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Original article

Coffee consumption and risk of hypertension in the SUN Project

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SUMMARY

Background & aims: Evidence on coffee consumption and its association with the incidence of hypertension is still inconsistent. The aim of this study was to examine the association of regular or decaffeinated coffee consumption with the risk of developing hypertension in a middle-aged Mediterranean cohort.

Methods: The SUN Project is a prospective open cohort with more than 22,500 Spanish university graduates. For the present study, we analyzed data from 13,374 participants initially free of hypertension (mean follow-up 9.1 years). The consumption of regular and decaffeinated coffee was obtained at baseline using a previously validated semi-quantitative food frequency questionnaire. Validated, self-reported medical diagnoses of hypertension were collected biennially. We used Cox regression models to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for incident hypertension according to baseline coffee consumption. We assessed the interaction with sex and baseline adherence to the Mediterranean diet.

Results: Among 121,397 person-years of follow-up, a total of 1757 participants developed hypertension. Overall, coffee consumption −either caffeinated or decaffeinated− was not significantly associated with the risk of hypertension. Only among women, higher consumption of regular coffee was associated with a 26% lower risk of hypertension (>=2 cups/d vs. never/seldom, 95% CI 9%−39%; p for interaction: 0.0236). Women with a low baseline adherence to the Mediterranean diet showed the strongest risk reduction (HR ≥ 2 cups/d vs. never/seldom 0.58, 95% CI (0.41−0.82) p for interaction = 0.0452).

Conclusion: In the SUN project we found an inverse association between regular coffee consumption and the risk of hypertension in women, which was strongest among women with a suboptimal food pattern (low adherence to the Mediterranean diet).

1. Introduction

The worldwide prevalence of hypertension was 22% in 2014 [1]. Hypertension bears an independent and continuous relationship with the incidence of several cardiovascular events (stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease as well as of end-stage renal disease) [2]. Worldwide, 7•6 million premature deaths (about 13•5% of the total mortality) are estimated to be attributable to hypertension [3].

Dietary habits, among other lifestyle factors, have been linked to changes in blood pressure (BP) [4]. Specifically, coffee consumption has long been a suspected cause of hypertension [5]. Coffee is one of the most widely consumed beverages around the world. In 2016 coffee consumption in the European Union reached 6.3 kg/person, followed by the United States with a measured consumption of coffee of 5.6 kg/person in the adult population [6]. Short-term experimental studies have shown that caffeine intake acutely increases BP because of raised plasma levels of several stress hormones [7]. Nevertheless, adaptation to the cardiovascular effects of coffee drinking occurs quickly and the cardiovascular responses seem to develop during regular use tolerance [8]. Randomized trials assessing the long-term effects of coffee consumption are not available. On another note, coffee also contains other minor

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compounds which have been shown to have antioxidant properties. This could explain the beneficial effects on the cardiovascular system [9–11] and partly illustrate the conflicting findings of studies examining the relationship between coffee and hypertension.

Prospective observational studies have observed associations between coffee consumption and hypertension [12,13], but findings are inconsistent [14–17]. In addition, and to our knowledge, the association between coffee consumption and the risk of hypertension has not been studied in a Mediterranean cohort nor has coffee consumption been studied in the context of the Mediterranean diet. The Mediterranean diet has shown to be inversely associated with the risk of hypertension in previous reports [18–21]. Taking this into account, together with the idea that foods and nutrients interact with each other because they are not consumed in isolation [22], our cohort offers a unique opportunity to assess the interaction between adherence to the traditional Mediterranean diet and coffee consumption in their association with incident hypertension. Therefore, the aim of our study was to ascertain the association between coffee consumption and the risk of hypertension in a middle-aged Mediterranean cohort and to assess this relationship according to the degree of adherence to the Mediterranean diet.

2. Materials and methods

2.1. Study population

The objectives, design, and methods of the SUN Project have been described elsewhere [23]. Briefly, the SUN Project is a multipurpose, cohort, with permanently open recruitment, designed to assess the association between diet and several chronic diseases and health conditions. It was developed following the models of the Nurses' Health Study and the Health Professionals Follow-up Study. Participants are all university graduates. The recruitment of participants started in December 1999 and it is permanently open. After the initial questionnaire, additional questionnaires are mailed biennially in order to follow up the participants. Up to December 1st 2015, we had recruited 22,476 participants (61% women, with a median age of 36 years, interquartile range 28–47 years).

Participants (n = 798) in the SUN study (Fig. 1) who were recruited later than March 2013 (2.75 years before December 1st 2015 to ensure sufficient time to complete at least 1 follow-up questionnaire), those without information on follow-up (n = 2009), and those who left >10 items blank in the FFQ (n = 1922) were excluded. Among the available 17,747 participants, we excluded those with total energy intake outside of predefined limits (<800 or >4000 kcal/day for men and <500 or >3500 kcal/day for women) (n = 1633). Subjects reporting a diagnosis of cancer, chronic heart disease or diabetes at baseline were also excluded (n = 1488) because of possible dietary changes following the diagnosis of these disorders. We also excluded those participants reporting a medical diagnosis of hypertension at baseline, or taking anti-hypertensive medication (n = 1228). Finally, data from 13,374 participants were included in our analyses.

2.2. Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Institutional Review Board at the University of Navarra. We considered a response to the initial questionnaire as informed consent to participate in the study.

2.3. Coffee consumption assessment

Diet was assessed using a semi-quantitative food-frequency questionnaire previously validated in Spain [24–26], including two questions on coffee consumption, one for regular coffee and another one for decaffeinated coffee consumption. Participants were asked to estimate their average intake over the previous year of regular coffee and of decaffeinated coffee (cup, size 50 cc) choosing between nine categories. 'never/seldom', '1–3 per month', '1 per week', '2–4 per week', '5–6 per week', '1 per day', '2–3 per day', '4–6 per day' '6 + per day'.

2.4. Assessment of blood pressure

Hypertensive status was defined by previously validated, self-reported medical diagnosis of hypertension [27]. Participants were asked whether they had ever had a medical diagnosis of hypertension. They were also asked if they took antihypertensive medication. Those who had a medical diagnosis or were under treatment for hypertension at baseline were excluded from the analyses. In addition, we requested information from all participants about their usual systolic BP (SBP) and diastolic BP (DBP) levels. The participants could choose between the following categories for SBP (mmHg): lower than 100; 101–110; 111–120; 121–130; 131–140; 141–150; 151–160; 161–175; greater than 175. For DBP they could choose between (mmHg): lower than 60; 61–70; 71–80; 81–90; 91–100; 101–110; 111–120; 121–130; greater than 130. No specific recommendations about timing or device for BP measurements were given. We considered participants to have previously undiagnosed hypertension if they did not report a medical diagnosis or treatment for hypertension, but reported that their SBP was at least 140 mmHg and/or their DBP was at least 90 mmHg in the baseline questionnaire. We followed the criteria from the Eighth Report of the Joint National Committee [4]. This case-definition allowed us to capture mainly incident cases of hypertension, excluding those who might have been labelled as 'hypertensive' prior to our assessment.

Information on month and year of hypertension diagnosis is collected in all follow-up questionnaires. For participants with self-reported information on medical diagnosis of hypertension but missing information on date of diagnosis, the mid-point between the date of completion of the follow-up questionnaire with the self-reported medical diagnosis of hypertension and the previous follow-up questionnaire was used to impute the date of diagnosis.

2.5. Other covariates

The baseline questionnaire also included questions about different socio-demographic factors (sex, age, marital and employment status, university degree), anthropometric variables (weight, height), health-related habits (smoking status, number of cigarettes smoked at different ages, alcohol consumption, physical activity) and clinical variables (use of medication, personal and family history of CHD, cancer and other diseases). Body mass index (BMI) was calculated as the self-reported weight in kilograms divided by the square of height in meters. Self-reported BMI has been previously validated in this cohort and showed adequate accuracy [28]. Information on leisure-time physical activity was collected with a validated questionnaire [29]. It included questions on 17 different activities; frequency options ranged from never to 11 + h/wk with 9 possible answers, and participants also provided information on the number of months/y engaging in each activity to account for stationarity. To quantify the amount of activity during leisure time, an activity metabolic equivalent (MET) index was computed by assigning a multiple of resting metabolic rate (MET

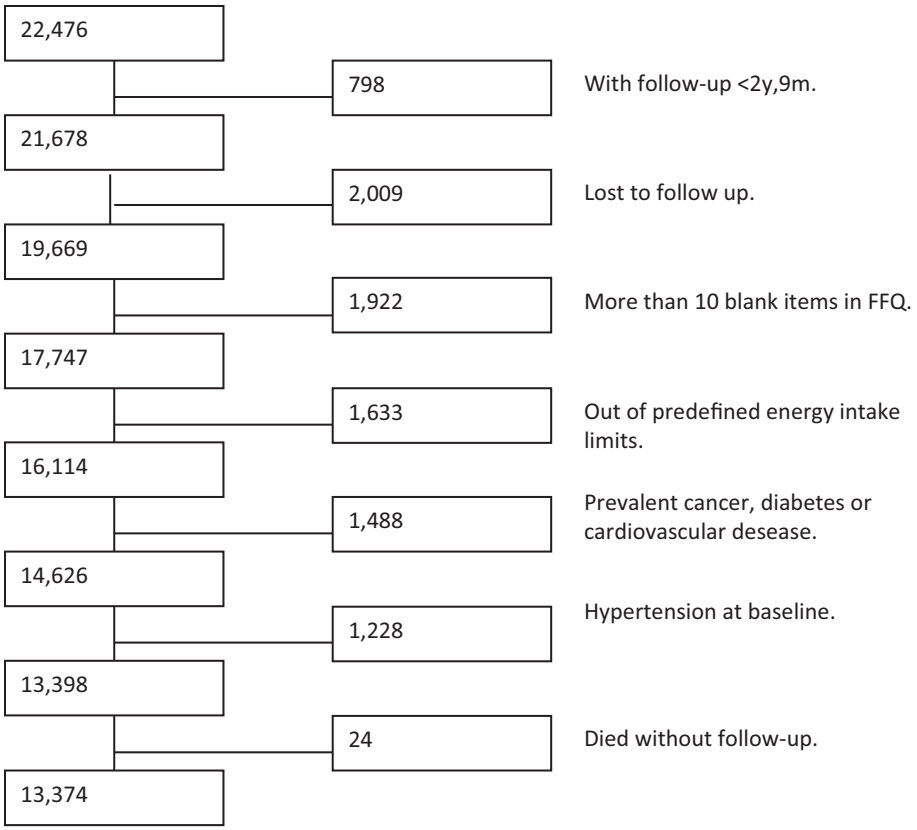


Fig. 1. Flow chart.

score) to each activity. Time spent in each of the activities was multiplied by the MET score specific to each activity, and then summed over all activities obtaining a value of overall weekly MET-hours/week. Mediterranean dietary pattern was assessed by an a priori 9-point Mediterranean-diet scale as proposed by Trichopoulou et al. This score incorporated the salient characteristics of this diet (range of scores, 0 to 9, with higher scores indicating greater adherence) [30]. In this latter score, participants receive 1 point if they are above the sex-specific median for the consumption of each of 6 elements typical of the traditional Mediterranean diet (vegetables, fruits and nuts, monounsaturated:saturated fatty acid intake, fish, legumes and cereals), and another point if they are below the sex-specific median for the consumption of 2 elements considered contrary to the traditional Mediterranean diet (red meat and meat products and dairy products). One additional point is given for moderate alcohol consumption (10–50 g/d in men and 5–25 g/d in women). Coffee consumption is not considered as part of this score. The baseline questionnaire also included three Likert-type questions on personality traits (range 0–10) (conformist-competitive; calm-tense; dependent-independent).

2.6. Statistical analysis

The main outcome for our analyses was incident hypertension, as previously described. Participants were categorized into 4 groups based on their regular coffee consumption: never/seldom, less than one cup per day, one cup per day, two or more cups per day.

For foods other than coffee, food consumption was adjusted for total energy intake using the residuals method [31]. Time-to-event data were analyzed using Cox regression models with age as underlying time variable. Person-time was calculated from the date of enrolment to the date of self-reported diagnosis of hypertension, date of death or last follow-up questionnaire, whichever occurred first, and up to December 1st 2015, when the dataset used for the present analysis was closed. After adjusting for age, we fitted a model adjusted for sex, age and recruitment period. In a subsequent model, we additionally adjusted for other risk factors of cardiovascular disease [sex, age, BMI (quartiles), alcohol intake (quintiles), smoking status, package-years of smoking (continuous), family history of hypertension, sodium intake (quintiles), whole-fat and low-fat dairy products consumption (quintiles), diet and sugar-sweetened beverages (three categories), physical activity (continuous), adherence to Mediterranean diet (using the score by Trichopoulou (continuous)), type of personality (conformist-competitive; calm-tense; dependent-independent (continuous)), time spent watching TV (continuous), and fried and fast-food consumption (tertiles)].

For all subjects, we calculated the category-specific median of regular or decaffeinated coffee consumption and treated the resulting value as quantitative for calculating the linear trend tests.

We calculated the p for interaction between regular or decaffeinated coffee consumption (4 categories of consumption) and three prespecified variables: smoking (3 categories), sex or age (continuous) with the likelihood-ratio test. The a priori selection of these interactions was based on previous literature. In order to test for the interaction with age, we changed the underlying time variable and used time-on-study as underlying time variable and used age as continuous variable. Once a statistically significant interaction was identified, the subsequent analyses were stratified according to the categories of the effect modifier.

We also stratified our analyses according to baseline adherence to the Mediterranean diet (0–3 points/4–9 points). We also calculated the p value for another prespecified interaction between

baseline adherence to the Mediterranean diet [high (4–9 points in the score of adherence to the Mediterranean diet) vs. low (0–3 points in the score of adherence to the Mediterranean diet)] and regular or decaffeinated coffee consumption (≥1 cup/vs. never/seldom) with the likelihood-ratio test.

All the interactions that we tested were specified a priori.

We repeated our analyses for total coffee consumption, considering the consumption of both decaffeinated and regular coffee together.

As sensitivity analyses, we changed the assumptions on induction periods changing our censoring after six, eight or ten years of follow-up.

Analyses were performed with Stata version 12 (Stata Corp., TX, USA). All p values were two-tailed. Statistical significance was set at the conventional 0.05 level.

3. Results

After exclusions, we included 13,374 participants of the SUN cohort in our analyses (Fig. 1). The median time of follow-up was 10.1 years. Among them, we observed 1757 new diagnoses of hypertension during 121,397 persons-years of follow-up. Thus, the crude incidence rate of hypertension was $1.4*10^{-2}$ person-years^{-1}.

Table 1 shows the main baseline characteristics of population according to coffee consumption (never/seldom coffee consumption, less than one cup per day, one cup per day, or two or more cups per day). The mean age of participants was 35.7 (SD: 10.4) years, and 36.1% were men. Participants who consumed more than one cup of coffee had lower levels of physical activity, higher intake of alcohol and were more likely to be current smokers. Participants who consumed less than one cup of coffee per day had a higher consumption of high-fat dairy products. In general, older persons were more likely to drink coffee.

Table 2 shows the hazard ratios (95% CI) for the risk of hypertension, according to regular coffee consumption. We observed no significant association between baseline coffee consumption and subsequent risk of hypertension in any model. The linear trends test was not statistically significant either.

We found a significant interaction between regular coffee consumption (4 categories) and sex (p = 0.0236). In women, we found an inverse association between regular coffee consumption and hypertension. Women who consumed at least 2 cups of regular coffee per day showed a HR = 0.74 (95% CI 0.61–0.91) in comparison with women who never/seldom consumed coffee (Table 3). No significant interactions between coffee consumption and smoking or coffee consumption and age were found on the risk of incident hypertension.

In order to appraise the influence of Mediterranean diet we evaluated the interaction between coffee consumption and the Mediterranean dietary pattern. We found a significant interaction in women (p = 0.0452). Female participants who had a lower adherence to Mediterranean diet and consumed at least 2 cups of regular coffee had a Hazard Ratio of 0.58 (95% CI 0.41–0.82) of developing hypertension as compared to women who never/seldom drank coffee in the fully adjusted model, whereas no significant association between regular coffee consumption and the risk of hypertension was observed among women with a high baseline adherence to the Mediterranean diet (Fig. 2). No significant interaction between coffee consumption and adherence to the Mediterranean diet in their association with hypertension was observed among men.

Table 3 shows the hazard ratios (95% CI) for hypertension according to baseline regular coffee consumption stratified by sex. Table 4 shows the hazard ratios (95% CI) for hypertension according to decaffeinated coffee consumption with the same adjustments as described for regular coffee consumption. We found no significant association between decaffeinated coffee consumption and risk of hypertension.

No significant interactions between decaffeinated coffee consumption and sex, age, smoking or adherence to the Mediterranean diet were found on the risk of incident hypertension.

Table 5 shows the results on the association between caffeinated coffee consumption and hypertension allowing for different induction periods in women. The point estimates did not change substantially, although the associations were no longer significant with shorter induction period.

Table 1
Baseline characteristics of the participants by caffeinated Coffee consumption (cups per day) in the SUN Project from 1999 to 2013 (N = 13,369).

	Caffeinated Coffee, cups per day			
	Never	<1	1	≥2
N	3058	2600	3208	4508
Person/year	26,892	23,432	28,932	42,141
Sex (men), %	33	40	34	37
Age, y	34 (11)	34 (11)	36 (10)	37 (10)
Period of inclusion	2004 (3)	2004 (3)	2003 (3)	2003 (3)
Body mass index, kg/m^2	22.8 (3.2)	23.1 (3.3)	23.0 (3.2)	23.4 (3.3)
Alcohol intake, g/d	3.3 (6.3)	4.3 (6.6)	4.5 (6.9)	5.3 (8.5)
Smoking status, %				
Former	18.5	16.1	25.9	39.6
Current	15.3	17.3	21.9	45.5
Smoking (packs per year)	3.5 (7.5)	3.9 (7.7)	4.8 (8.3)	7.4 (10.1)
Family history of hypertension, %	23.3	19.0	23.6	34.2
Sodium intake, g/d	3.4 (1.8)	3.4 (2.5)	3.3 (2.0)	3.3 (1.9)
Whole-fat dairy products, g/d	206 (187)	215 (185)	199 (175)	196 (192)
Low-fat dairy products, g/d	210 (236)	208 (233)	222 (233)	257 (265)
Non-sugared carbonated beverages, cans/day	0.8 (1.5)	0.7 (1.2)	0.7 (1.4)	0.7 (1.4)
Sugar-sweetened beverages, cans/day	1.5 (1.5)	1.6 (1.4)	1.4 (1.4)	1.5 (1.5)
Adherence to the Mediterranean diet (0–9 score)	4.1 (1.8)	4.0 (1.7)	4.2 (1.8)	4.2 (1.8)
Physical activity METs/d	23.4 (24.9)	23.2 (24.0)	21.4 (22.3)	20.9 (21.1)
Conformist-competitive personality (0–10 score)	7.0 (1.8)	7.0 (1.7)	7.0 (1.8)	7.0 (1.7)
Dependent–independent personality (0–10 score)	3.6 (2.8)	3.7 (2.8)	3.5 (2.8)	3.5 (2.8)
Calm-tense personality (0–10 score)	6.0 (2.3)	5.9 (2.2)	5.9 (2.2)	6.0 (2.1)
Time spent watching TV, hours/d	1.7 (1.2)	1.6 (1.2)	1.6 (1.2)	1.6 (1.2)
Fried foods, times per week	3.6 (4.0)	3.7 (4.1)	3.7 (4.2)	3.8 (4.3)
Fast food consumption, g/d	23 (21)	25 (22)	23 (19)	23 (21)

Table 2
Hazard ratios (95% CI) of hypertension according to baseline regular coffee consumption.

	Regular coffee consumption (Cups per day)					Hazard ratio for 2 additional cups/d
	Never/seldom	<1	1	≥2	P for trend	
N	3058	2600	3208	4508		
Person/year	26,892	23,432	28,932	42,141		
Crude model	1 Ref.	0.96 (0.83–1.12)	0.94 (0.82–1.08)	0.90 (0.80–1.03)	0.129	0.97 (0.91–1.05)
Age, sex and period adj.	1 Ref.	0.92 (0.79–1.06)	0.93 (0.81–1.07)	0.91 (0.80–1.03)	0.251	0.98 (0.92–1.06)
Multivariable adj[a]	1 Ref.	0.90 (0.77–1.04)	0.93 (0.81–1.08)	0.86 (0.75–0.99)	0.061	0.95 (0.88–1.03)

[a] Adjusted for sex, age, body mass index (BMI), alcohol intake, smoking status and package-years of smoking, family history of hypertension, sodium intake, whole and low fat dairy products consumption, sugar-sweetened beverages, non-sugared carbonated beverages, physical activity, adherence to Mediterranean diet (Trichopoulou index), kind of personality (conformist-competitive; calm-tense; dependent-independent), time spent watching TV and fried and fast-food consumption.

Table 3
Hazard ratios (95% CI) of hypertension according to baseline regular coffee consumption stratified by sex.

	Regular coffee consumption (cups per day)					
	Never	<1	1	≥2	P for trend	Hazard ratio for 2 additional cups/d
	Men					
n	1005	1048	1103	1668		
Person/years	8718	9284	9711	15219		
Crude model	1 Ref.	1.09 (0.89–1.33)	1.17 (0.97–1.41)	1.04 (0.87–1.24)	0.855	1.00 (0.91–1.10)
Age, and period adj.	1 Ref.	1.09 (0.90–1.33)	1.15 (0.96–1.40)	1.04 (0.87–1.25)	0.884	1.00 (0.91–1.10)
Multivariable adj[a]	1 Ref.	1.05 (0.86–1.29)	1.11 (0.92–1.35)	0.97 (0.81.1.17)	0.389	0.97 (0.87–1.07)
	Women					
n	2053	1552	2105	2840		
Person/year	18174	14148	19221	26923		
Crude model	1 Ref.	0.75 (0.59–0.94)	0.73 (0.59–0.90)	0.77 (0.64–0.93)	0.079	0.96 (0.85–1.07)
Age, and period adj.	1. Ref.	0.73 (0.58–0.93)	0.72 (0.59–0.89)	0.78 (0.65–0.94)	0.110	0.96 (0.86–1.08)
Multivariable adj[a]	1 Ref.	0.72 (0.57–0.92)	0.74 (0.60–0.92)	0.74 (0.61–0.91)	0.039	0.92 (0.82–1.04)

[a] Adjusted for age, body mass index (BMI), alcohol intake, smoking status and package-years of smoking, family history of hypertension, sodium intake, whole and low fat dairy products consumption, sugar-sweetened beverages, non-sugared carbonated beverages, physical activity, adherence to Mediterranean diet (Trichopoulou index), kind of personality (conformist-competitive; calm-tense; dependent-independent), time spent watching TV and fried and fast-food consumption.

Results for the different induction periods for the association between decaffeinated coffee consumption and the risk of hypertension are shown in Table 6. We observed no relevant changes with respect to our main analyses.

Supplemental Tables 1 and 2 show the results for the association between regular and decaffeinated coffee and incident hypertension with changing follow-up periods in the entire cohort. Associations between total coffee consumption (regular and decaffeinated coffee considered together) are presented in Supplemental Table 3 for the entire cohort.

In Supplemental Table 4 we show the results for decaffeinated coffee consumption stratified by sex and in Supplemental Table 5 the associations for decaffeinated coffee consumption in women according to their baseline adherence to the MedDiet.

4. Discussion

The results of our long-term prospective study showed that neither caffeinated nor decaffeinated coffee consumption were significantly associated with incident hypertension in this middle-aged Mediterranean cohort. We found a significant interaction between regular coffee consumption and sex. In women, we observed an inverse association between coffee consumption and the risk of incident hypertension. We also found a significant interaction between regular coffee consumption and the MedDiet in women, so that women with the lowest adherence to the MedDiet showed the strongest inverse association between coffee consumption and the risk of hypertension.

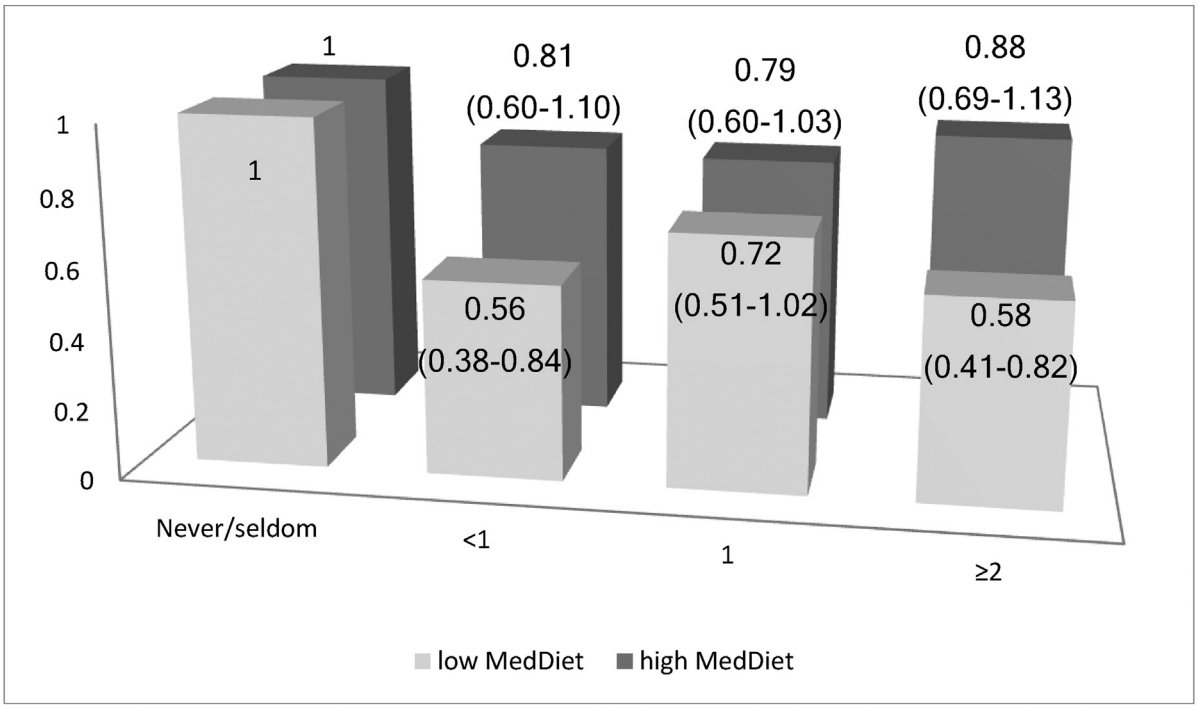
It is difficult to make comparisons between studies of coffee consumption from different regions because there is a wide variety in preparation methods, sources and types of coffee [32], and, to our knowledge, this study is the first to evaluate the effect of regular and decaffeinated coffee consumption on the risk of hypertension in a Mediterranean cohort.

A recent meta-analysis [7] of observational prospective cohort studies revealed a pooled risk for developing hypertension among all groups of coffee consumption of 1.03, which was not statistically significant (95% CI 0.98–1.08). Nevertheless, in this meta-analysis, there was heterogeneity between studies and the authors did not stratify by sex. Consistently with our studies, the largest prospective cohort studies that have examined the influence of coffee intake on the risk of hypertension, found different results for men and women. Winkelmayer et al. [14] demonstrated a marginally significant inverse association between coffee consumption and the risk of hypertension in 155,594 US women followed up over 12 years. Furthermore, Klag et al. [12] studied a cohort of 1017 men followed up over 33 years, finding no significant association with incident hypertension after multivariate adjustment, suggesting that coffee drinking plays only a minor role on the risk of hypertension among men.

In addition, the traditional MedDiet has shown a potential beneficial effect on the risk of hypertension [18,33,34]. Interestingly, we observed that coffee consumption showed an inverse association with the risk of hypertension among those women with the lowest adherence to the MedDiet. This observation suggests that coffee consumption may counterbalance the excess risk induced by a poor adherence to a healthy dietary pattern. No previous large cohort has assessed the potential effect of coffee consumption on blood pressure in a Mediterranean setting, and thus, addressed the potential interaction between coffee consumption and the MedDiet on the risk of hypertension.

For a long time, coffee consumption has been suggested to increase blood pressure. This effect is largely attributed to its caffeine

A. Women:



B. Men:

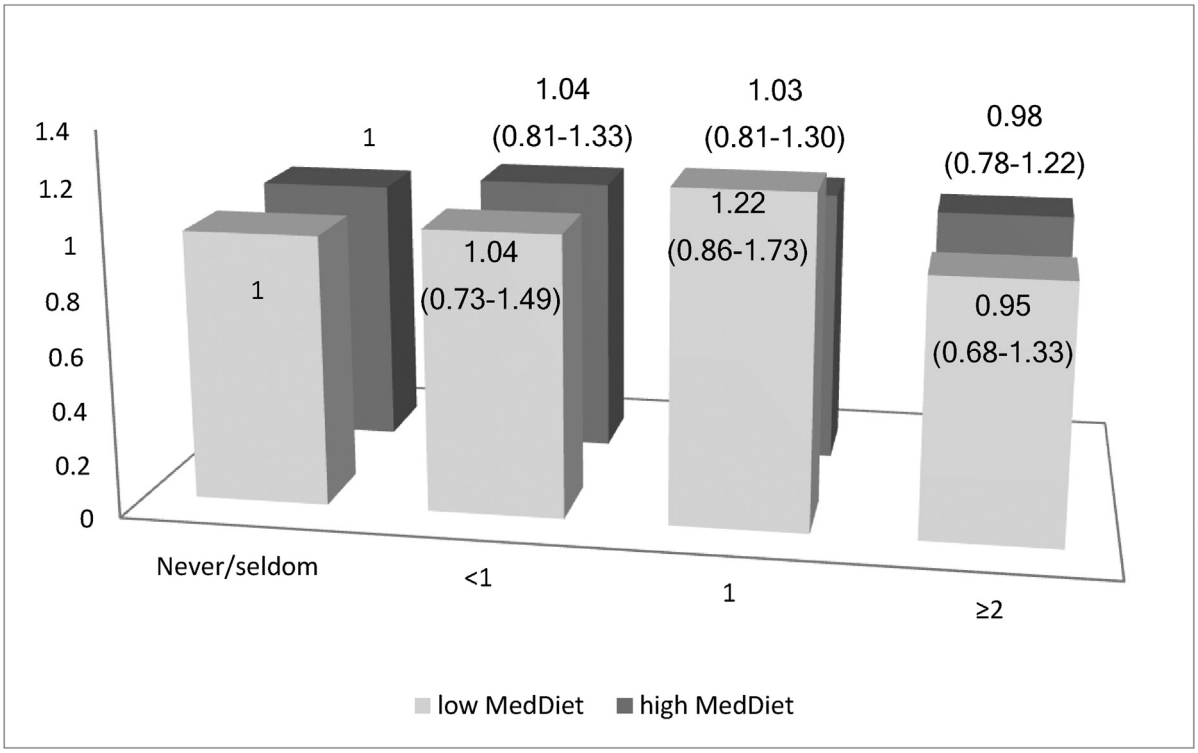


Fig. 2. Multivariable adjusted hazard ratios (95% CI) for hypertension according to regular coffee consumption stratified by sex and adherence to the Mediterranean diet.

(1,3,7-trimethylxanthine) content, which has acute pressor effects. A meta-analysis of controlled trials of chronic coffee or caffeine (pill form) consumption concluded that coffee drinking was associated with higher systolic blood pressure [35]. It is noteworthy that the authors of this latter meta-analysis observed a significant interaction by caffeine dose, so that a blood pressure rising effect was observed only with high caffeine doses (≥410 mg/day). Furthermore, the pressor effect of caffeine was lower when consumed in

Table 4
Hazard ratios (95% CI) of hypertension according to baseline decaffeinated coffee consumption.

	Decaffeinated coffee consumption (Cups per day)					Hazard ratio for 2 additional cups/d
	Never/seldom	<1	1	≥2	P for trend	
N	8423	3430	1134	387		
Person/years	75,479	32,083	10,357	3478		
Crude model	1 Ref	0.95 (0.85–1.06)	0.94 (0.79–1.11)	1.05 (0.82–1.35)	0.960	1.05 (0.90–1.24)
Age, sex and period adj.	1 Ref.	1.00 (0.89–1.12)	1.01 (0.85–1.19)	1.19 (0.93–1.52)	0.228	1.16 (0.99–1.36)
Multivariable adj.[a]	1 Ref.	1.03 (0.91–1.15)	0.98 (0.82–1.16)	1.06 (0.82–1.36)	0.858	1.06 (0.90–1.25)

[a] Adjusted for sex, age, body mass index (BMI), alcohol intake, smoking status and package-years of smoking, family history of hypertension, sodium intake, whole and low fat dairy products consumption, sugar-sweetened beverages, non-sugared carbonated beverages, physical activity, adherence to Mediterranean diet (Trichopoulou index), kind of personality (conformist-competitive; calm-tense; dependent-independent), time spent watching TV and fried and fast-food consumption.

Table 5
Sensitivity analyses restricting the follow-up periods to the first six, eight and ten years in regular coffee consumption in women.

	Regular coffee consumption (Cups per day)					HR for 2 additional cups/d
	Never	Less than 1	1	≥2	P for trend	
Six years of follow up						
Crude model	1 Ref.	0.77 (0.55–1.08)	0.69 (0.51–0.94)	0.86 (0.66–1.13)	0.722	1.06 (0.90–1.25)
Age and period adj.	1 Ref.	0.76 (0.54–1.06)	0.68 (0.50–0.92)	0.87 (0.66–1.13)	0.788	1.07 (0.91–1.26)
Multivariable adj[a]	1 Ref.	0.74 (0.53–1.04)	0.72 (0.53–0.97)	0.84 (0.64–1.11)	0.221	1.25 (0.91–1.73)
Eight years of follow up						
Crude model	1 Ref.	0.78 (0.57–1.05)	0.74 (0.56–0.97)	0.86 (0.68–1.09)	0.625	1.03 (0.89–1.20)
Age and period adj.	1 Ref.	0.76 (0.56–1.02)	0.73 (0.55–0.95)	0.86 (0.68–1.10)	0.689	1.04 (0.90–1.21)
Multivariable adj[a]	1 Ref.	0.76 (0.56–1.04)	0.78 (0.59–1.02)	0.86 (0.67–1.10)	0.231	1.20 (0.89–1.62)
Ten years of follow up						
Crude model	1 Ref.	0.83 (0.64–1.09)	0.76 (0.59–0.97)	0.85 (0.68–1.05)	0.363	1.00 (0.88–1.14)
Age and period adj.	1 Ref.	0.81 (0.62–1.06)	0.75 (0.59–0.96)	0.85 (0.69–1.06)	0.471	1.01 (0.89–1.16)
Multivariable adj[a]	1 Ref.	0.81 (0.62–1.07)	0.79 (0.62–1.02)	0.84 (0.67–1.06)	0.142	1.17 (0.89–1.55)

[a] Adjusted for age, body mass index (BMI), alcohol intake, smoking status and package-years of smoking, family history of hypertension, sodium intake, whole and low fat dairy products consumption, sugar-sweetened beverages, non-sugared carbonated beverages, physical activity, adherence to Mediterranean diet (Trichopoulou index), kind of personality (conformist-competitive; calm-tense; dependent-independent), time spent watching TV and fried and fast-food consumption.

Table 6
Sensitivity analyses restricting the follow-up periods to the first six, eight and ten years in decaffeinated coffee consumption in women.

	Decaffeinated coffee consumption (Cups per day)					HR for 2 additional cups/d
	Never	Less than 1	1	2 or more	P for trend	
Six years of follow up						
Crude model	1 Ref.	0.94 (0.74–1.20)	1.02 (0.73–1.45)	0.79 (0.44–1.41)	0.568	0.92 (0.64–1.32)
Age and period adj.	1 Ref.	0.95 (0.75–1.22)	1.07 (0.75–1.51)	0.83 (0.46–1.49)	0.749	0.97 (0.67–1.39)
Multivariable adj[a]	1 Ref.	1.01 (0.78–1.30)	1.06 (0.74–1.52)	0.68 (0.37–1.24)	0.331	0.85 (0.57–1.23)
Eight years of follow up						
Crude model	1 Ref.	0.92 (0.74–1.14)	0.93 (0.67–1.28)	0.73 (0.43–1.25)	0.254	0.85 (0.61–1.20)
Age and period adj.	1 Ref.	0.93 (0.75–1.16)	0.96 (0.70–1.33)	0.75 (0.44–1.29)	0.352	0.88 (0.63–1.24)
Multivariable adj[a]	1 Ref.	0.98 (0.78–1.24)	0.93 (0.66–1.29)	0.61 (0.35–1.06)	0.087	0.77 (0.54–1.09)
Ten years of follow up						
Crude model	1 Ref.	0.96 (0.79–1.17)	1.00 (0.75–1.32)	0.86 (0.54–1.35)	0.580	0.96 (0.72–1.28)
Age and period adj.	1 Ref.	0.97 (0.80–1.19)	1.02 (0.77–1.35)	0.88 (0.56–1.38)	0.700	0.98 (0.74–1.31)
Multivariable adj[a]	1 Ref.	1.02 (0.83–1.25)	0.98 (0.73–1.32)	0.72 (0.45–1.16)	0.207	0.86 (0.64–1.17)

[a] Adjusted for age, body mass index (BMI), alcohol intake, smoking status and package-years of smoking, family history of hypertension, sodium intake, whole and low fat dairy products consumption, sugar-sweetened beverages, non-sugared carbonated beverages, physical activity, adherence to Mediterranean diet (Trichopoulou index), kind of personality (conformist-competitive; calm-tense; dependent-independent), time spent watching TV and fried and fast-food consumption.

the form of coffee than when consumed in pill form, suggesting that other compounds found in coffee may counteract the pressor effects of chronic caffeine intake. Accordingly, coffee is a complex mixture of compounds containing chlorogenic acid, flavonoids, melanoidins, and various lipid-soluble compounds such as furans, pyrroles, and maltol [32]. Some of these compounds have been shown to have antioxidant properties and they could explain the beneficial effects on the cardiovascular system ([9–11]). Chlorogenic acid and its metabolites, concretely, have been suggested to increase nitric oxide bioavailability and to decrease oxidative stress [36–38]. This latter effect would lead to inhibition of vascular smooth muscle cell proliferation and lower renin-angiotensin-converting enzyme activity [39–41]. Also, coffee is rich in blood pressure-lowering minerals such as potassium and magnesium [17]. These latter compounds found in coffee may outweigh the blood pressure-rising effect of caffeine and partly explain the conflicting findings of studies examining the relationship between coffee and hypertension.

Strengths of our study include a high retention rate (>90%) which limit the room for selection bias. Also, we have long follow-up time, with an average follow-up longer than 10 years. In addition, we have accounted for a wide array of potential confounders in our analyses and have considered a previously validated outcome in our cohort. We acknowledge some limitations of this

study. Firstly, we used self-reported data on coffee consumption. However, this information was collected with a previously validated and repeatedly used food-frequency questionnaire [24–26], though we acknowledge that information on coffee consumption was not specifically validated. However, given the adequate validity of other foods and nutrients with higher within-person variability than coffee [25] using our FFQ, an appropriate validity can be assumed for coffee in our cohort. In our study of reproducibility, we found a de-attenuated correlation coefficient = 0.80 for caffeine intake when it was repeatedly assessed less than 1 year apart and r = 0.66 for longer than 1 year apart [26]. Secondly, coffee consumption was ascertained once at study inception, although it has been suggested that coffee consumption tends to stay roughly constant throughout time [7]. Also, we carried out an analysis to restrict the follow-up periods at the first six, eight or ten years to avoid the bias due to possible changes in coffee consumption during the follow-up and to be able to assume different induction periods and the results were robust. Thirdly, we could not differentiate between different types of coffee (e.g. filtered, boiled) beyond regular or decaffeinated coffee. Fourthly, hypertension diagnosis was based on self-reported information; however, this outcome has been previously validated in our cohort and the data showed enough validity as to be used in this large cohort study [27]. Fifthly, although the differential effect of coffee consumption on blood pressure in men and women is consistent with previous studies, no clear physiologic process has been suggested to explain this differential association. It can be speculated that the difference may be partially due to a more accurate reporting of dietary intake or coffee consumption among women. However, further research is needed to elucidate the underlying mechanisms of this differential association. Sixthly, some misclassification of the exposure might have affected our results. Nevertheless, we expect that classification to bias our results is likely to be towards the null value and attenuate the results. Finally, there might have been some misclassification in the outcome and we admit that it would be more likely that we might have missed some cases of incident hypertension rather than erroneously considering a non-hypertensive participant as hypertensive. Our incidence rates of hypertension were lower than in other studies using samples of the general population [42]. Had we had more cases of hypertension, we would have had a higher statistical power. Also, this misclassification is likely to be non-differential and the potential bias would therefore most likely attenuate our results.

In conclusion, consumption of regular coffee could reduce the risk of hypertension among women, especially among those with a lower adherence to the MedDiet.

Statement of authorship

MAMG and ET conceived and designed the experiments; MAMG and MRC contributed to data collection; AMN and ET analyzed the data and wrote the paper. AG and RR provided insight into result interpretation. All authors have revised the manuscript critically for important intellectual content and have given final approval of the version to be published. All co-authors have read the manuscript and given their permission for it to be published.

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Conflict of interest

All authors declare they have no conflict of interest relevant to the content of this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.12.009.

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