# *Association between coffee consumption and total dietary caffeine intake with cognitive functioning: cross-sectional assessment in an elderly Mediterranean population*

**the PREDIMED-Plus Investigators**


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ORIGINAL CONTRIBUTION

# Association between coffee consumption and total dietary caffeine intake with cognitive functioning: cross-sectional assessment in an elderly Mediterranean population

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## Abstract

**Purpose** Coffee is rich in compounds such as polyphenols, caffeine, diterpenes, melanoidins and trigonelline, which can stimulate brain activity. Therefore, the possible association of coffee consumption with cognition is of considerable research interest. In this paper, we assess the association of coffee consumption and total dietary caffeine intake with the risk of poor cognitive functioning in a population of elderly overweight/obese adults with metabolic syndrome (MetS).

**Methods** PREDIMED-plus study participants who completed the Mini-Mental State Examination test (MMSE) ($n = 6427$; mean age = $65 \pm 5$ years) or a battery of neuropsychological tests were included in this cross-sectional analysis. Coffee consumption and total dietary caffeine intake were assessed at baseline using a food frequency questionnaire. Logistic regression models were fitted to evaluate the association between total, caffeinated and decaffeinated coffee consumption or total dietary caffeine intake and cognitive impairment.

**Results** Total coffee consumers and caffeinated coffee consumers had better cognitive functioning than non-consumers when measured by the MMSE and after adjusting for potential confounders (OR 0.63; 95% CI 0.44–0.90 and OR 0.56; 95% CI 0.38–0.83, respectively). Results were similar when cognitive performance was measured using the Clock Drawing Test (CDT) and Trail Making Test B (TMT-B). These associations were not observed for decaffeinated coffee consumption. Participants in the highest tertile of total dietary caffeine intake had lower odds of poor cognitive functioning than those in the reference tertile when screened by the MMSE (OR 0.64; 95% CI 0.47–0.87) or other neurophysiological tests evaluating a variety of cognitive domains (i.e., CDT and TMT-A).

**Conclusions** Coffee consumption and total dietary caffeine intake were associated with better cognitive functioning as measured by various neuropsychological tests in a Mediterranean cohort of elderly individuals with MetS.

A complete list of PREDIMED-Plus investigators is included as an acknowledgements.

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Extended author information available on the last page of the article

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**Keywords** Cognitive impairment · Mini-Mental State Examination · Coffee · Caffeine · PREDIMED-plus

## Introduction

The metabolic syndrome (MetS) is a recognized risk factor in the development of non-communicable chronic diseases such as diabetes and cardiovascular disease (CVD). In recent years, it has been suggested that individuals with MetS are also at high risk of developing neurological alterations characterized by cognitive decline, which may progress to Alzheimer's disease (AD) or other types of dementia [1–3]. According to the latest World Health Organization guidelines for reducing the risk of cognitive decline and dementia [4], the net number of individuals with dementia is increasing exponentially in parallel with population aging. This important public health concern is expected to have a considerable negative effect on society and the economy.

Lifestyle changes such as modifications in diet, physical activity, social enrichments and cognitive training may preserve and enhance cognitive performance in older adults [4]. In terms of diet, numerous studies have indicated that adherence to healthy dietary patterns is associated with better cognitive performance throughout the adult life span [5, 6] and therefore might play an important role in preventing cognitive decline and dementia. The association between cognitive performance and certain food groups, nutrients and/or bioactive compounds such as coffee consumption and caffeine intake has also been of research interest [7–9].

It has been reported that coffee and caffeine may act as psychoactive stimulants that improve cognitive performance in the short term. Studies on animals have demonstrated that caffeine [10, 11] and other bioactive components of coffee [12] have a protective effect on cognition. The few randomized clinical trials that have studied the potential effect of coffee or caffeine consumption on cognitive performance have focused on short-term effects, and none of them has analyzed the effect on cognitive decline or the risk of dementia [8]. Studies evaluating decaffeinated coffee consumption are even more scarce and have focused on the acute effects on cognitive performance.

Epidemiological studies that have analyzed potential associations between coffee and caffeine consumption and cognitive function or the risk of dementia in humans have provided inconsistent results [13–15]. This is partly due to the differences in the populations studied, the study design, the exposure variables and the method for assessing them (studies have focused on total coffee consumption but excluded the type of coffee consumed (caffeinated/decaffeinated) from their analyses, the reported outcome (AD, dementia, cognitive impairment, cognitive decline) and the criteria or tools used to define the outcome [14].

Moreover, most epidemiological studies have been conducted on healthy or non-Mediterranean populations and their results cannot be extrapolated to elderly populations at high risk of developing neurological disorders. Since there is evidence to suggest that MetS may increase the incidence of vascular dementia and the risk of progression from cognition impairment to dementia in aged individuals, studying the possible associations between coffee/caffeine consumption and cognition is of great value.

In this paper, we aimed to assess the association of coffee consumption and caffeine intake with the odds of poor cognitive functioning in a population of overweight/obese elderly adults with MetS. We hypothesize that individuals who consume higher amounts of coffee or caffeine have better cognitive functioning.

## Methods

### Study design and participants

A cross-sectional analysis using baseline data from the PREDIMED-Plus study was conducted. Briefly, the PREDIMED-Plus is an ongoing parallel-group, randomized and controlled clinical trial conducted in 23 Spanish centers, which aims to evaluate the effect of an intensive weight loss intervention (based on an energy-restricted Mediterranean diet, physical activity promotion and behavioral support) on CVD events compared to a control group that is given usual care advice. A detailed description of the PREDIMED-Plus study is also available at https://www.predimedplus.com. This study was registered at the International Standard Randomized Controlled Trials (ISRCTN; https://www.isrctn.com/ISRCTN89898870) on July 24, 2014.

Between October 2013 and December 2016, 6,874 participants were recruited at 23 centers from various universities, hospitals and research institutes in Spain and randomly allocated in a 1:1 ratio to an intensive lifestyle intervention or to usual medical care. Eligible participants were overweight or obese (BMI 27–40 kg/m$^2$) men and women (aged 55–75 years) who satisfied at least three criteria for the MetS (waist circumference > 102 cm in men and > 88 cm in women; serum triglyceride ≥ 150 mg/dL or drug treatment for elevated triglycerides; HDL-c < 40 mg/dL in men and < 50 mg/dL in women or drug use for low HDL-c; blood pressure ≥ 130/85 mmHg or antihypertensive

drug treatment; and fasting plasma glucose level ≥ 100 mg/dL or hypoglycemic treatment) [16] and were free of CVD. Detailed inclusion and exclusion criteria have been extensively described elsewhere [17].

All participants provided written informed consent, and the institutional review boards of each participating center approved the final protocol and procedures.

For the present study, PREDIMED-Plus participants who had baseline information missing from the food frequency questionnaire (FFQ) or whose total energy intake was extreme (women < 500 and > 3500 kcal/day, and men < 800 and > 4000 kcal/day) were excluded ($n = 241$). Participants with missing data on covariates (education level, hypertension, hypercholesterolemia) or who had been diagnosed with dementia were excluded from our analyses ($n = 19$). Associations were tested for those participants who had completed the various cognitive tests. As not all participants completed every cognitive test, there were slightly different samples for the Mini-Mental State Examination test ($n = 6427$), the semantic and phonemic Verbal Fluency Test ($n = 6563$), the Clock Drawing Test ($n = 6400$), Trail Making Test A ($n = 6533$) and B ($n = 6457$) and the Digit Span Test forward score ($n = 5128$).

## Assessment of coffee consumption and caffeine intake

At baseline, a trained dietitian administered a 143-item FFQ during a face-to-face visit. Participants were asked about their frequency of consumption of each item in the preceding year. The nine possible answers ranged from never to more than six times per day, which were transformed into grams or milliliters per day using the standard portion size of each item. Two items on the FFQ were specifically related to coffee consumption (one for caffeinated coffee and one for decaffeinated coffee). Total coffee consumption was considered to be the sum of caffeinated and decaffeinated coffee consumption. Two Spanish food composition tables were used to calculate total energy and nutrient intake [18, 19]. Total dietary caffeine consumption was computed from the FFQ using the caffeine contained in caffeinated coffee (400 mg/l), decaffeinated coffee (10.7 mg/l), tea (100 mg/l), regular sodas (79.2 mg/l), artificially sweetened soda (128 mg/l) and chocolate (180 mg/kg). Reference values from the European Food Safety Authority [20] were used to calculate caffeine intake.

## Neuropsychological assessment

The MMSE questionnaire validated for the Spanish population [21] was administered by trained PREDIMED-Plus staff. MMSE is the most commonly used brief cognitive screening test. This 30-point questionnaire examines cognitive functions including orientation, registration, concentration, memory, language and copying a figure. It is divided into two sections, the first of which requires vocal responses only (maximum score of 21). The second section tests the respondent's ability to name, follow verbal and written commands, write a sentence spontaneously and copy a complex polygon similar to a Bender–Gestalt figure (maximum score of 9). The MMSE, therefore, has a maximum total score of 30, and higher scores indicate the absence of cognitive decline [22].

We also evaluated other cognitive domains using several neuropsychological tests such as the Verbal Fluency Test (VFT), the Digit Span Test (DST) of the Wechsler Adult Intelligence Scale-III (WAIS-III), the Trail Making Test (TMT) and the Clock Drawing Test (CDT).

The VFT assesses verbal ability and executive control and consists of two parts: (1) the phonemic fluency task, in which participants are asked to recite, in 60 s, as many words as possible that start with the letter P (not including the names of people or places or repetitions of the same word with different suffixes), and (2) the semantic fluency task, in which the participants name as many animals as they can without repetition in 60 s. The total raw score for each task is the number of words the participant produces [23].

The DST of the WAIS-III Spanish version [24] is made up of two different subtests: DST forward recall and DST backward recall. DST forward recall requires participants to orally repeat a series of three to nine random single digits in the same order they hear them. On the other hand, DS backward recall requires participants to repeat a series of two to eight random single digits in reverse order. In this study, the performance on the DST was reported via a direct score of 1–16 for the forward performance and a direct score of 1–14 for backward performance.

The TMT is a tool that assesses executive function and tests processing speed, sequence alternation, cognitive flexibility, visual search, motor performance and executive functioning [25]. It is considered sensitive enough to detect cognitive impairment associated with dementia (i.e., AD). The TMT consists of 25 circles spread over two sheets of paper (parts A and B). In part A (TMT-A), participants are asked to connect consecutive numbers (1–2–3–4–…) in the correct order by drawing a line. In part B (TMT-B), they are asked to connect consecutive numbers and letters in an alternating numeric and alphabetic sequence (1-A, 2-B, 3-C-…). Each part is scored according to the time taken to complete the task (lower scores imply better performance).

The CDT [26] is used as a neuropsychological screening tool to detect cognitive impairment and dementia [27]. It evaluates visuoconstructive and visuospatial skills, symbolic and conceptual representation, hemiattention, semantic memory and executive function (including organization,

planning and parallel processing). For this study, we used a validated Spanish version ranging from 0 to 7 [28].

## Assessment of covariates

Covariates were evaluated by trained staff in a face-to-face interview using self-reported general questionnaires on socio-demographics (sex, age, level of education and employment status), and lifestyle (smoking habits, physical activity), history of illness and medication use. Trained PREDIMED-Plus staff followed the study protocol to measure anthropometric variables and blood pressure. Blood samples were collected in fasting conditions, and biochemical analyses were performed on fasting plasma glucose, triglycerides, cholesterol and other biochemical parameters by routine laboratory methods. Leisure time physical activity was estimated using a validated short version of the Minnesota Leisure Time Physical Activity Questionnaire [29, 30]. Adherence to an energy-reduced MedDiet was assessed using a 17-item questionnaire [31] adapted from a previously validated one [32]. The score obtained from the questionnaire ranged from 0 to17. Finally, depressive symptoms were evaluated using the Beck Depression Inventory II (BDI-II). Cutoff points for depressive status risk were established as scores $\leq 19$ for mild depression and scores $> 19$ for moderate-to-severe depression [33].

## Statistical analysis

For our analyses, we used the PREDIMED-Plus database updated to March 2019. Participants were categorized as non-coffee consumers and coffee consumers. Coffee consumers were further differentiated according to the type of coffee they consumed (caffeinated coffee consumers and decaffeinated coffee consumers). The Chi-square test and *t* test were used to compare the baseline characteristics between non-consumers and coffee consumers, or non-consumers and caffeinated coffee consumers or decaffeinated coffee consumers, respectively.

The MMSE was used for our main analyses to evaluate the odds of poor cognitive functioning (established as MMSE score $\leq 24$ points). Several logistic regression models were fitted to assess the association [odds ratio (OR); 95% confidence interval (CI)] between coffee consumption and the odds of poor cognitive functioning. Model 1 was adjusted for age (years), sex, body mass index (kg/m$^2$), educational level (primary or lower, secondary or academic or graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), prevalence of diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and participating center (in quartiles by number of participants). Model 2 was further adjusted for food groups [consumption of vegetables, fruits, nuts and dried fruits, biscuits, fish, dairy products, meat and poultry, legumes, olive oil and cereals (g/day)]. Finally, model 3 was further adjusted for depression status (mild/moderate to severe). Models 2 and 3 for caffeinated coffee consumers and decaffeinated coffee consumers were further adjusted for decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively.

We also evaluated the associations between coffee consumption and the odds of poor cognitive functioning using other neuropsychological tests. The cutoff points for the VFTs and DSTs were established as $\leq$ than the mean $-$ 1.5SD. The TMT's cutoff points were established as $\geq$ the mean + 1.5SD. The clock test cutoff point was established as $\leq 4$ points. The same covariates as above were used to fit the fully adjusted models. The models for caffeinated coffee consumers and decaffeinated coffee consumers were further adjusted for decaffeinated or caffeinated coffee consumption (ml/day), respectively. It was not possible to run logistic regression models for the DST backward test because of the low number of impairment cases. We also explored the associations (OR, 95% CI) between servings of caffeinated coffee, decaffeinated coffee, and total coffee consumed and the odds of poor cognitive functioning as assessed by the MMSE test. The same adjustments were used to analyze these models.

We also evaluated the association (OR, 95% CI) between total dietary caffeine intake and the odds of poor cognitive functioning as assessed by the aforementioned neuropsychological tests. For each test, tertiles of caffeine intake were calculated and the lowest tertile was used as the reference category. The fully adjusted model was used.

To assess the linear trend in the logistic regression models, the median value of each serving category of total, caffeinated and decaffeinated coffee consumption and the median value of each tertile of total caffeine intake were assigned to each participant, and this new variable was modeled as continuous.

We conducted statistical analyses to evaluate whether the associations observed could be modified by age (years) and sex (men/women). Interaction was tested with likelihood ratio tests, which involved comparing models with and without cross-product terms.

All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. The data were analyzed using the Stata 14 software program (StataCorp), and statistical significance was set at a two-tailed $p$ value $< 0.05$.

## Results

Table 1 shows the general characteristics of the population under study according to coffee consumption. Among coffee consumers, mean coffee consumption was 85 ± 52 ml/day, of which 45 ± 55 ml/day and 39 ± 49 ml/day were consumed in the form of caffeinated coffee and decaffeinated coffee, respectively. Coffee consumers were younger, more likely to smoke, and more likely to present T2DM or hypercholesterolemia than non-coffee consumers. Coffee consumers also had higher energy intake, consumed higher amounts of red meat/poultry, dairy products and alcohol (irrespective of the type of coffee consumed) and had a lower consumption of vegetables, nuts and legumes. In addition, their MMSE scores were higher and their adherence to the MedDiet was lower than that of non-coffee consumers. No other significant associations were observed. The general characteristics of the study population in terms of MMSE performance are shown in Supplementary Table 1.

The association (OR, 95% CI) between coffee consumption and the odds of poor cognitive functioning (MMSE test) is shown in Table 2. Compared to non-coffee consumers, coffee consumers and caffeinated coffee consumers proved to have better cognitive functioning (0.59, 0.42–0.82) and (0.47, 0.33–0.67), respectively, even after adjusting for potential confounders [(0.63, 0.44–0.90) and (0.56, 0.38–0.83), respectively]. No significant associations were found between decaffeinated coffee consumers and the odds of poor cognitive functioning by the MMSE test.

Table 3 shows the association (OR, 95% CI) between the number of servings (50 ml) of total coffee, caffeinated coffee and decaffeinated coffee and the odds of poor cognitive functioning using the MMSE test. Compared to those participants with < 1 serving/day of total coffee intake, participants who consumed > 2 servings/day of total coffee were more likely to have better cognitive performance in the test even after adjusting for potential confounders. For caffeinated coffee, participants who consumed 1 to < 2 servings/day and > 2 servings/day had significantly lower odds of cognitive impairment (37% and 46%, respectively) than those who consumed < 1 serving per day. There were no significant associations between the consumption of servings of decaffeinated coffee and the odds of cognitive impairment. Supplementary Table 2 shows the association (OR, 95% CI) between the number of servings (50 ml) of total coffee and its subtypes and the odds of poor cognitive functioning when non-consumers (0 servings/day) category is considered as the referent group, and results remain in the same direction.

Table 4 shows the association (OR, 95% CI) between cognitive status and coffee consumption measured using various neuropsychological tests. Regardless of the type of coffee consumed, coffee consumers were more likely to have better cognitive functioning, when cognitive status was evaluated by TMT-B. No other significant associations were observed with any other neuropsychological test.

Figure 1 and Supplementary Table 3 show the association (OR, 95% CI) between tertiles of total dietary caffeine intake and various neuropsychological tests. Coffee consumption contributed to 68.6% of total dietary caffeine intake in our population (data not shown). Participants in the highest tertile of caffeine intake performed better in the cognition domains than those in the lowest tertile (reference category) when evaluated by MMSE, CDT and TMT-A.

When the heart rate and systolic blood pressure were added to our models as covariates, the results were in the same direction and remain significant (data not shown). Interactions between sex ($p = 0.07$) and age ($p = 0.27$) with coffee consumption were not significant.

## Discussion

To the best of our knowledge, this is the first study to evaluate the association between coffee consumption and cognition in an elderly population at high cardiovascular risk using a cross-sectional design. We observed that total coffee consumers and caffeinated coffee consumers have lower odds of poor cognitive functioning than non-coffee consumers measured by the MMSE, CDT and TMT-B tests. In addition, participants in the highest tertile of total dietary caffeine intake had lower odds of poor cognitive functioning than those in the reference tertile when screened by the MMSE and other neuropsychological tests that evaluate different cognitive domains (i.e., CDT and TMT-B).

Coffee is one the most widely consumed beverages around the world, and the level of consumption by the Spanish population is no exception [34–36]. Coffee is a seed, made of complex matrices rich in vitamins, minerals, and bioactive phytochemicals that protect the plant's DNA from oxidative stress, thus facilitating the perpetuation of the species [37]. As such, coffee is rich in polyphenols (with antioxidant properties), caffeine, diterpenes, melanoidins and trigonelline [38]. For these reasons, the effect of coffee consumption on several health outcomes has been the object of research interest, especially in relation to cardio-metabolic health, cancer incidence and mortality [38–40]. However, coffee composition can depend on the type of coffee bean and the brewing process, which may influence the biological effects it has on the human body [39].

Previous studies have explored the association coffee and caffeine intake has with cognitive performance. In a cross-sectional study conducted on a representative British population, it was observed that total coffee consumption, and

**Table 1** General characteristics of the studied population according to coffee consumption and subtype

| | Non-coffee consumers ($n=537$) | Coffee consumers ($n=5890$) | $p$ value[a] | Caffeinated coffee consumers ($n=3419$) | $p$ value[b] | Decaffeinated coffee consumers ($n=3365$) | $p$ value[c] |
|---|---|---|---|---|---|---|---|
| Coffee consumption, ml/day | 0 | 85 ± 52 | < 0.01 | 91 ± 54 | < 0.01 | 83 ± 51 | < 0.01 |
| Caffeinated coffee consumption, ml/day | 0 | 45 ± 55 | < 0.01 | 78 ± 52 | < 0.01 | 15 ± 33 | < 0.01 |
| Decaffeinated coffee consumption, ml/day | 0 | 39 ± 49 | < 0.01 | 14 ± 30 | < 0.01 | 69 ± 46 | < 0.01 |
| Age, years | 66 ± 5 | 65 ± 5 | < 0.01 | 64 ± 5 | < 0.01 | 65 ± 5 | 0.04 |
| Women, % ($n$) | 58 (311) | 47 (2794) | < 0.01 | 43 (1474) | < 0.01 | 51 (1719) | < 0.01 |
| BMI, kg/m$^2$ | 32 ± 4 | 33 ± 3 | 0.37 | 32 ± 3 | 0.80 | 33 ± 3 | 0.15 |
| Central obesity, % ($n$) | 92 (495) | 93 (5483) | 0.43 | 93 (3171) | 0.64 | 93 (3141) | 0.32 |
| Type 2 diabetes, % ($n$) | 23 (125) | 32 (1856) | < 0.01 | 31 (1049) | < 0.01 | 33 (1102) | < 0.01 |
| Hypertension % ($n$) | 94 (505) | 94 (5522) | 0.79 | 93 (3171) | 0.28 | 95 (3199) | 0.31 |
| Hypercholesterolemia, % ($n$) | 56 (303) | 61 (3590) | 0.04 | 61 (2088) | 0.04 | 61 (2059) | 0.04 |
| MMSE > 24, % ($n$) | 92 (494) | 95 (5604) | < 0.01 | 96 (3285) | < 0.01 | 94 (3173) | 0.04 |
| MMSE ≤ 24, % ($n$) | 8 (43) | 5 (286) | | 4 (134) | | 6 (192) | |
| BDI-II score | 9 ± 8 | 8 ± 7 | 0.16 | 8 ± 7 | 0.06 | 9 ± 7 | 0.33 |
| Education level, % ($n$) | | | | | | | |
| Up to primary education | 52 (282) | 49 (2902) | 0.33 | 44 (1519) | < 0.01 | 53 (1771) | 0.90 |
| Secondary education | 28(148) | 29 (1700) | | 30 (1028) | | 28 (949) | |
| Academic or graduate | 20 (107) | 22 (1288) | | 26 (872) | | 19 (645) | |
| Smoking habit, % ($n$) | | | | | | | |
| Never a smoker | 55 (297) | 43 (2549) | < 0.01 | 39 (1336) | < 0.01 | 46 (1564) | < 0.01 |
| Former smoker | 37 (196) | 44 (2589) | | 47 (1595) | | 42 (1415) | |
| Current smoker | 8 (44) | 13 (752) | | 14 (488) | | 12 (386) | |
| Leisure time physical activity, METs. min./week | 1986 [895–3469] | 1867 [848–3382] | 0.36 | 1846 [848–3390] | 0.46 | 1888 [863–3357] | 0.21 |
| Total energy intake (Kcal/day) | 2284 ± 570 | 2372 ± 549 | < 0.01 | 2405 ± 553 | < 0.01 | 2351 ± 539 | < 0.01 |
| Food group consumption, g/day | | | | | | | |
| Fruits | 371 ± 227 | 358 ± 203 | 0.17 | 349 ± 198 | 0.02 | 365 ± 208 | 0.54 |
| Vegetables | 339 ± 142 | 327 ± 139 | 0.04 | 326 ± 139 | 0.03 | 326 ± 139 | 0.03 |
| Nuts | 16 ± 18 | 15 ± 17 | 0.03 | 15 ± 17 | 0.02 | 15 ± 17 | 0.04 |
| Olive oil | 41 ± 18 | 40 ± 17 | 0.20 | 39 ± 17 | 0.07 | 40 ± 17 | 0.29 |
| Cereals | 149 ± 78 | 151 ± 78 | 0.61 | 152 ± 78 | 0.38 | 149 ± 78 | 0.88 |
| Red meat and poultry | 138 ± 56 | 149 ± 58 | < 0.01 | 152 ± 61 | < 0.01 | 147 ± 56 | < 0.01 |
| Fish and seafood | 98 ± 46 | 102 ± 48 | 0.05 | 103 ± 48 | 0.03 | 102 ± 47 | 0.09 |
| Dairy products | 301 ± 210 | 349 ± 199 | < 0.01 | 342 ± 197 | < 0.01 | 365 ± 201 | < 0.01 |
| Biscuits | 26 ± 30 | 27 ± 30 | 0.46 | 27 ± 31 | 0.40 | 28 ± 30 | 0.20 |
| Legumes | 22 ± 13 | 21 ± 11 | 0.03 | 21 ± 11 | 0.04 | 20 ± 11 | 0.01 |
| Alcohol | 2 [0–10] | 5 [0.7–14.8] | < 0.01 | 6 [1.5–17] | < 0.01 | 4[0.7–13] | < 0.01 |
| MedDiet score (17 points) | 9 ± 3 | 8 ± 3 | < 0.01 | 8 ± 3 | < 0.01 | 9 ± 3 | < 0.01 |

Data were expressed as means ± SD or median [P25–P75] and percentages (number) for continuous and categorical variables, respectively. $p$ values for comparisons between non-coffee consumers and coffee consumers[a], non-coffee consumers and caffeinated coffee consumers[b], and non-coffee consumers and decaffeinated coffee consumers[c] were tested by $t$ test or Chi-square test, as appropriate

*BDI-II* Beck Depression Inventory, *BMI* body mass index, *MedDiet* Mediterranean diet, *MMSE* Mini-Mental State Examination

**Table 2** Association (odds ratio, 95% CI) between type of coffee consumption and odds of poor cognitive functioning (MMSE)

| | Non-coffee consumers ($n=537$) | Coffee consumers ($n=5890$) | $p$ value[a] | Caffeinated coffee consumers ($n=3419$) | $p$ value[b] | Decaffeinated coffee consumers ($n=3365$) | $p$ value[c] |
|---|---|---|---|---|---|---|---|
| MMSE ≤ 24, % ($n$) | 8 (43) | 5 (286) | | 4 (134) | | 6 (192) | |
| Crude model | 1 (ref.) | 0.59 (0.42–0.82) | < 0.01 | 0.47 (0.33–0.67) | < 0.01 | 0.70 (0.49–0.98) | 0.04 |
| Model 1 | 1 (ref.) | 0.66 (0.46–0.93) | 0.02 | 0.58 (0.40–0.84) | < 0.01 | 0.73 (0.51–1.05) | 0.09 |
| Model 2 | 1 (ref.) | 0.63 (0.45–0.90) | 0.01 | 0.57 (0.39–0.84) | < 0.01 | 0.70 (0.48–1.03) | 0.07 |
| Fully adjusted | 1 (ref.) | 0.63 (0.44–0.90) | 0.01 | 0.56 (0.38–0.83) | < 0.01 | 0.70 (0.48–1.02) | 0.06 |

Risk of cognitive impairment was defined as a MMSE score ≤ 24 points. Multivariable logistic regression models were fitted: outcome: MMSE score > 24 (0) vs. MMSE score ≤ 24 points (1). Model 1: adjusted for age (years), sex, body mass index (kg/m$^2$), educational level (up to primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes prevalence risk (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and participating center (in quartiles by number of participants). Model 2: additionally, adjusted for food groups [consumption of vegetables, fruits, dried fruits, biscuits, fish, dairy products, meat and poultry, legumes, olive oil and cereals (g/day)]. Fully adjusted: model 2 additionally adjusted for depression status (mild/moderate-to-severe depression). Models 2 and fully adjusted for caffeinated coffee consumers and decaffeinated coffee consumers were additionally adjusted by decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation

*MMSE* Mini-Mental State Examination, *CI* confidence interval, *OR* odds ratio

$p$ values between non-consumers and coffee consumers[a], between non-consumers and caffeinated coffee consumers[b], and between non-consumers and decaffeinated coffee consumers[c]

especially caffeine intake, had a dose–response relationship with improving several domains of cognitive performance [7]. The same study also reported that older participants had a greater scope than younger participants for increasing their level of cognitive functioning in relation to caffeine intake [7]. This might suggest that individuals at risk of cognitive impairment (i.e., older age) are more prone to the benefits of coffee consumption and its components. However, we cannot discard reverse causation. In the ELSA-Brasil cohort, a battery of neuropsychological tests (including semantic and phonemic VFTs and TMT-B) was used to cross-sectionally assess the association between coffee consumption and cognitive function [41]. The above study reported that elderly individuals who consumed ≥ 3 cups/day of total coffee performed better on the semantic verbal fluency test than those who rarely consumed coffee or did not consume it at all. However, these associations were not observed among elderly participants in the phonemic verbal fluency test or the TMT-B. Although, in our study conducted in a senior population, this association was observed in the Trail Making Test B. Neither were any associations reported between coffee consumption and cognitive performance in younger adults in the ELSA-Brasil cohort.

A systematic review and meta-analysis of nine prospective studies [13] reported that individuals who consumed between 1 and 2 cups/day had a lower risk of incidence of cognitive disorders such as Alzheimer's disease, dementia, cognitive decline and cognitive impairment than low coffee consumers (< 1 cup/day). The review also reported a J-shaped association between total coffee consumption and incident cognitive disorders, with the lowest risk observed at a consumption level of 1–2 cups of coffee per day. This association was not observed in our study, where no difference was observed between participants who consumed between 1–2 servings/day and those who consumed more than 2 servings/day. However, this may be due to the different tests used by each study.

Our results on total dietary caffeine intake are in line with those of previous studies that have reported that caffeine can act as a psychoactive stimulant, improving cognitive performance in the short term and decreasing the risk of cognitive impairment, dementia and AD in the long term [7–9, 14]. The mechanisms underlying the association between caffeine intake and cognitive ability or dementia are not completely understood. Some animal studies have demonstrated that caffeine intake has a beneficial effect on cognitive performance in the short term. Moreover, some in vitro and preclinical animal models suggest that some of the bioactive components of coffee have neuroprotective mechanisms of action that attenuate β-amyloid peptide (Aβ) production and prevent neuronal damage, synaptotoxicity and cognitive deficit in rats induced by Aβ in the long term [42]. Unfortunately, to the best of our knowledge, there was no evidence of this in humans.

In a double-blind placebo-controlled trial conducted in 2018 [8], healthy Japanese adults completed a battery of four tests that measured performance in several cognitive domains, including reaction time, cognitive flexibility, processing speed, executive function, working memory and sustained attention. The authors found that participants who were acutely given 200 mg/day of caffeine performed

**Table 3** Association (odds ratio, 95% CI) between servings of total coffee, caffeinated coffee and decaffeinated coffee consumption and the odds of cognitive impairment (MMSE test)

| Servings of total coffee consumption (50 ml) | < 1/day<br>*n* = 1201 | 1–2/day<br>*n* = 2891 | > 2/day<br>*n* = 2335 | *p* trend |
|---|---|---|---|---|
| Odds of poor cognitive functioning, % (*n*) | 6.2 (75) | 5.4 (156) | 4.2 (98) | |
| Crude model | 1 (ref.) | 0.86 (0.65–1.14) | 0.66 (0.48–0.90) | < 0.01 |
| Model 1 | 1 (ref.) | 0.79 (0.59–1.06) | 0.74 (0.54–1.01) | 0.11 |
| Model 2 | 1 (ref.) | 0.77 (0.57–1.03) | 0.70 (0.50–0.97) | 0.06 |
| Fully adjusted | 1 (ref.) | 0.77 (0.57–1.03) | 0.70 (0.50–0.97) | 0.06 |
| Servings of caffeinated coffee (50 ml) | < 1/day<br>*n* = 3492 | 1–2/day<br>*n* = 1629 | > 2/day<br>*n* = 1306 | *p* trend |
| Odds of poor cognitive functioning, % (*n*) | 6.2 (218) | 4.0 (66) | 3.5 (45) | |
| Crude model | 1 (ref.) | 0.63 (0.48–0.84) | 0.54 (0.39–0.74) | < 0.01 |
| Model 1 | 1 (ref.) | 0.76 (0.57–1.01) | 0.80 (0.57–1.12) | 0.10 |
| Model 2 | 1 (ref.) | 0.65 (0.47–0.89) | 0.66 (0.46–0.97) | 0.02 |
| Fully adjusted | 1 (ref.) | 0.65 (0.47–0.90) | 0.66 (0.45–0.96) | 0.02 |
| Servings of decaffeinated coffee (50 ml) | < 1/day<br>*n* = 3694 | 1–2/day<br>*n* = 1678 | > 2/day<br>*n* = 1055 | *p* trend |
| Odds poor cognitive functioning, % (*n*) | 4.8 (176) | 5.9 (99) | 5.1 (54) | |
| Crude model | 1 (ref.) | 1.25 (0.97–1.62) | 1.08 (0.79–1.47) | 0.40 |
| Model 1 | 1 (ref.) | 1.00 (0.77–1.30) | 0.93 (0.67–1.28) | 0.68 |
| Model 2 | 1 (ref.) | 0.91 (0.68–1.22) | 0.79 (0.54–1.15) | 0.21 |
| Fully adjusted | 1 (ref.) | 0.92 (0.69–1.22) | 0.79 (0.54–1.15) | 0.69 |

*CI* confidence interval, *OR* odds ratio

Risk of cognitive impairment was defined as a MMSE score ≤ 24 points. Multivariable logistic regression models and median regression models were fitted: Outcome: MMSE score > 24 points (0) vs. MMSE score ≤ 24 points (1). Model 1: adjusted for age (years), sex, body mass index (kg/m$^2$), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and participating center (in quartiles by number of participants). Model 2: additionally adjusted for food groups [consumption of vegetables, fruits, dried fruits, biscuits, fish, dairy products, meat, legumes, olive oil and cereals (g/day)]. Fully adjusted: Model 2 additionally adjusted for depression status (mild/moderate-to-severe depression). Models for caffeinated coffee consumers and decaffeinated coffee consumers were additionally adjusted by decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation

better on the shifting attention test but not in other cognitive domains.

Caffeine is structurally similar to adenosine, an endogenous neurotransmitter with mostly inhibitory effects on the central nervous system, when acting through A1 receptors. In general, adenosine inhibits adenyl cyclase via A1 receptors and stimulates adenyl cyclase via A2 receptors [43]. The effects of caffeine on the brain are mediated through the blockade of adenosine A1 and A2A receptors, which disable the capacity of adenosine to bind the receptors. The ability of caffeine to interact with neurotransmission in different regions of the brain may promote behavioral functions, such as vigilance, attention, mood and arousal [12].

The association between long-term caffeine consumption in humans and cognition or cognitive disorders has been explored using cross-sectional and prospective study designs. A cross-sectional analysis conducted in more than 9000 British adults [6] showed that caffeine intake had a dose–response relationship with better cognitive performance when measured by several tests and after adjusting for potential confounders. A systemic review and meta-analysis published in 2010 [14] that included nine prospective cohort studies and two case–control studies reported a trend towards a protective relationship of caffeine intake on various measures of cognitive impairment/decline, although considerable methodological heterogeneity between studies made it difficult to interpret the results. After this meta-analysis, a new prospective study conducted in the context of the Women's Health Initiative Memory Study [9] also showed an inverse association between total caffeine intake and the risk of age-related cognitive impairments in women aged ≥ 65 years.

In our analysis, a protective trend against poor cognitive performance was observed for decaffeinated coffee consumption, although it was not statistically significant. Few studies have analyzed the potential effect of decaffeinated

**Table 4** Association (odd ratio, 95% CI) between type of coffee consumed and cognitive status measured by various neuropsychological tests

| Neuropsychological tests | Non-coffee consumers | Coffee consumers | Caffeinated coffee consumers | Decaffeinated coffee consumers |
|---|---|---|---|---|
| Phonological verbal fluency of letter P ($n=6563$) | ($n=553$) | ($n=6010$) | ($n=3500$) | ($n=3435$) |
| Odds of poor cognitive functioning, % ($n$) | 6.7 (37) | 5.1 (308) | 4.1 (143) | 5.7 (196) |
| Crude model | 1 (ref.) | 0.75 (0.53–1.07) | 0.59 (0.41–0.86) | 0.84 (0.59–1.21) |
| Fully adjusted model | 1 (ref.) | 0.83 (0.57–1.20) | 0.71 (0.47–1.06) | 0.95 (0.65–1.40) |
| Semantic verbal fluency of animals ($n=6563$) | ($n=553$) | ($n=6010$) | ($n=3500$) | ($n=3435$) |
| Odds of poor cognitive functioning, % ($n$) | 5.4 (30) | 4.5 (269) | 3.6 (125) | 5.0 (173) |
| Crude model | 1 (ref.) | 0.82 (0.55–1.22) | 0.65 (0.42–0.98) | 0.92 (0.61–1.39) |
| Fully adjusted model | 1 (ref.) | 0.93 (0.62–1.41) | 0.84 (0.54–1.30) | 0.98 (0.64–1.52) |
| Clock test ($n=6400$) | ($n=534$) | ($n=5866$) | ($n=3403$) | ($n=3353$) |
| Odds of poor cognitive functioning, % ($n$) | 13.9 (74) | 10.9 (640) | 9.3 (318) | 12.0 (402) |
| Crude model | 1 (ref.) | 0.76 (0.59–0.99) | 0.64 (0.49–0.84) | 0.85 (0.65–1.11) |
| Fully adjusted model | 1 (ref.) | 0.80 (0.61–1.05) | 0.72 (0.54–0.96) | 0.89 (0.67–1.18) |
| Trail making test: A, total time (seconds), ($n=6533$) | ($n=547$) | ($n=5986$) | ($n=3489$) | ($n=3418$) |
| Odds of poor cognitive functioning, % ($n$) | 7.5 (41) | 5.9 (351) | 5.1 (177) | 6.7 (228) |
| Crude model | 1 (ref.) | 0.77 (0.55–1.08) | 0.66 (0.46–0.94) | 0.88 (0.62–1.25) |
| Fully adjusted model | 1 (ref.) | 0.88 (0.61–1.25) | 0.83 (0.56–1.21) | 0.95 (0.66–1.37) |
| Trail making test: B, total time (s), ($n=6457$) | ($n=542$) | ($n=5915$) | ($n=3452$) | ($n=3375$) |
| Odds of poor cognitive functioning, % ($n$) | 14.2 (77) | 9.4 (556) | 8.7 (300) | 9.6 (323) |
| Crude model | 1 (ref.) | 0.63 (0.48–0.81) | 0.57 (0.44–0.75) | 0.64 (0.49–0.84) |
| Fully adjusted model | 1 (ref.) | 0.63 (0.48–0.84) | 0.67 (0.49–0.90) | 0.63 (0.47–0.86) |
| Digit forward score ($n=5128$) | ($n=423$) | ($n=4705$) | ($n=2707$) | ($n=2715$) |
| Odds of poor cognitive functioning, % ($n$) | 5.9 (25) | 5.9 (277) | 4.5 (123) | 6.6 (178) |
| Crude model | 1 (ref.) | 1.00 (0.65–1.52) | 0.76 (0.49–1.18) | 1.12 (0.73–1.72) |
| Fully adjusted model | 1 (ref.) | 1.19 (0.77–1.82) | 1.03 (0.64–1.65) | 1.33 (0.84–2.09) |

Cutoff points for the phonological verbal fluency, the semantic verbal fluency and the digit forward score were established as ≤ the mean − 1.5SD. For Trail Making Tests A and B cutoff points were established as ≥ of the mean + 1.5SD. For the clock test, the cutoff point was established as ≤ 4 points. Multivariable logistic regression models were fitted. Outcome (several neuropsychological tests). Fully adjusted model: adjusted for age (years), sex, body mass index (kg/m$^2$), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption in g/day (and adding the quadratic term), diabetes prevalence risk (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), consumption of vegetables (g/day), fruits (g/day), dried fruits (g/day), biscuits (g/day), fish (g/day), dairy products (g/day), meat (g/day), legumes (g/day), olive oil (g/day), cereals (g/day), depression status (mild/moderate-to-severe depression), and participating center (in quartiles by number of participants). The models for caffeinated coffee consumers and decaffeinated coffee consumers were additionally adjusted by decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. Data are expressed as ORs (95%, CI)

*CI* confidence interval, *OR* odds ratio

coffee on cognition although the results are inconsistent [15, 44–46]. It has been suggested that coffee compounds other than caffeine, which are also found in decaffeinated coffee, may also have a protective effect on cognition [47, 48]. These include chlorogenic acids (polyphenols with antioxidant properties), which may help to reduce oxidative stress and neuroinflammation [49]. It has been suggested that the antioxidant capacity of coffee depends on its ability to increase the concentration of glutathione in plasma [38], while levels of glutathione in the brain tend to decrease with aging, Parkinson's disease and Alzheimer's disease [50]. A prospective study conducted with healthy Afro-American adults reported an association between increased levels of oxidative stress, as reflected by low or progressively decreasing glutathione levels, and a decline in executive function with aging [51]. Furthermore, coffee components such as quinic acid, caffeic acid, quercetin, and phenylindane have been associated with anti-inflammatory properties, protection against amyloid toxicity, tau aggregation and Aβ inhibition [47, 48]. However, the results from a recently published study conducted in older American adults reported no significant association between decaffeinated coffee and different dimensions of cognitive performance [15], which is in line with our

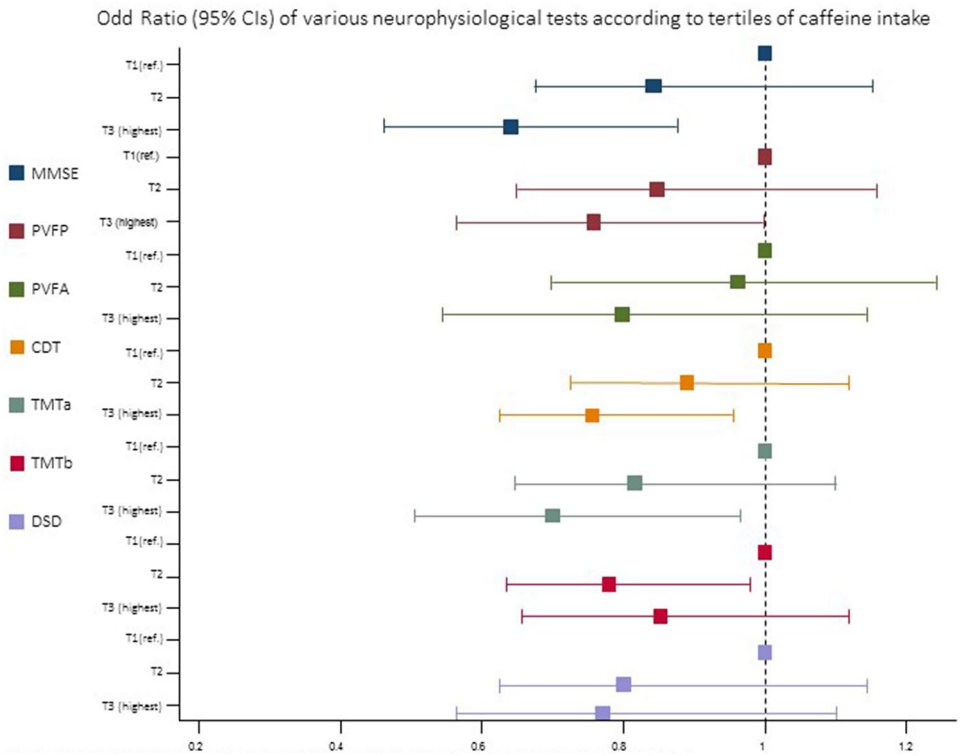


**Fig. 1** Odds ratio (95% CIs) of various neurophysiological tests according to tertiles of caffeine intake. *MMSE* Mini-Mental State Examination, *PVFP* phonological verbal fluency, *SVFA* semantic verbal fluency, *Clock T* clock test, *TMTa* trail making tests A, *TMTb* trail making tests B, *DSD* digit forward score. Multivariable logistic regression model. Adjusted for age (years), sex, body mass index (kg/m$^2$), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), consumption of vegetables (g/day), fruits (g/day), dried fruits (g/day), biscuits (g/day), fish (g/day), dairy products (g/day), meat (g/day), legumes (g/day), olive oil (g/day), cereals (g/day), depression status (mild/moderate-to-severe depression) and participating center (in quartiles by number of participants). All analyses were conducted with robust estimates of the variance to correct for intracluster correlation

observations and the results reported by Johnson-Kozlow et al. [44].

The results for total and decaffeinated coffee reinforce the hypothesis that it is the synergic effect of polyphenols, caffeine and other coffee compounds, not only caffeine, that gives coffee consumption its protective effect against cognitive impairment. It should be noticed that the positive associations between total coffee and caffeinated coffee consumption and cognitive performance observed in our study and others [9, 44] have been reported using various neuropsychological screening tests. The different results provided by the different tests may be the consequence of each test measuring different cognitive domains that are more prone to influence by coffee consumption and its components in different forms. For example, it is accepted that caffeine can increase alertness, improve sustained attention and working memory and reduce reaction time and fatigue [43, 52]. This may explain the associations observed for the MMSE, CDT and TMT tests which examine cognitive functions such as memory, orientation, registration, concentration, processing speed, visual search and hemiattention, which are prone to be affected by coffee consumption.

Our study has certain limitations that must be considered. Firstly, as MMSE and the battery of neuropsychological tests used in this study are screening tools that cannot substitute a complete diagnostic workup, the results must be taken with caution. However, using several neuropsychological tests to evaluate cognitive status gives our findings greater value. Secondly, given the cross-sectional design, it is not possible to determine causality between coffee consumption and caffeine intake, and cognitive function. Thirdly, the caffeine content in coffee, other beverages (e.g., tea and soft drinks) and food varies greatly, which may lead to under- or overestimation. However, we should point out that we have explored the association between cognitive performance and decaffeinated coffee, which gives greater insight into the potential effect of coffee consumption as a whole and not just caffeine on cognition. Finally, our study has been conducted in aged individuals with overweight/obesity

and metabolic syndrome; therefore, our findings cannot be extrapolated to other population groups.

## Conclusion

In this cross-sectional study, total and caffeinated coffee consumption and total caffeine intake were associated with lower odds of poor cognitive functioning measured by a battery of neurophysiological tests in a Mediterranean cohort of elderly individuals with MetS. Long-term and interventional studies are needed to clarify these associations, and if they are confirmed, dietary recommendations on coffee consumption and caffeine intake could be part of strategies for preventing cognitive decline.

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**Availability of data and materials** There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: jordi.salas@urv.cat. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

## Compliance with ethical standards

**Conflict of interest** JS-S serves on the board of (and receives grant support through his institution from) the International Nut and Dried Fruit Council and the Eroski Foundation. He also serves on the Executive Committee of the Instituto Danone, Spain, and on the Scientific Committee of the Danone International Institute. He has received research support from the Patrimonio Comunal Olivarero, Spain, and Borges S.A., Spain. He receives consulting fees or travel expenses from Danone, the Eroski Foundation, the Instituto Danone, Spain, and Abbot Laboratories. ER has received research funding through his institution from the California Walnut Commission, Folsom, CA, USA; was a paid member of its Health Research Advisory Group; and is a nonpaid member of its Scientific Advisory Council.

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## References

1. Yates KF, Sweat V, Yau PL et al (2012) Impact of metabolic syndrome on cognition and brain. Arterioscler Thromb Vasc Biol 32:2060–2067. https://doi.org/10.1161/ATVBAHA.112.252759
2. Atti AR, Valente S, Iodice A et al (2019) Metabolic syndrome, mild cognitive impairment, and dementia: a meta-analysis of longitudinal studies. Am J Geriatr Psychiatry 27:625–637. https://doi.org/10.1016/j.jagp.2019.01.214
3. Solas M, Milagro FI, Ramírez MJ, Martínez JA (2017) Inflammation and gut-brain axis link obesity to cognitive dysfunction: plausible pharmacological interventions. Curr Opin Pharmacol 37:87–92. https://doi.org/10.1016/j.coph.2017.10.005
4. WHO (2019) Risk reduction of cognitive decline and dementia: WHO guidelines
5. Singh B, Parsaik AK, Mielke MM et al (2014) Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. Alzheimer Dis 39:271–282. https://doi.org/10.3233/jad-130830

6. Berendsen AAM, Kang JH, van de Rest O et al (2017) The dietary approaches to stop hypertension diet, cognitive function, and cognitive decline in American older women. J Am Med Dir Assoc 18:427–432. https://doi.org/10.1016/j.jamda.2016.11.026
7. Jarvis MJ (1993) Does caffeine intake enhance absolute levels of cognitive performance? Psychopharmacology 110:45–52. https://doi.org/10.1007/BF02246949
8. Konishi Y, Hori H, Ide K et al (2018) Effect of single caffeine intake on neuropsychological functions in healthy volunteers: a double-blind placebo-controlled study. PLoS One 13:e0202247. https://doi.org/10.1371/journal.pone.0202247
9. Driscoll I, Shumaker SA, Snively BM et al (2016) Relationships between caffeine intake and risk for probable dementia or global cognitive impairment: the women's health initiative memory study. J Gerontol Ser A Biol Sci Med Sci 71:1596–1602. https://doi.org/10.1093/gerona/glw078
10. Cao C, Wang L, Lin X et al (2011) Caffeine synergizes with another coffee component to increase plasma GCSF: linkage to cognitive benefits in Alzheimer's mice. J Alzheimer Dis 25:323–335. https://doi.org/10.3233/JAD-2011-110110
11. Chu Y, Chang W, Black R et al (2012) Crude caffeine reduces memory impairment and amyloid β(1–42) levels in an Alzheimer's mouse model. Food Chem 135:2095–2102. https://doi.org/10.1016/j.foodchem
12. Basurto-Islas G, Blanchard J, Tung YC et al (2014) Therapeutic benefits of a component of coffee in a rat model of Alzheimer's disease. Neurobiol Aging 35:2701–2712. https://doi.org/10.1016/j.neurobiolaging.2014.06.012
13. Wu L, Sun D, He Y (2017) Coffee intake and the incident risk of cognitive disorders: a dose-response meta-analysis of nine prospective cohort studies. Clin Nutr 36:730–736. https://doi.org/10.1016/j.clnu.2016.05.015
14. Santos C, Costa J, Santos J et al (2010) Caffeine intake and dementia: systematic review and meta-analysis. J Alzheimer Dis 20:S187–S204. https://doi.org/10.3233/JAD-2010-091387
15. Dong X, Li S, Sun J et al (2020) Association of coffee, decaffeinated coffee and caffeine intake from coffee with cognitive performance in older adults: National Health and Nutrition Examination Survey (NHANES) 2011–2014. Nutrients 12:840. https://doi.org/10.3390/nu12030840
16. Alberti K, Eckel R, Grundy S et al (2009) Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International. Circulation 120:1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644
17. Martínez-González M, Buil-Cosiales P, Corella D et al (2019) Cohort profile: design and methods of the PREDIMED-Plus randomized trial. Int J Epidemiol 48:387–388o. https://doi.org/10.1093/ije/dyy225
18. Mataix Verdú J (2003) Tabla de composicion de alimentos. [Food Composition Tables]. Granada, Spain
19. Moreiras O, Carvajal A, Cabrera L, Cuadrado C (2005) Tablas de composición de alimentos" Food Composition Tables" Pirámide. Madrid, Spain
20. Zucconi S, Volpato C, Adinolfi F et al (2013) Gathering consumption data on specific consumer groups of energy drinks. EFSA Support Publ 10:190. https://doi.org/10.2903/sp.efsa.2013.EN-394
21. Blesa R, Pujol M, Aguilar M et al (2001) Clinical validity of the 'mini-mental state' for Spanish speaking communities. Neuropsychologia 39:1150–1157. https://doi.org/10.1016/S0028-3932(01)00055-0
22. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198. https://doi.org/10.1016/0022-3956(75)90026-6
23. Benton AL, Hamsher KD, Sivan AB (1994) Multilingual Aphasia Examination: Manual of Instructions, 3rd edition. Iowa City, IA: AJA Associates
24. TEA SA (1999) WAIS-III: Escala de inteligencia de Wechsler para Adultos. [WAIS-III: Wechsler adult Intelligence scale. Third version]
25. Llinàs-Reglà J, Vilalta-Franch J, López-Pousa S et al (2017) The trail making test: association with other neuropsychological measures and normative values for adults aged 55 years and older from a Spanish-speaking population-based sample. Assessment 24:183–196. https://doi.org/10.1177/1073191115602552
26. Aprahamian I, Martinelli J, Neri Liberalesso A, Sanches Yassuda M (2009) The Clock Drawing Test a review of its accuracy in screening for dementia. Dement Neuropsychol 3:74–80. https://doi.org/10.1590/S1980-57642009DN30200002
27. Paganini-Hill A, Clark L (2011) Longitudinal assessment of cognitive function by clock drawing in older adults. Dement Geriatr Cogn Disord Extra 1:75–83. https://doi.org/10.1159/000326781
28. del Ser QT, García de Yébenes M, Sánchez Sánchez F et al (2004) Cognitive assessment in the elderly. Normative data of a Spanish population sample older than 70 years. Med Clin (Barc) 122:727–740. https://doi.org/10.1157/13062190
29. Elosua R, Marrugat J, Molina L et al (1994) Validation of the Minnesota leisure time physical activity questionnaire in Spanish men. Am J Epidemiol 139:1197–1209. https://doi.org/10.1093/oxfordjournals.aje.a116966
30. Elosua R, Garcia M, Aguilar A et al (2000) Validation of the Minnesota leisure time physical activity questionnaire in Spanish women. Med Sci Sport Exerc 32:1431–1437. https://doi.org/10.1097/00005768-200008000-00011
31. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M et al (2018) Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus Trial. Diabetes Care 42:dc180836. https://doi.org/10.2337/dc18-0836
32. Schröder H, Fitó M, Estruch R et al (2011) A short screener is valid for assessing mediterranean diet adherence among older Spanish men and women. J Nutr 141:1140–1145. https://doi.org/10.3945/jn.110.135566
33. Sanz J, Perdigón AL, Vázquez C (2003) Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): 2. Propiedades psicométricas en población general. Clínica y Salud [en linea] 14:249–280
34. Nissensohn M, Sánchez-Villegas A, Ortega RM et al (2016) Beverage consumption habits and association with total water and energy intakes in the Spanish population: findings of the ANIBES study. Nutrients. https://doi.org/10.3390/nu8040232
35. Ferreira-Pêgo C, Babio N, Fenández-Alvira JM et al (2014) Fluid intake from beverages in Spanish adults; cross-sectional study. Nutr Hosp 29:1171–1178. https://doi.org/10.3305/nh.2014.29.5.7421
36. Paz Graniel I, Babio N, Serra Majem L et al (2019) Fluid and total water intake in a senior mediterranean population at high cardiovascular risk: demographic and lifestyle determinants in the PREDIMED-Plus study. Eur J Nutr. https://doi.org/10.1007/s00394-019-02015-3
37. Ros E, Hu FB (2013) Consumption of plant seeds and cardiovascular health. Circulation 128:553–565. https://doi.org/10.1161/CIRCULATIONAHA.112.001119
38. Godos J, Pluchinotta FR, Marventano S et al (2014) Coffee components and cardiovascular risk: beneficial and detrimental effects. Int J Food Sci Nutr 65:925–936. https://doi.org/10.3109/09637486.2014.940287

39. Butt MS, Tauseef Sultan M (2011) Critical reviews in food science and nutrition coffee and its consumption: benefits and risks. Crit Rev Food Sci Nutr 51:363–373. https://doi.org/10.1080/10408390903586412
40. Navarro AM, Martinez-Gonzalez MÁ, Gea A et al (2018) Coffee consumption and total mortality in a Mediterranean prospective cohort. Am J Clin Nutr 108:1113–1120. https://doi.org/10.1093/ajcn/nqy198
41. Fortunato Araújo L, Giatti L, Padilha dos Reis RC et al (2015) Inconsistency of association between coffee consumption and cognitive function in adults and elderly in a cross-sectional study (ELSA-Brasil). Nutrients. https://doi.org/10.3390/nu7115487
42. Jackson NHH (2015) The effects of coffee consumption on cognition and dementia diseases. J Gerontol Geriatr Res. https://doi.org/10.4172/2167-7182.1000233
43. Fisone G, Borgkvist A, Usiello A (2004) Caffeine as a psychomotor stimulant: mechanism of action. Cell Mol Life Sci 61:857–872. https://doi.org/10.1007/s00018-003-3269-3
44. Johnson-Kozlow M, Kritz-Silverstein D, Barrett-Connor E, D. M, (2002) Coffee consumption and cognitive function among older adults. Am J Epidemiol 156:842–850. https://doi.org/10.1093/aje/kwf119
45. Camfield DA, Silber BY, Scholey AB et al (2013) A randomised placebo-controlled trial to differentiate the acute cognitive and mood effects of chlorogenic acid from decaffeinated coffee. PLoS One 8:e82897. https://doi.org/10.1371/journal.pone.0082897
46. Haskell-Ramsay C, Jackson P, Forster J et al (2018) The acute effects of caffeinated black coffee on cognition and mood in healthy young and older adults. Nutrients 10:1386. https://doi.org/10.3390/nu10101386
47. Mancini RS, Wang Y, Weaver DF (2018) Phenylindanes in brewed coffee inhibit amyloid-beta and tau aggregation. Front Neurosci. https://doi.org/10.3389/fnins.2018.00735
48. Colombo R, Papetti A (2020) An outlook on the role of decaffeinated coffee in neurodegenerative diseases. Crit Rev Food Sci Nutr 60:760–779. https://doi.org/10.1080/10408398.2018.1550384
49. Castelli V, Grassi D, Bocale R et al (2018) Diet and brain health: which role for polyphenols? Curr Pharm Des 24:227–238. https://doi.org/10.2174/1381612824666171213100449
50. Sian J, Dextert D, Lees A et al (1994) Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. Ann Neurol 36:348–355. https://doi.org/10.1002/ana.410360305
51. Ihab H, Hayek SS, Goldstein FC et al (2018) Oxidative stress predicts cognitive decline with aging in healthy adults: an observational study. J Neuroinflamm. https://doi.org/10.1186/s12974-017-1026-z
52. Kromhout MA, Ottenheim NR, Giltay E et al (2019) Caffeine and neuropsychiatric symptoms in patients with dementia: a systematic review. Exp Gerontol 122:85–91. https://doi.org/10.1016/j.exger.2019.04.017


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