat distribution [31]. Two-level linear mixed effect models with random intercepts at recruiting center and patient levels were used to assess the association between changes in coffee consumption and concurrent changes in DXA derived adipose tissues. The following variables were assessed as the main exposures: caffeinated coffee, decaffeinated coffee, total coffee and caffeine intake. In an ancillary analysis, the association between changes in coffee consumption and concurrent changes in BMI and WC was studied. All standard errors were calculated using the Huber/White/sandwich estimator [32]. The form of the relationship between each adiposity indicator and coffee consumption was hypothesized to be linear or J-shaped considering prior studies studying health benefits conferred by coffee consumption [33]. Therefore, consumption of caffeinated, decaffeinated, total coffee and caffeine was studied as a linear variable, as a categorical variable, and also using restricted cubic splines.

Concurrent changes in coffee consumption and changes in adiposity were assessed using repeated measures during follow-up (baseline, 6 months, 12 months, 3 years). Four main models were examined: (I) a crude model without any adjustment except for random intercepts at recruiting center and patient level; (II) additionally adjusting for age and sex; (III) additionally adjusting for intervention group; (IV) and additionally adjusting for educational level (academic degree, secondary education, primary education), smoking habits (current, never or former smoker), sedentary time (hours/day), PA (METs-min/d), energy-reduced MedDiet (score in 17-item screener), total energy intake (kcal/day) and sugar added to coffee (yes/no). Multicollinearity did not occur in any of these models. If independent variables had missing values during follow-

up, values were imputed by the preceding observations at earlier time points (last observation carried forward, LOCF). As a sensitivity analysis, we used multiple imputation procedures to replace the LOCF method.

Cubic spline models were performed with three knots. We used coffee intake as a continuous variable by adjusting coffee consumption for total energy intake and following the residuals method [16]. Potential confounders were adjusted for and we included them as covariates in the multivariable model used for the spline analyses.

Robustness of our findings was tested with several sensitivity analyses. First, we additionally adjusted for changes in sodium, saturated, total fat, monounsaturated and polyunsaturated fatty acid, alcohol, and fiber intake, and, also, for fruit and vegetable consumption, drinks of fruit juice, tea, sugar sweetened beverages as well as for baseline prevalence of depression, diabetes, hypertriglyceridemia and hypertension. Second, we used an alternative categorization of coffee consumption into 4 different groups (no coffee consumption/<1 cup/day/1 cup/day/>1 cup/day). Third, we applied alternative exclusion criteria for total energy intake (1st/99th percentiles and 5th/95th percentiles instead of the energy limits defined by cut-offs proposed by Willett [16]). Fourth, we excluded smokers and former smokers. And finally, analyses were run after applying the LOCF method (or multiple imputation methods) to dependent variables.

We conducted stratified analyses and we tested for statistically significant interactions between coffee/caffeine intake and the following variables: age (<65 or ≥ 65 years), T2D prevalence (yes or no), study arm (control or intervention), sedentary behavior (very sedentary ≥7 h/day or not very sedentary<7 h/day), overall obesity (BMI ≥30 kg/m^2 or BMI <30 kg/m^2), abdominal obesity (WC ≥ 102 cm (men) and ≥88 cm (women) or below these values). For this purpose, in the multivariable-adjusted models the cross-product terms between these variables and the categories of coffee or caffeine intake were tested.

All statistical analyses were performed using Stata v16.0 program, with statistical significance set at $p < 0.05$. We used the latest DXA database from PREDIMED-Plus, generated on 11th June 2021.

3. Results

Table 1 summarizes the characteristics of the cohort as a whole and according to consumption of caffeinated coffee. The cohort showed a relatively low average level of caffeinated coffee intake since 357 (53.9%) participants drank no coffee or less than 3 cups per month, 222 (47.3%) consumed one to seven cups per week and

Table 1
Cohort description at baseline according to consumption of caffeinated coffee.

	Variables	Total	≤3 cups/month	1-7 cups/week	>1 cup/day	
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
	n	1483	662	469	352	
Sex	Women [n, %]	705 (47.5%)	357 (53.9%)	222 (47.3%)	126 (35.8%)	<0.001
Group assignment	Intervention group [n, %]	742 (50.0%)	334 (50.5%)	232 (49.5%)	176 (50.0%)	0.948
	Age [years]	65.3 (5.0)	65.9 (4.9)	65.3 (4.8)	64.1 (5.2)	<0.001
Coffee consumption	Caffeinated coffee [mL/day]	46.5 (57.2)	0.1 (0.5)	44.9 (11.9)	136.1 (39.0)	<0.001
	Decaffeinated coffee [mL/day]	33.0 (46.8)	58.8 (52.6)	16.0 (29.6)	7.2 (23.2)	<0.001
	Total coffee [mL/day]	79.6 (57.2)	58.9 (52.6)	60.9 (31.2)	143.3 (44.4)	<0.001
	Caffeine from all sources [mg/day]	63.4 (64.1)	14.3 (19.1)	60.3 (21.3)	159.9 (46.1)	<0.001
Body composition − DXA measurements	BMI [kg/m^2]	32.7 (3.3)	32.7 (3.3)	32.6 (3.3)	32.9 (3.2)	0.358
	Waist circumference [cm]	107.9 (9.3)	107.0 (9.2)	107.6 (9.0)	109.8 (9.4)	<0.001
	Total lean mass [%]	56.5 (6.6)	55.7 (6.7)	56.8 (6.5)	57.6 (6.2)	<0.001
	Total fat mass [%]	40.4 (6.9)	41.3 (7.1)	40.1 (6.9)	39.3 (6.5)	<0.001
	Visceral adipose tissue [%]	2.6 (0.8)	2.6 (0.8)	2.6 (0.8)	2.8 (0.8)	0.006
	Trunk fat [%]	23.9 (3.6)	24.3 (3.6)	23.6 (3.6)	23.7 (3.5)	0.002
	SAT [%]	1.7 (0.8)	1.8 (0.8)	1.7 (0.8)	1.6 (0.8)	0.003
	Android-gynoid ratio	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.003
Physical activity	Physical activity (Met.min/week)	2683 (2322)	2673 (2342)	2784 (2366)	2569 (2225)	0.417
	Sedentary time [h/day]	3.1 (1.7)	3.2 (1.7)	3.1 (1.6)	3.0 (1.6)	0.243
Diet	Total energy intake [kcal/day]	2390 (533)	2350 (522)	2368 (520)	2497 (556)	<0.001
	SFA [% of total fat]	10.1 (1.9)	10.1 (1.9)	10.0 (2.0)	10.3 (2.0)	0.058
	PUFA [% of total fat]	6.7 (1.8)	6.7 (1.8)	6.9 (2.0)	6.7 (1.8)	0.181
	MUFA [% of total fat]	21.3 (4.2)	21.3 (4.2)	21.1 (4.3)	20.9 (4.1)	0.301
	Trans-FA [mg/day]	614 (389)	569 (368)	616 (383)	698 (422)	<0.001
	Sodium [mg/day]	3281 (1028)	3209 (1038)	3238 (969)	3474 (1064)	<0.001
	Fiber [g/day]	26.2 (8.1)	26.2 (8.1)	25.9 (8.3)	24.8 (8.4)	0.036
	Pure alcohol [g/day]	9.4 (13.4)	9.4 (13.4)	12.5 (15.6)	14.0 (17.1)	<0.001
	Fruits [g/day]	342 (200)	349 (196)	356 (210)	311 (190)	0.003
	Vegetables [g/day]	310 (121)	316 (119)	307 (122)	303 (124)	0.209
	er-MedDiet [17-item score]	8.4 (2.6)	8.6 (2.7)	8.3 (2.5)	7.9 (2.5)	<0.001
Family status	Married [n, %]	1122 (75.7%)	511 (77.2%)	350 (74.6%)	261 (74.1%)	0.474
Education level	Academic degree	317 (21.4%)	119 (18.0%)	101 (21.5%)	97 (27.6%)	<0.001
	Secondary/high school	445 (30.0%)	179 (27.0%)	149 (31.8%)	117 (33.2%)	
	Primary school	721 (48.6%)	364 (55.0%)	219 (46.7%)	138 (39.2%)	
Tobacco habits	Never-smoker	620 (41.8%)	325 (49.1%)	192 (40.9%)	103 (29.3%)	<0.001
	Smoker	190 12.8%)	67 (10.1%)	60 (12.8%)	63 (17.9%)	
	Former smoker	673 45.4%)	270 (40.8%)	217 (46.3%)	186 (52.8%)	
Prevalent diseases	Hypercholesterolemia [n, %]	1000 (67.4%)	447 (67.5%)	318 (67.8%)	235 (66.8%)	0.910
	Arterial hypertension [n, %]	1254 (84.6%)	577 (87.2%)	383 (81.7%)	294 (83.5%)	0.035
	Diabetes [n, %]	329 (22.2%)	148 (22.4%)	108 (23.0%)	73 (20.7%)	0.726
	Hypertriglyceridemia [n, %]	826 (55.7%)	357 (53.9%)	266 (56.7%)	203 (57.7%)	0.451
	Depression [n, %]	393 (26.5%)	190 (28.7%)	131 (27.9%)	72 (20.5%)	0.013

BMI: body mass index; DXA measurements in % of DXA-derived total body mass (sum of total bone, fat and muscle mass); SAT: subcutaneous adipose tissue; SFA: saturated fatty acids; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids; FA: fatty acids; er-MedDiet: energy reduced Mediterranean diet score.

126 (35.8%) drank more than one cup per day. Most relevant differences between these groups were that those with higher consumption of caffeinated coffee had a higher percentage of men and tended to be younger. Also, a higher prevalence of smoking, higher total energy intake, higher salt and trans-unsaturated fatty acid (TFA) intake, higher intake of pure alcohol and less fruit consumption, lower adherence to the er-MedDiet and more pronounced abdominal obesity were found among those consuming more than one cup of coffee per day reflecting a generally unhealthier lifestyle. However, a higher educational level was associated with higher coffee consumption. Differences in lifestyle between participants with high intake of decaffeinated coffee and those with little consumption of decaffeinated coffee were small, except for salt intake (Supplementary Table 1). In a cohort description grouped by categories of total coffee consumption, differences between groups were observed for sex, age, total energy intake, MUFA, TFA, sodium, adherence to the er-MedDiet, educational level, tobacco habits and depression prevalence (Supplementary Table 2). Covariable distribution according to categories of caffeine intake largely overlapped with the distribution across groups of caffeinated coffee (Supplementary Table 3).

During the follow-up, anthropometric measures of BMI and WC and lifestyle factors such as PA and dietary patterns improved in comparison to their baseline levels in both trial arms combined ($p < 0.05$ for all characteristics, see Supplementary Table 4). Unlike many other dietary habits, average coffee consumption did not significantly change over time at the cohort level, as a whole. Supplementary tables 5-7 summarize the number of participants with changes in coffee consumption during follow-up, according to caffeinated, decaffeinated and total coffee consumption.

Table 2 shows the main associations observed between changes in consumption of caffeinated coffee and concurrent changes in body fat distribution. After controlling for potential confounders in the multivariable adjusted model, lower total body fat was observed in participants who changed from low to moderate (intermediate) coffee consumption as compared to those who remained with low consumption (no or infrequent consumption), $\beta_{\text{multivariable adjusted}}$ = - 0.06 z-score (95% CI: - 0.11; - 0.02; $p = 0.006$). Similar results were observed for changes in trunk fat ($\beta_{\text{multivariable adjusted}}$ = - 0.07; z-score; 95% CI: - 0.12; - 0.02; $p = 0.009$) and visceral adipose tissue ($\beta_{\text{multivariable adjusted}}$ = - 0.07 z-score; 95% CI: - 0.13; - 0.01; $p = 0.029$). No significant associations were found for participants who changed from low to higher levels of caffeinated coffee consumption. SAT and the android-to-gynoid fat ratio were not associated with any of the changes in caffeinated coffee intake. In the multivariable adjusted model, the variable on adding sugar to coffee was not associated with changes in any adipose tissue. The results, from the crude model and the age and sex-adjusted model, are shown at Supplementary Table 8. A linear dose–response relationship was not found and no significant associations were observed for the highest intake category of caffeinated coffee as compared to the lowest coffee intake category. The basic anthropometric measures, namely, BMI and WC, were not associated with any change in coffee consumption of any kind.

A stratified analysis by sex suggested slightly stronger associations of concurrent changes in total fat and trunk fat with moderate intake of caffeinated coffee in men, though the confidence intervals were wider for both men and women subgroups, as expected because of the lower sample size within each stratum (Supplementary table 9) and no statistically significant multiplicative interaction was observed between sex and coffee consumption.

Cubic spline models confirmed a J-shaped dose–response relationship for the association between caffeinated coffee and total and trunk fat. The model for VAT did not reach statistical significance (see Fig. 1 and Supplementary Figs. 2 and 3).

Analyses assessing the association between decaffeinated coffee consumption and adiposity markers did not show any statistically significant results (see Supplementary Tables 10 and 11). Inverse associations of total coffee consumption with total fat, trunk fat and VAT were attenuated in comparison to caffeinated coffee (see Supplementary Table 12). The magnitude of the associations with total fat and trunk fat shrank, however it maintained its statistical significance, whereas moderate consumption of total coffee was not inversely related to VAT.

Table 2
Associations between concurrent changes in consumption of **caffeinated** coffee and fat distribution.

Δ z-scores – DXA derived adipose measurement	Increase in caffeinated coffee consumption from low (≤3 cups/month) to moderate and high consumption		
	Δ to moderate (1–7 cups/week) from low, β (95% CI)	Δ to high (>1 cup/day) from low, β (95% CI)	p for trend
Total body fat			
Minimally-adjusted	**−0.05 (-0.10 to -0.01)**	−0.00 (−0.05 to 0.05)	0.793
Multivariable-adjusted	**−0.06 (-0.11 to -0.02)**	−0.02 (−0.07 to 0.03)	0.737
Trunk fat			
Minimally-adjusted	**−0.06 (-0.11 to -0.01)**	0.01 (−0.05 to 0.07)	0.470
Multivariable-adjusted	**−0.07 (-0.12 to -0.02)**	−0.01 (−0.07 to 0.05)	0.931
Subcutaneous adipose tissue			
Minimally-adjusted	0.02 (−0.04 to 0.09)	−0.00 (−0.07 to 0.07)	0.937
Multivariable-adjusted	0.02 (−0.05 to 0.08)	−0.01 (−0.08 to 0.06)	0.745
Visceral adipose tissue			
Minimally-adjusted	−0.06 (−0.12 to 0.00)	0.04 (−0.03 to 0.11)	0.164
Multivariable-adjusted	**−0.07 (-0.13 to -0.01)**	0.02 (−0.05 to 0.09)	0.429
Android-to-gynoid fat ratio			
Minimally-adjusted	−0.02 (−0.07 to 0.03)	0.02 (−0.04 to 0.08)	0.416
Multivariable-adjusted	−0.03 (−0.08 to 0.02)	0.01 (−0.05 to 0.08)	0.572

1 cup equals 50 mL. Total fat mass, trunk fat, subcutaneous adipose tissue, visceral fat tissue (% of DXA-derived total body mass (sum of total bone, fat and muscle mass)) and android-to-gynoid fat ratio were normalized into a sex-specific z-scores for analysis. The consumption of coffee was categorized in three categories: low - ≤ 3 cups/month; moderate - 1–7 cups/week; high - 1 cup/day. Analyses were performed using linear mixed-effects models with random intercepts at recruiting center and patient level. In the model beta represents changes in adiposity indicators expressed as sex-specific z-scores, associated with changes in comparison to no or sporadic coffee consumption, the reference category. Minimally-adjusted model controlled for age, sex and study arm. Multivariable-adjusted model further included total energy intake, educational level (academic degree, secondary/high school, primary school), tobacco habits (current smoker, former smoker, never smoker), adherence to the Mediterranean diet (17 item score), physical activity (METs-min/week), sedentary behaviour (h/day) and adding sugar to coffee (yes/no). Updated values of covariates were used, in case of missing values the last observation was carried forward.

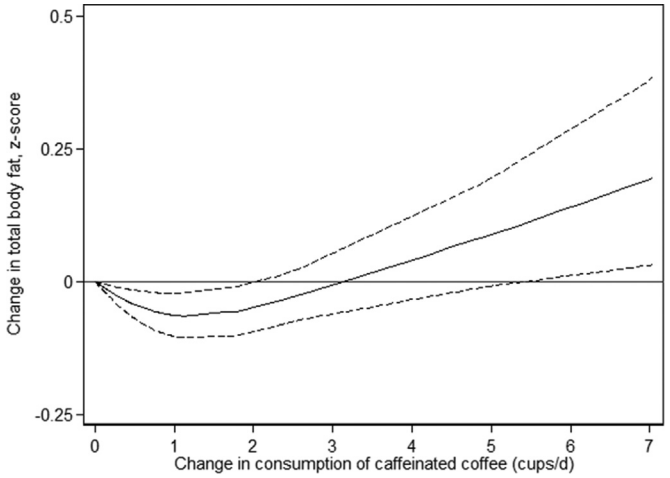

Fig. 1. Multivariable adjusted cubic spline model testing the association between concurrent changes in consumption of caffeinated coffee and total body fat.
Adjusted for age, study arm, total energy intake, educational level (academic degree, secondary/high school, primary school), tobacco habits (current smoker, former smoker, never smoker), adherence to the energy-reduced Mediterranean diet (17 item score), physical activity (METs-min/week), sedentary behavior (h/day). P for non-linearity: $p < 0.001$.

The results of the analyses focusing on caffeine intake from all food sources were similar to those for caffeinated coffee. Inverse associations with total body and trunk fat were observed for the comparison between the intermediate category of caffeine intake and the lowest category. Statistically significant associations for VAT were not found for caffeine (see Supplementary Table 13). The sources of caffeine included caffeinated coffee, decaffeinated coffee, tea, chocolate and energy drinks, among which caffeinated coffee was clearly the dominant contributor.

Sensitivity analyses confirmed the robustness of the association between moderate consumption of caffeinated coffee and fat tissues (Supplementary Figs. 4–6). However, in the analysis excluding smokers the association of caffeinated coffee with VAT lost statistical significance, and in the analysis restricted to never smokers an inverse association between caffeinated coffee and any fat tissue could not be substantiated. Analyses using imputed data of DXA measurements during follow-up showed slightly attenuated associations.

No evidence for effect modification by age group, T2D prevalence, study arm, sedentary lifestyle, BMI or particularly pronounced abdominal obesity (WC $\geq$ 102 cm for men; WC $\geq$ 88 cm for women) was found for the studied exposures (caffeinated coffee, decaffeinated coffee, total coffee or caffeine intake). Stratified analyses assessing possible effect modification resulted in null results for exposure to caffeinated coffee.

4. Discussion

Our study used repeated measures over three years in an elderly cohort at high cardiovascular risk with high prevalence of obesity, dyslipidemia and T2D. The follow-up on both dietary habits and highly precise DXA measurements of body composition allowed to relate their changes with each other. We found that an increase from no or infrequent drinking to a moderate consumption of caffeinated coffee was associated with a reduction of total fat, trunk fat and VAT. To the best of our knowledge, this study is the first prospective assessment using repeated measurements which can relate moderate consumption of caffeinated coffee with a reduction in fat tissues using highly precise DXA measurements.

The article derived from the NHANES study which could overcome the limitations of simple anthropometric measures by using DXA measurements, reported an inverse association between coffee consumption and both total body fat and trunk fat at a cross-sectional level [12]. Our study only included participants with MetS at baseline and may account for a different susceptibility to a potential anti-obesity effect of coffee related to higher baseline VAT. This possibility should further be explored in future studies comprising subjects with and without MetS. Among the discussed mechanisms are the actions of caffeine, a booster of catecholamine activity in the sympathetic nervous system which preferentially targets visceral adipocytes instead of subcutaneous adipocytes [10,34,35].

Longitudinal studies have found an association between increases in coffee consumption and a modest attenuation of weight gain [11,36]. It is noteworthy that previous studies could not find weight loss among participants with habitually stable higher coffee consumption, but indicated that fat tissue is only affected by dynamic changes in the quantity of coffee consumed. Randomized trials mainly reported metabolic changes only over short follow-up periods but without providing results on typical clinical adiposity measures like BMI or WC [37–39]. Our study gives support to previous interpretations that weight loss as well as changes in BMI and WC are likely to be due to an increase in coffee consumption and this can be reflecting a specific reduction in fat tissue. We identified trunk fat and VAT as fat tissues primarily associated with changes in caffeinated coffee. Unfortunately, we could not deal with the question whether a certain stable level of coffee consumption entails an anti-obesity effect because only very few participants maintained their baseline coffee consumption over three years, reducing the cohort too much for an analysis of this question.

In a Mendelian Randomization study, an allele-score associated with coffee consumption did not predict changes in anthropometric measures after adjustment for age and sex. However, in agreement with known limitations and strong assumptions of that design, the authors pointed out the difficulty to draw firm conclusions from the results as their allele score was associated with pleiotropic effects influencing clinical drugs, procarcinogens, steroids and even with age, highlighting potential confounding [41,42]. Indeed, a reduction in adiposity measures by the found allele score was found when not adjusted for age. Our study adds valuable evidence and intensive correction for many potential confounders and minimized the risk of reverse causation. However, given the inconsistencies of the available literature, a causal relation between coffee consumption and obesity remains contentious and asks for large RCTs to give definite answers on the question of causality.

Efforts to explain the biological plausibility of coffee's anti-obesity effect often refer to the complex profile of coffee's bioactive metabolites. Chlorogenic acid, lipids, especially diterpenes such as cafestol and kahweol, trigonelline, caffeine and phenolic compounds as epigallocatechin gallate and caffeoylquinic acids are intensively studied [43]. It is believed that a key transformation happening during obesity development is an increase in the number of adipocytes, their size and the release of proinflammatory signals [44]. In particular phenolic compounds proved to inhibit adipocyte hyperplasia [43]. Caffeine boosts catecholamine activity in the sympathetic nervous system, increases energy expenditure, and modulates metabolism in fat tissue favoring weight loss [10,34,45,46]. Visceral adipocytes show higher sensitivity to catecholamines, having richer sympathetic innervation than SAT and therefore VAT was hypothesized to be preferentially targeted by caffeine [35,47].

In our studies we found no association between changes in decaffeinated coffee and changes in adipose tissue. As during the

decaffeination process, other bioactive components might be extracted, too, just as caffeine, caffeine levels may represent a marker within the decaffeination process but not mirror the entire spectrum of involved substances. Therefore, entirely attributing to caffeine the observed weight loss with moderate consumption of caffeinated coffee seems to be premature.

Our study has several methodological strengths: first, the cohort was comprised of elderly subjects at high CVD risk with MetS, thus contributing to shed light on an important patient group in clinical practice which is in need for effective weight loss strategies. Yet this specific patient group had been poorly studied in the context of coffee consumption previously and given changed pharmacokinetics due to age and overweight previous results of studies could not be directly applied to the described cohort [49]. Aging populations and increased obesity prevalence worldwide emphasize the need for evidence-based knowledge on a multitude of approaches useful to prevent obesity and more specifically abdominal obesity. Second, our study had a prospective, design with repeated measurements and a relatively large sample size overcoming the limitations of a cross-sectional design. Data were gathered by trained dietitians using a validated FFQ providing detailed information on habitual dietary intake allowing the control of many potential confounders in sensitivity analyses. Our study collected measures of exposure and outcome repeatedly at the same timepoints and consequently provided reliable longitudinal information on dynamic changes in both the exposure and the outcome. Third, body composition was objectively and accurately determined by DXA providing information on total adiposity and its distribution in different tissues and overcame the lack of specificity of anthropometric measures. Fourth, several sensitivity analyses proved the results to be robust, also after additional correction for more potential confounders.

Despite the numerous strengths our study was subject to several limitations. First, the results did not suggest a linear dose–response pattern, which is one of the best-known criteria for causality. However, it is biologically plausible that some relationships in nature might be non-linear. Also, we acknowledge that the average levels of coffee consumption in our cohort (particularly, the low number of participants drinking more than one cup per day), may limit the ability to capture a clinically important association for higher levels of coffee consumption. Second, our study did not capture the specific coffee blends or preparation techniques and therefore lacks detailed information on the profile of bioactive components, which could provide mechanistic explanations for the supposed anti-obesity effect of coffee. Third, these analyses represent a sub-study nested within the PREDIMED-Plus study and as coffee consumption was not randomized, reverse causation cannot be excluded. However, we were able to adjust for a wide array of potential confounders. Some participants with hypertension might have abstained from coffee because of a widely believed preconception that caffeinated coffee worsens cardiovascular health. As hypertension often coincides with obesity, the higher obesity level among non-consumers might have been a consequence of the explained precautionary measure. Fourth, heavy coffee consumption is associated with numerous risk factors including unfavorable dietary habits which could overshadow a beneficial association with fat tissue among heavy coffee drinkers despite intensive confounder control. That is why we interpret the J-shaped dose–response relationship in our study with caution, asking for more prospective studies and trials to reach final conclusions on the shape of the relation. Besides, our cohort was comprised of senior subjects at high cardiovascular risk with MetS and potentially altered pharmacokinetics. This fact may impede the transfer of the findings to the general population. Nevertheless, they represent a sector of the population of greatest clinical interest.

The reduction of VAT is supposed to confer benefits on metabolic health and considering other numerous health benefits a recommendation in favor of moderate coffee consumption could be included in weight-loss strategies for the elderly at high cardiovascular risk. Further studies are needed to confirm our findings. Despite the small absolute magnitude of the observed association, its impact might have some public health relevance as coffee is one of the most widely consumed beverages. Moreover, future research is needed to elucidate the properties and associations of different coffee types and their profiles of bioactive molecules. In particular, the question on the origins of differences in the association with caffeinated and decaffeinated coffee, might be answered in future studies investigating composition of coffee compounds within a clinical context. Studies with other beverages could help to elucidate whether caffeine is the principal acting compound affecting fat tissue or merely a surrogate of caffeinated coffee.

5. Conclusion

In a Mediterranean cohort of elderly people at high cardiovascular risk, increase to moderate consumption of caffeinated coffee (1–7 cups per week), but not higher levels of consumption, was associated with a reduction in total body fat, trunk fat and VAT. Decaffeinated coffee was not linked to adiposity indicators. Moderate consumption of caffeinated coffee may be part of a weight management strategy in an elderly population with obesity.

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Author contribution

M Henn conceived the present study, conducted statistical analyses, interpreted the results and drafted the manuscript. M Ruiz-Canela and MA Martínez-González supervised the study. All

authors were involved in oversight of recruitment, data collection, revision of the manuscript and read and approved the final manuscript.

Conflict of Interest

The authors do not have any conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.02.004.

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