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Caffeine Intake is Associated with a Lower Risk of Cognitive Decline: A Cohort Study from Portugal

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Abstract. Alzheimer's disease has emerged in recent decades as a major health problem and the role of lifestyles in the modulation of risk has been increasingly recognized. Recent epidemiological studies suggest a protective effect for caffeine intake in dementia. We aimed to quantify the association between caffeine dietary intake and cognitive decline, in a cohort of adults living in Porto. A cohort of 648 subjects aged $\geqslant$ 65 years was recruited between 1999–2003. Follow-up evaluation (2005–2008) was carried out on 58.2% of the eligible participants and 10.9% were deceased. Caffeine exposure in the year preceding baseline evaluation was assessed with a validated food frequency questionnaire. Cognitive evaluation consisted of baseline and follow-up Mini-Mental State Examination (MMSE). Cognitive decline was defined by a decrease $\geqslant$ 2 points in the MMSE score between evaluations. Relative risk (RR) and 95% confidence interval (95%CI) estimates adjusted for age, education, smoking, alcohol drinking, body mass index, hypertension, and diabetes were computed using Poisson regression. Caffeine intake ($>$ 62 mg/day [3rd third] vs. $<$ 22 mg/day [1st third]) was associated with a lower risk of cognitive decline in women (RR $=$ 0.49, 95%CI 0.24–0.97), but not significantly in men (RR $=$ 0.65, 95%CI 0.27–1.54). Our study confirms the negative association between caffeine and cognitive decline in women.

Keywords: Caffeine, cohort studies, dementia, gender

INTRODUCTION

Alzheimer's disease (AD) and other aging-related neurodegenerative disorders have emerged in the last decades as a major health problem in our society [1]. The efficacy of available treatments for these disorders is at present quite limited. The importance of identifying potential risk factors whose modulation might decrease the risk or attenuate the progression of these neurodegenerative disorders is thus obvious. The role of lifestyles in the prevention of AD has been emphasised [2], as had been the case for Parkinson's disease, another neurodegenerative condition sharing similarities with AD [3].

Caffeine is widely consumed worldwide and acts as a nonspecific antagonist of adenosine receptors [4]. The blockade of A_{2A} receptors has recently been demonstrated to limit the synaptotoxic effect of amyloid-

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β (Aβ), a peptide that accumulates in the brain of AD patients [5]. Experimental studies conducted in animal models have also shown that adenosine A_{2A} and metabotropic glutamate 5 receptors are co-located and that the former play a permissive role in mGlu5R receptor-mediated potentiation of NMDA effects in the hippocampus [6].

Epidemiological studies aiming to evaluate caffeine intake and the risk of Parkinson's disease have so far suggested a protective role for this substance, more pronounced in men than in women [3]. Few studies have tested a possible association between regular caffeine intake and the risk for AD. A small case-control study suggested that caffeine exposure was significantly inversely associated with AD [7]. A prospective study also showed that regular consumption of coffee was associated with a reduced risk of AD after 5-year follow-up. This study evaluated both coffee and tea consumption, but the total amount of caffeine intake was not considered, and the association found might have been biased due to the exclusion of a large number of decedents [8]. Other epidemiological studies used a different approach, assessing whether caffeine consumption could influence cognitive decline, with conflicting results [9–11]. Recently, a large epidemiological prospective study (the Three City Study), enrolling about 7,000 participants aged 65 and over, showed that women with high rates of caffeine consumption (over three units per day, which is equivalent to about 300 mg of caffeine) had less decline in memory performance than women consuming one unit or less [12]. The protective effect of caffeine increased with age and was not observed in men. However, the incidence of AD was not decreased in caffeine consumers.

The aim of the present study is to assess, in a different elderly population, the association between caffeine intake and cognitive decline, and to further elucidate the gender dependency of the potential effect. The hypothesis that caffeine intake could decrease the risk of decline by at least 2 points in the score of a widely used cognitive test, the Mini-Mental State Examination (MMSE), was specifically tested in the participants of the EPIPorto study aged 65 and over.

METHODS

Study population

This study was based on the evaluation of a cohort of adults living in Porto. The recruitment of the initial sample has been previously described [13]. Briefly, the recruitment of the cohort was conducted between 1999 and 2003 and comprised the evaluation of 2485 individuals, selected by random digit dialing having households as the sampling unit. When a household was selected, all residents were identified by age and gender, and one resident (aged 18 or more years) was randomly selected as the respondent, without replacement if there was a refusal. The participation rate was 70% [14]. A visit to the Department of Hygiene and Epidemiology of Porto Medical School was scheduled by telephone according to the participant's convenience. A personal interview, using a structured questionnaire comprising data on socio-demographic, clinical, and lifestyle exposures, and a physical examination were performed by trained interviewers. From the whole cohort, 648 participants were aged 65 and over and 531 were selected for the present study, after exclusion of 62 cognitively impaired at baseline (the criteria used to define cognitive impairment is defined below), 32 for whom there was no baseline MMSE, and 23 for whom there was no information on caffeine intake.

Follow-up evaluation

The follow-up evaluation of the cohort took place between May 2005 and May 2008. The participants were scheduled to visit Porto Medical School and underwent a questionnaire and physical examination. Among the 531 eligible participants, 309 (58.2%) completed the follow-up evaluation (median follow-up: 48 months), 58 (10.9%) died before follow-up could be accomplished, and there were 164 (30.9%) losses to follow-up.

Participants who died during the follow up period were more likely to be older and hypertensive (women), to have a lower BMI (men), and lower MMSE score (women). No statistically significant differences between the groups were found regarding education, diabetes, smoking, alcohol, and caffeine consumption (Table 1).

Cognitive testing

The MMSE [15,16] was used to assess global cognitive function at baseline and at follow-up. The MMSE, which includes questions on orientation, registration, attention and calculation, recall, language and visual construction, was originally designed for clinical practice, but is now extensively used in epidemiological studies. Although it does not assess executive function,

Table 1
Socio-demographic, clinical, and behavioral characteristics of the cohort, according to gender

	Women				Men			
	Followed in 2005–2008 ($n = 181$)	Deceased during follow-up ($n = 26$)	Not followed in 2005–2008 ($n = 104$)	P	Followed in 2005–2008 ($n = 128$)	Deceased during follow-up ($n = 32$)	Not followed in 2005–2008 ($n = 60$)	P
Age (years)*	70 (67–73)	75 (71–79)	73 (69–77)	$<$ **0.001**	71 (68–74.5)	72.5 (68–77)	71.5 (69–75.5)	0.386
Age (% $\geqslant$ 75 years)	17.7	50.0	35.6	$<$ **0.001**	25.0	43.8	33.3	0.094
Education (years)*	4 (3–6)	4 (3–4)	4 (3–6)	0.241	4 (4–9)	4 (4–9)	4 (4–9)	0.907
Education (%)								
Illiterate	10.5	11.5	12.5	0.962	0.8	0.0	3.3	0.639
$<$ 12 years	77.9	80.8	76.9		81.2	81.2	80.0	
$\geqslant$ 12 years	11.6	7.7	10.6		18.0	18.8	16.7	
Body mass index (Kg/m^2)*	28.7 (26.2–31.3)	29.2 (25.5–32.7)	28.7 (25.3–31.6)	0.811	26.2 (23.6–29.0)	24.0 (21.2–28.0)	26.9 (24.0–30.2)	**0.039**
Body mass index (%)								
$\leqslant$ 25.0 Kg/m^2	17.3	20.8	20.2	0.702	34.9	56.2	35.0	**0.016**
25.0–29.9 Kg/m^2	50.8	37.5	44.4		50.0	31.2	35.0	
$\geqslant$ 30.0 Kg/m^2	31.8	41.7	35.4		15.1	12.5	30.0	
Smoking (% ever smokers)	8.3	7.7	2.9	0.194	65.6	71.9	66.7	0.798
Alcohol drinking (% ever drinkers)	79.0	61.5	78.8	0.126	96.1	100.0	98.3	0.601
Hypertension (%)	81.1	100.0	91.9	**0.004**	77.6	82.8	87.9	0.244
Diabetes (%)	12.8	12.0	13.5	0.976	10.9	21.9	13.3	0.262
MMSE*	28 (26–29)	25.5 (24–28)	27 (25–28.5)	**0.010**	28 (27.5–29)	28.5 (27–29)	28 (27–29)	0.214
Caffeine intake (mg/day)*	32.2 (10.7–78.8)	31.5 (13.4–57.2)	31.6 (4.9–60.8)	0.554	33.2 (9.5–78.8)	52.2 (20.4–81.6)	33.4 (25.4–79.6)	0.382

*results are presented as median (percentile 25-percentile 75).

a major feature of cognitive decline [17], the MMSE is a reliable and valid test for cognitive impairment, has high test-retest reliability, and is a good indicator of clinically significant cognitive decline [18]. The cut-off values adjusted for education levels were used as proposed in other studies [19,20]. The normative cut-off values of MMSE adjusted for education for the Portuguese population were used [16]. Subjects that had a MMSE score below cutoff at baseline were considered to be cognitively impaired and therefore excluded. Participants had to score above 15 if they were illiterate, above 22 if they had $\leqslant 11$ years of education, and above 27 if they had > 11 years of education.

A decline of at least 2 points in the score of the MMSE from baseline to the follow-up visit was considered meaningful from a clinical point of view [12].

Caffeine dietary intake

Dietary habits in the 12 months preceding the baseline interview were evaluated using a semi-quantitative food frequency questionnaire (FFQ) comprising 82 food and beverage items or groups. It was designed according to Willett et al. [21], and was adapted by inclusion of a variety of typical Portuguese food items. For each FFQ item, subjects were asked the average frequency of consumption (nine possible responses ranging from never to six or more times per day), and the portion size usually consumed (based on a photograph manual with small, medium and large portion sizes). This information was used to estimate the average daily intake of each item by multiplying the usual frequency of intake per day by the average portion size of the corresponding item. Food Processor Plus®, version 5.0, was used to obtain estimates of caffeine dietary intake. The food items/groups of the FFQ from which caffeine could be obtained were: coffee (including all beverages containing coffee); tea (green and black); iced tea; soft drinks; and chocolate (including candy bars and cocoa powder).

The FFQ was validated with four 7-day food records in 75 women and 71 men, and the reproducibility was evaluated through the comparison of two FFQ evaluations conducted in 72 men and 78 women with a one-year interval [22]. For caffeine, the Spearman correlation coefficients were 0.65 for validity and 0.68 for reproducibility.

Socio-demographic, clinical, and other behavioral factors

Education was recorded as completed years of schooling and further categorized into the same three groups used for the normative MMSE cut-offs adjusted for education in the Portuguese population.

Blood pressure was measured on a single occasion by non-physician trained interviewers, using a mercury sphygmomanometer, taking phase I and V Korotkoff sounds as systolic and diastolic blood pressure, respectively, and following the recommendations of the American Heart Association [23]. Two measurements of blood pressure separated by at least 5 minutes were taken after a 10-minute rest. When the difference was larger than 5 mm Hg for systolic or diastolic blood pressure a third measurement was taken and the mean of the 2 closest values was registered. Arterial hypertension was defined as systolic blood pressure $\geqslant$ 140 mmHg and/or diastolic blood pressure $\geqslant$ 90 mmHg and/or current antihypertensive drug therapy [24].

A 12-hour overnight fasting serum sample was obtained to assess glycaemia. Participants on anti-diabetic therapy and/or with fasting plasma glucose concentrations $\geqslant$ 126 mg/dL and/or diagnosed with diabetes by a health professional were considered to have diabetes mellitus [25].

Anthropometric measurements were obtained after an overnight fast, with the participant wearing light clothing and no footwear. Body weight was measured to the nearest 0.1 kg using a digital scale, and height was measured to the nearest centimeter in the standing position using a wall stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2), and further divided into the following categories [26]: obese ($\geqslant$ 30 kg/m^2), overweight (25.0–29.9 kg/m^2), normal and underweight ($<$24.9 kg/m^2).

Regarding smoking habits, subjects were classified as smoker (one or more cigarettes per day, on average), occasional smoker (less than one cigarette per day, on average), ex-smoker (for more than six months) and never smoker, according to World Health Organization categories [27]. Regarding the consumption of alcoholic beverages, participants were classified as non-drinker, ex-drinker (for more than six months), occasional drinker (consumption of less than a drink per week, on average) and usual drinker (consumption of at least one drink per week, on average). For analysis, participants were further categorized in never- and ever-smokers and never- and ever-drinkers.

Statistical analysis

Data analysis was conducted in 309 subjects who at baseline were aged 65 or more and had a MMSE not compatible with cognitive impairment, and who were re-evaluated. Comparison of the baseline characteristics between subjects that were followed, died or were lost to follow up was done using the Chi-Square or the Kruskal-Wallis tests, as appropriate, to compare all groups.

The association between caffeine intake and the development of cognitive impairment was quantified through crude and age-, education-, diabetes-, smoking- and alcohol drinking-adjusted relative risks (RR) and respective 95% confidence intervals (95%CI) using Poisson regression. Data were analysed using STATA®, version 9.2.

Decline in cognitive performance was defined in the primary analysis as a decrease of at least two points on the MMSE from the baseline assessment to follow up [12]. Additional analyses were conducted using impairment in cognitive performance at follow-up (using normative cut-off values of MMSE adjusted for education for the Portuguese population) as the outcome.

To define categories of exposure to caffeine we used the estimated sample tertiles of dietary intake as cut-off points, and the average caffeine content in one *espresso* – 75 mg [28]. For stratified analyses according to age or smoking status we used the median caffeine intake (33 mg) as cut-off to maximize the power of the study for the comparisons in each group.

Separate analyses were conducted for men and women, as previous studies have shown gender-specific effects of caffeine on neurodegenerative diseases [3,12]. The option for this stratified analysis and the small number of subjects presenting the outcomes of interest did not allow the choice of potential confounding factors included in the multivariate models to be based on statistical criteria. We selected factors whose association with neurodegenerative disorders is established or under discussion, namely age [17], education [29, 30], smoking [31,32], alcohol intake [33,34], hypertension [35], diabetes [36], obesity [36,37], and likely to be related to caffeine consumption (especially through coffee intake), even if this association is to a large extent culturally determined and varies with gender and across population settings [38,39].

Ethics

This study was approved by a local Ethics Committee, and all participants gave written informed consent.

RESULTS

Cognitive decline defined as $\Delta MMSE \leqslant -2$ between baseline and follow-up

Caffeine dietary intake was associated with a lower risk of cognitive decline in both women and men (Table 2). In women, this 50% reduction in the risk of cognitive decline was essentially unchanged after adjustment for potentially important confounding factors, and was also observed for a caffeine consumption equivalent to more than one *espresso* per day (average amount, 75 mg, Table 2). The inverse association between caffeine intake and cognitive decline was not statistically significant in men, although the magnitude of the association was similar to that found in women, and was attenuated when confounding was controlled (Table 2).

The negative association between caffeine intake and cognitive decline was apparent in both genders for participants aged below 75 years and for the older subjects (men $<$ 75 years: $\geqslant$ 33 mg caffeine/day vs. $<$ 33 mg caffeine/day, adjusted RR $=$ 0.68, 95% CI 0.31–1.48; men $\geqslant$ 75 years: $\geqslant$ 33 mg caffeine/day vs. $<$ 33 mg caffeine/day, adjusted RR $=$ 0.66, 95% CI 0.11–3.38; women $<$ 75 years: $\geqslant$ 33 mg caffeine/day vs. $<$ 33 mg caffeine/day, adjusted RR $=$ 0.66, 95% CI 0.36–1.19; women $\geqslant$ 75 years: $\geqslant$ 33 mg caffeine/day vs. $<$ 33 mg caffeine/day, adjusted RR $=$ 0.69, 95% CI 0.22–2.16).

The estimated RR obtained with stratified analysis for smoking habits suggests a stronger protective effect of caffeine in non-smoking men (non-smoking men: $\geqslant$ 33 mg/day vs. $<$ 33 mg/day, adjusted RR $=$ 0.30, 95% CI 0.08–1.14; smoking men: $\geqslant$ 33 mg/day vs. $<$ 33 mg/day, adjusted RR $=$ 0.75, 95% CI 0.32–1.78). Only 15 women were smokers, and stratified analysis according to smoking status was therefore not conducted in the female gender group.

Cognitive impairment defined as abnormal MMSE at follow-up

Among women, caffeine intake was associated with a decreased risk of cognitive impairment defined as a MMSE score below cut-off at follow-up, more strongly after adjustment for age, education, diabetes, hypertension, BMI, smoking, and alcohol consumption (Table 3). The results were similar when considering the traditional MMSE cut-off of 24 points [15] to define cognitive impairment, instead of the normative

Table 2

Association between daily caffeine dietary intake and cognitive decline (Δ MMSE $\leqslant -2$), according to gender

	Women				Men			
	Follow-up		RR (95% CI)		Follow-up		RR (95% CI)	
	Person-months	Δ MMSE $\leqslant -2$	Crude	Adjusted[e]	Person-months	Δ MMSE $\leqslant -2$	Crude	Adjusted[e]
Caffeine (mg)								
< 22[a]	3192	28	1 [reference]	1 [reference]	2196	16	1 [reference]	1 [reference]
22–62[b]	3468	22	0.72 (0.41–1.26)	0.65 (0.37–1.17)	2292	14	0.83 (0.40–1.71)	0.91 (0.43–1.91)
> 62[c]	3096	14	0.51 (0.27–0.97)	**0.49 (0.24–0.97)**	2400	9	0.51 (0.22–1.16)	0.65 (0.27–1.54)
Caffeine (mg)								
< 75[d]	7200	55	1 [reference]	1 [reference]	4728	31	1 [reference]	1 [reference]
$\geqslant 75$	2556	9	0.46 (0.22–0.93)	**0.47 (0.22–0.99)**	2160	8	0.56 (0.25–1.22)	0.66 (0.29–1.47)

RR – Relative risk; 95% CI – 95% Confidence Interval; MMSE – Mini-Mental State Examination; Δ – MMSE at follow-up – MMSE at baseline.
[a]1st third; [b]2nd third; [c]3rd third; [d]average caffeine content in one *espresso*; [e]adjusted for age (continuous), education (continuous), diabetes, smoking (never/ever), and alcohol drinking (never/ever).

Table 3

Association between daily caffeine dietary intake and development of cognitive impairment*, according to gender

	Women				Men			
	Follow-up		RR (95% CI)		Follow-up		RR (95% CI)	
	Person-months	Cognitive impairment*	Crude	Adjusted[e]	Person-months	Cognitive impairment*	Crude	Adjusted[e]
Caffeine (mg)								
< 22[a]	3192	9	1 [reference]	1 [reference]	2196	2	1 [reference]	1 [reference]
22–62[b]	3468	6	0.61 (0.21–1.72)	0.54 (0.19–1.59)	2292	–	–	–
> 62[c]	3096	2	0.22 (0.04–1.06)	**0.10 (0.01–0.81)**	2400	3	1.37 (0.22–8.21)	1.53 (0.21–10.94)
Caffeine (mg)								
< 75[d]	7200	15	1 [reference]	1 [reference]	4728	2	1 [reference]	1 [reference]
$\geqslant 75$	2556	2	0.37 (0.08–1.64)	0.19 (0.02–1.48)	2160	3	3.28 (0.54–19.64)	3.36 (0.51–22.10)

RR – Relative risk; 95% CI – 95% Confidence Interval; MMSE – Mini-Mental State Examination.
[a]1st third; [b]2nd third; [c]3rd third; [d]average caffeine content in one *espresso*; [e]adjusted for age (continuous), education (continuous), body mass index (continuous), diabetes, hypertension, smoking (never/ever), and alcohol drinking (never/ever).
*The normative cut-off values of MMSE adjusted to the education for the Portuguese population were used [16]. Subjects were classified as cognitively impaired at follow-up when having a MMSE score below 16 if they were illiterate, 23 if they had $\leqslant 11$ years of education, 28 if they had > 11 years of education.

cut-off values of MMSE adjusted to education for the Portuguese population (data not shown).

Among men, a non-significant positive association was observed, but the reduced number of events had a dramatic effect on precision (Table 3).

DISCUSSION

The present study shows a protective effect of caffeine intake on cognitive decline, as defined by the decrease in two or more points in the MMSE. In women, the results were concordant across different criteria to define levels of exposure to caffeine and when using two different endpoints, either the decrease in two or more points in the MMSE or the presence of a MMSE score below the cut-off for cognitive impairment. Among men the findings were similar when considering the decrease in the MMSE score of two or more points, but the reduced precision of the RR estimates, due to the small number of cognitive impairment events, precluded more robust conclusions.

The results obtained are in agreement with several previously reports which suggested that caffeine reduces the risk of dementia or cognitive decline [7,8,11, 12,40].

A case-control study, also conducted in Portugal, showed an inverse association between caffeine intake and dementia (odds ratio (OR) adjusted for hypertension, diabetes, stroke, head trauma, smoking habits, alcohol consumption, education, family history of dementia and drugs: 0.40; 95%CI 0.25–0.67). No distinction was made for gender-specific effects [7].

When investigating the association between dietary factors and neurodegenerative diseases, prospective designs may provide stronger evidence by overcoming important methodological flaws of case-control designs, especially regarding misclassification of the exposure.

The largest cohort study conducted so far had an average follow up of 3.5 years and aimed to evaluate cognitive performance in several domains. Regarding the decline in MMSE score, no significant association was found ($>$ 3 units of caffeine/day vs. $<$ 1 unit of caffeine/day, RR adjusted for age, education, baseline cognitive performance and center: 0.91; 95% CI 0.73–1.14), and this was attributed to the limitations of MMSE to detect more subtle cognitive deterioration. However, a protective effect of caffeine was observed in women, both for verbal and visuospatial memory performances ($>$ 3 units of caffeine/day vs. $<$ 1 unit of caffeine/day: OR $=$ 0.67; 95% CI 0.53–0.85, for verbal memory; OR $=$ 0.82; 95% CI 0.65–1.03, for visuospatial memory) [12].

A previously published large cohort study with a 5-year follow up period had shown that coffee consumption was associated with a lower risk of dementia (OR adjusted for age, gender and education: 0.69, 95%CI 0.48–0.99). However, these results were not stratified by gender, and the percentage of decedents was 16.1% of the eligible participants. These were also demonstrated to be considerably different from the participants who remained in the study, namely older, less educated, and diagnosed with chronic diseases, which may reflect survival bias [8]. The cohort study with the longest follow-up (median: 28 years), with baseline exposures more likely to reflect the exposure experience of an inception cohort, showed no significant association between coffee consumption and cognitive impairment. Nevertheless, the ascertainment of cognitive status was performed only at the follow-up evaluation and by telephone interview [41].

The present study adds to previous research the consistency of the findings when using different categories of exposure to caffeine and definitions of cognitive impairment, based solely on the MMSE evaluation of cognitive status. Both the strength of the association and the apparent dose-response relationship, despite using only three categories of exposure, favor a causal relationship between caffeine and cognitive decline. Also, the assessment of exposure was done using the FFQ, which allowed the investigators to collect information on the vast majority of caffeine food sources available. Despite this, caffeine intake was assessed only at baseline and it is possible that participants may have changed their dietary habits throughout follow-up. Assuming that the putative neuroprotective role of caffeine was to be exerted during that period, misclassification might have occurred in these cases. It is reasonable to assume that individuals more likely to decrease coffee consumption are probably those more prone to chronic conditions and cognitive decline. This change in habits could therefore lead to an underestimation of the protective effect of caffeine. On the other hand, the strong risk reduction observed for relatively low dietary intakes of caffeine (corresponding to approximately one cup of coffee per day), may be explained, at least partially, by bias and uncontrolled confounding. Alternatively, low consumptions at baseline might be conveying information on the effect of higher intakes in the past that changed over time, especially in older individuals. Van Gelder and colleagues reported

an inverse J-shaped association between the number of cups of coffee consumed and cognitive decline, with the least decline for three cups a day [11]. These results also suggest a protective effect for moderate daily consumptions of coffee.

A consensus paper recently published suggested that a decrease of 3 or more points in MMSE for a period of six months could be used to define rapid cognitive decline in patients with mild to moderately severe AD [42], and it is reasonable to assume that it corresponds to a clinically meaningful deterioration also in subjects not cognitively impaired at baseline. This threshold, and even more so for higher thresholds, would only detect the most serious conditions within the spectrum of severity of cognitive decline and thus be affected by a lower sensitivity. Previous studies on this topic defined cognitive decline as a variation of 2 or more points in the MMSE score over a 3-year period [12], or a variation in at least one point in MMSE over a 1-year period [43]. Given the median 48-month follow-up in our cohort we considered that a variation of MMSE score in one or more points would have a poor specificity and we adopted the same criterion followed by Ritchie et al. [12].

According to the 2001 census [44] of the population, 63.4% of adults aged 65 years or older were women and 36.6% were men, while among the 648 participants in the cohort aged 65 years or older these proportions were 59.4% and 40.6%, respectively. Thus, men were slightly overrepresented in the study sample compared with the population, due to a higher participation rate among men than women, as previously reported [14]. When comparing men and women who did and did not accept to participate, there were no differences regarding marital status, education, or occupation [14]. Thus, the study sample at baseline can be considered representative of the target population in what concerns these socio-demographic characteristics.

There is an important potential for bias in cohort designs, resulting from incomplete follow-up as well as selection criteria. The relatively large proportion of losses to follow-up in the present study (the analyses were restricted to 58.2% of the initial eligible group) could have contributed to biased conclusions. The comparison between participants for whom the follow-up evaluation was accomplished and those lost during this period shows minor differences regarding education, diabetes, smoking, and alcohol drinking habits, as well as for caffeine intake and MMSE (among men). The non-differential drop-outs argue in favor of the validity of our RR estimates, if the relation between caffeine and cognitive decline among the non-participants is expected to be similar to the observed among the participants. However, a lower baseline MMSE score was observed in non-participant women, and known risk factors for dementia such as hypertension or older age [17] were more frequent among subjects lost during follow-up (especially in women), possibly contributing to a higher risk of cognitive decline [17], and ultimately for the overestimation of the protective effect observed for caffeine, partially explaining the stronger associations observed among women. However, data on their cognitive performance evolution would have been invaluable to a proper understanding of the impact of follow-up losses on our results.

The observation that the participants deceased during follow-up were older and more likely to have been hypertensive or to have scored lower in the MMSE at baseline is also in accordance with methodological concerns regarding another potential source of bias common to other prospective evaluations of elderly subjects, called survival bias. In fact, exposure to caffeine in this cohort did not just begin at the time that follow up was initiated, and its influence on the outcomes may have been exerted before the study period, leading to survival bias [45,46]. Only an inception cohort, assuring that every individual would be observed from the beginning of exposure, would provide results free from this type of bias, which can hardly be achieved when assessing the effect of caffeine intake on conditions that tend to occur later in life. It is difficult to predict to what extent such bias may have affected our RR estimates due to the complex relation between caffeine intake and other exposures associated with higher mortality. For example, smoking is associated with coffee consumption and is a major determinant of early mortality [45]. Therefore, subjects who were smokers and coffee drinkers would have been at a higher risk for cognitive decline, had they survived, but were underrepresented in our non-inception cohort, contributing to an overestimation of the negative association between caffeine intake and dementia. On the other hand, it is also important to note that caffeine half-life is decreased in smokers, contributing to a weaker protective effect under the same dietary exposures [47]. This is in keeping with our observation of a lower RR for the association between caffeine and cognitive decline among male non-smokers. Such an interaction could also contribute to explain an overall smaller beneficial effect of caffeine among men, more frequently smokers [48,49], observed in our study as well as by Ritchie et al. [12].

Conversely, hypertension also accounts for early mortality. Even though most epidemiological evidence suggests that regular intake of caffeinated coffee does not increase the risk of hypertension [50], general public awareness makes hypertensive patients less likely to drink coffee [51]. For this reason, it is possible that individuals at a high risk for cognitive impairment and with lower coffee consumption habits are underrepresented in our cohort, thus contributing to an underestimation of an inverse relation between caffeine intake and cognitive decline.

The impact of survival bias tends to increase with the age of the cohort members at baseline [45]. In our study, however, the RR estimates were similar in participants aged below 75 years and in older subjects, arguing in favour of the validity of our estimates. Moreover, smoking was an exceptional habit in the women in this cohort, and typical of the higher social class categories [48]. Given the social and behavioural gender-related particularities of our cohort, it is possible that the survival bias might have been more pronounced in men, with a more accurate estimate of risk in women, in what concerns the potential effects of this specific type of bias.

Regarding confounding, we conducted multivariate analyses including a large number of potential confounders. Smoking and alcohol intake were dichotomized due to sample size limitations, but variables such as age, education, and BMI were included in the models as continuous in an attempt to provide a finer adjustment to minimize residual confounding. We also conducted analyses including physical activity, consumption of fruit and vegetables, and previous history of stroke or ischemic heart disease, and the results remained virtually unchanged (data not shown). Nevertheless, uncontrolled confounding may have contributed to the negative association between caffeine intake and cognitive decline observed in our study. In a recently published study, Smith and colleagues concluded that caffeine consumption was found to be associated with a reduced risk of depression [52]. Not having controlled for the potential confounding effect of depression may have contributed to overestimate the association in our study, as caffeine non-consumers are more likely to be depressed [12], and depressive symptoms may be responsible for poor performance in cognitive testing, namely in the MMSE [17]. We could not take into account the potential confounding effect of factors related to intellectual activity associated both with higher caffeine intake and a lower probability of cognitive impairment. Adjustment for professional occupation (past or present) could provide some degree of confounding control at this level, and education may also be seen as a surrogate for this variable, but still it would have been important to classify participants according to the mental activity involved in their present or former line of work. The MMSE score at baseline may also be seen as a surrogate marker of intellectual activity and was further included in the models (data not shown) yielding virtually no changes in the RR estimates.

Gender differences have been suggested in the association between caffeine intake and Parkinson's disease. Ascherio and collaborators reported a strong inverse association in men and a U-shaped relationship in women, with the lowest risk of Parkinson's disease occurring at moderate intakes [53]. These authors described an interaction between the use of postmenopausal hormones and caffeine intake in the risk of Parkinson's disease, with an increased risk among women on hormonal replacement therapy with a high caffeine intake [54,55], although the reasons for this effect modification are not yet clear. In the present study, the number of women under hormonal replacement therapy at baseline was too small to allow the assessment of its potential to modify the association between caffeine intake and cognitive decline.

In conclusion, our findings do not rule out a negative association between caffeine intake and cognitive decline in men, and confirm the protective effect of caffeine in women. Several arguments discussed above favour the causal nature of this association. Despite this, potentially important confounding factors not accounted for could attenuate the magnitude of the observed association.

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