The neuroprotective effects of caffeine

A prospective population study (the Three City Study)

K. Ritchie, PhD*
I. Carrière, PhD*
A. de Mendonça, MD, PhD
F. Portet, MD, PhD
J.F. Dartigues, MD, PhD
O. Rouaud, MD
P. Barberger-Gateau, MD, PhD
M.L. Ancelin, PhD

Address correspondence and reprint requests to Dr. Karen Ritchie, INSERM U888 Nervous System Pathologies: Epidemiological and Clinical Research, La Colombière Hospital, 34093 Montpellier Cedex 5, France
ritchie@montp.inserm.fr

ABSTRACT

Objective: To examine the association between caffeine intake, cognitive decline, and incident dementia in a community-based sample of subjects aged 65 years and over.

Methods: Participants were 4,197 women and 2,820 men from a population-based cohort recruited from three French cities. Cognitive performance, clinical diagnosis of dementia, and caffeine consumption were evaluated at baseline and at 2 and 4 year follow-up.

Results: Caffeine consumption is associated with a wide range of sociodemographic, lifestyle, and clinical variables which may also affect cognitive decline. Multivariate mixed models and multivariate adjusted logistic regression indicated that women with high rates of caffeine consumption (over three cups per day) showed less decline in verbal retrieval (OR = 0.67, CI = 0.53, 0.85), and to a lesser extent in visuospatial memory (OR = 0.82, CI = 0.65, 1.03) over 4 years than women consuming one cup or less. The protective effect of caffeine was observed to increase with age (OR = 0.73, CI = 0.53, 1.02 in the age range 65 to 74; OR = 0.3, CI = 0.14, 0.63 in the range 80+). No relation was found between caffeine intake and cognitive decline in men. Caffeine consumption did not reduce dementia risk over 4 years.

Conclusions: The psychostimulant properties of caffeine appear to reduce cognitive decline in women without dementia, especially at higher ages. Although no impact is observed on dementia incidence, further studies are required to ascertain whether caffeine may nonetheless be of potential use in prolonging the period of mild cognitive impairment in women prior to a diagnosis of dementia. *Neurology*® 2007;69:536–545

In the absence of an effective clinical treatment for aging-related neurodegenerative disorders, research has focused on the identification of potential risk factors whose modulation may decrease risk or prolong autonomy. Previous studies suggest that caffeine, which is known to have positive effects on vigilance, attention, mood, and arousal,[1] may also be neuroprotective. While having multiple biologic effects (including increased cortical activity) the nonselective antagonism of adenosine receptors, particularly A_1 and A_{2A} receptors, is the only known central pharmacologic effect that occurs in the dose-range of voluntary caffeine intake.[2,3]

Blockade of adenosine A_{2A} receptors may attenuate damage caused by Aβ, the toxic peptide that accumulates in the brain of patients with Alzheimer disease (AD).[4,5] Long-term caffeine administration protects AD transgenic mice against cognitive impairment while limiting brain Aβ levels and increasing brain adenosine levels.[6] This finding suggests a potential role for caffeine in at least slowing the process of neurodegeneration. A small case-control study found lower caffeine intake during the preceding 20 years in

*These authors contributed equally to this work.

From INSERM U888 (K.R., I.C., F.P., A.d.M., M.L.A.), Montpellier; INSERM U593 (J.F.D., P.B.-G.), Bordeaux University 2; INSERM U708 (O.R.), University of Paris, France; and Department of Neurology and Laboratory of Neurosciences (A.d.M.), University of Lisbon, Portugal.

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patients with AD compared to controls,[7] and a prospective study found regular consumption of coffee but not tea to be associated with a reduced risk of AD at 5-year follow-up.[8] These small clinical studies were not able, however, to take into account the many other potential confounding variables likely to mediate cognitive decline. Two large cross-sectional population studies found a significant positive association between regular coffee intake and cognitive performance in older subjects (55+)[9] and in women.[10] The only prospective population study which has been conducted to date[11] reported a cross-sectional association between caffeine and verbal memory and improvement over time in psychomotor speed only.[12] However, this study did not stratify by sex or adequately adjust for other potential causes of cognitive change.

The aim of the present study is to examine the relationship over time between caffeine consumption and cognitive performance taking into account gender effects as well as pre-existing and current clinical and sociodemographic factors which may contribute to cognitive decline.

METHODS

Study population. Subjects were recruited as part of a multisite cohort study of community-dwelling persons aged 65 years and over from the electoral rolls of three French cities (Bordeaux, Dijon, and Montpellier) between 1999 and 2001 (the Three City Study). The study design has been described elsewhere.[13] The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. Thirty-seven percent of subjects initially contacted by telephone agreed to participate; refusers were replaced by another subject drawn from the same electoral area. Of the 9,077 dementia-free participants included in the cohort, 363 died, 631 were lost to follow-up, 281 did not have repeated cognitive testing, 38 had missing dietary caffeine data, and 747 had missing data for at least one baseline adjustment variable. The present analyses were thus conducted on 7,017 subjects. Among them, 1,073 subjects (15%) had only one follow-up examination. The average follow-up (SD) was 3.47 years (0.67). Subjects not included in the present analysis were more frequently women, older, with lower education level, lower caffeine or coffee (but not tea) consumption, and had lower baseline cognitive scores. The mean age (SD) of the sample was 73.6 (5.3) for men and 73.8 (5.2) for women.

Caffeine consumption. Questions relating to caffeine consumption were included in a standardized interview administered by either psychologists or research nurses. Number of cups normally consumed per day of tea and coffee were noted. Other forms of caffeine (e.g., colas, cocoa) were consumed too rarely by this elderly cohort to warrant inclusion, as already reported.[11] Only 15 subjects (0.21%) were currently taking medications containing more than 100 mg caffeine. Calculations were made on the assumption of one cup of coffee containing 100 mg of caffeine and tea 50 mg,[14] the total average consumption per day being calculated per subject in caffeine units (one unit = 100 mg).

Cognitive testing and diagnosis of dementia. The cognitive examination consisted of the Mini-Mental State Examination (MMSE),[15] a test of visuospatial recall, the Benton Visual Retention Test,[16] and a test of verbal recall and fluency, the Isaacs Set Test.[17] Scores on the Set Test were the number of words produced within 30 seconds. In Montpellier and Bordeaux all participants were examined by a neurologist. In Dijon only persons suspected of having a cognitive deficit underwent further examination by a specialist. In the three centers, the same standardized clinical protocol based on Diagnostic and Statistical Manual of Mental Disorders–IV criteria[18] was used to diagnose prevalent cases of dementia. All incident cases were validated by a panel of expert neurologists independently from the 3C Study investigators. The date of onset of dementia was the date of the follow-up interview when dementia was diagnosed.

Sociodemographic and clinical variables. The standardized interview included questions on demographic characteristics, education level (classified in four groups corresponding to 5, 9, 12, and 12+ years of education), monthly income, mobility and confinement to home and neighborhood, height, and weight. Information was obtained on type and quantity of alcohol consumption (number of units of alcohol per day; 0, 1 to 12, 13 to 36, >36 g/day) and tobacco use (classified as past, present, or never users). History of respiratory disorders, cancer, hypertension, hypercholesterolemia, diabetes, stroke, angina pectoris, myocardial infarction, and cardiac and vascular surgery was established according to standardized questions with additional information where necessary from general practitioners. For persons who reported the occurrence of vascular events during follow-up, further medical data were obtained from general practitioners, specialists, and hospital records. The interview also included an inventory of all drugs used during the preceding month, noting those with potential anticholinergic effects,[19] and past as well as present use of hormonal replacement therapy (HRT). Medical prescriptions and, where feasible, the medications themselves were seen by the interviewer. Depressive symptomatology was assessed by the Center for Epidemiologic Studies–Depression scale (CES-D)[20] with a 16 cutoff point. Blood pressure was measured during the interview using a digital electronic tensiometer OMRON M4. Fasting blood samples were taken for cholesterol levels and apolipoprotein E status.

Statistical analyses. Men and women were examined in separate analyses as they differed in both coffee consumption and cognitive abilities. The χ^2 test was used to identify gender-related differences. Associations between caffeine consumption and baseline sociodemographic and clinical variables were tested using polytomous logistic regression, modeling the odds of being in one class of consumption vs being in the ≤1 unit class. The ORs of taking caffeine are

adjusted by age, sex, and center. We used univariate and multivariate simple logistic regression analyses to determine if baseline consumption of caffeine was associated with odds of cognitive decline. These analyses were stratified by gender. Univariate ORs were adjusted on age, educational level, baseline cognitive score, and center. Multivariate adjusted logistic regression included covariates that were associated with cognitive decline ($p \leq 0.20$). Cognitive decline was defined as being in the lowest quintile of the difference between baseline score and either follow-up visit. We also used random-effect models to analyze the association between caffeine consumption and 4-year change on cognitive scores taken as continuous variables. For the Benton test and the MMSE, variables were transformed due to their skewed distribution using $(15-\text{Benton})^{1/2}$ and $(30-\text{MMSE})^{1/2}$, respectively.[21] Each model included time, caffeine, and time/caffeine interaction. The term caffeine represents the cross-sectional association between caffeine and the selected cognitive test at baseline. The term for time indicates the linear evolution per year on the cognitive test. The term for interaction between time and caffeine represents the additional annual modification on the selected cognitive tests for caffeine intake. A Cox model with delayed entry was used in the analysis of dementia incidence, adjusted on sex, educational level, and center, and taking age as the basic time scale and birth as the time origin.[22] This method avoids the problem of non-proportionality of the risk of dementia with age. Analyses were carried out using SAS software (version 9.1).

RESULTS Within this elderly community-dwelling population caffeine use is very common (table 1). Men and women were found to differ on a number of characteristics at baseline: age, education, depressive symptoms, rates of cardiovascular disease, diabetes, cancer, hypertension, hypercholesterolemia, body mass index, medication (e.g., LLA and drugs with anticholinergic effects), alcohol and tobacco use, and mobility. They also differed in baseline cognitive performance with a higher proportion of women showing low scores on the MMSE and Benton test.

Overall, women are higher consumers of caffeine than men, with 16.4% of women as opposed to 13.2% of men consuming more than three units per day ($p = 0.0006$). Caffeine consumption is also seen to drop with age, falling from 20% consumption of more than three units per day in the 65 to 69 age range to 10% in persons over 80. Caffeine intake was stable over time with only 10.3% of the cohort declaring a reduction of one or more cups over 4 years, and 3.2% reporting an increase. Baseline ORs of variables associated with caffeine consumption using polytomous logistic regression are thus adjusted by age and sex as well as study center (table 2). Caffeine consumption is seen to be significantly associated with higher education and numerous health variables. Caffeine consumption increases with (ever) smoking and to a lesser extent in subjects with cardiovascular disease and women currently taking HRT. Hypertension has a near-linear association with reduced consumption. Nonconsumers are more likely to be depressed or taking anticholinergic drugs. Consumers of alcohol tend to be more frequently in the median class of caffeine consumption. No significant association was found between caffeine consumption and BMI, hypercholesterolemia, LLA, mobility, cancer, diabetes, sleep disorders, or ApoE status.

In the longitudinal logistic regression analyses decline in cognitive performance was defined as a decrease from baseline of at least six points on the Isaacs test or at least two points on the Benton test and the MMSE (lowest quintiles) (table 3). In men caffeine consumption was not seen to be related to cognitive decline at follow-up on any of the tests. In women a significant association was observed in relation to the Isaacs test. The association is dose-dependent with ORs falling from 0.91 in women consuming one to two units per day at baseline to 0.82 with two to three units and 0.66 in women consuming more than three units per day compared to those consuming one unit or less. The relationship reaches significance only for the two higher groups (women consuming at least two units per day). A similar tendency was observed in relation to the Benton test, with ORs decreasing from 0.95 to 0.83 according to rates of consumption but not reaching significance, whereas no significant association was observed for the MMSE.

A multivariate model for longitudinal prediction of cognitive decline in women only was constructed incorporating all variables found to be associated ($p \leq 0.20$) with cognitive decline at baseline (table 4). In women, after adjustment, the significant predictors of decline over time on the Isaacs test are age, education, baseline cognitive performance, anticholinergic drug use, confinement to the home, and caffeine (p trend = 0.001). The dose-effect is still evident for caffeine after controlling for all other variables, but the protective effect only reaches significance over three units (OR = 0.67, CI = 0.53 to 0.85). Looking at possible interaction between caffeine intake and age (tested as multiplicative effects), the protective effect tended to be higher for the oldest women ($p = 0.11$); OR was 0.30 (CI = 0.14 to 0.63) for women over 80 and 0.73 (CI = 0.53 to 1.02) for younger women. While this interactive effect did not reach formal levels of significance, there is clearly a tendency for an age effect at higher ages which in the context of an epidemiologic study would normally be considered worthy

Table 1 Description of baseline population

	Men (n = 2,820), %	Women (n = 4,197), %	χ^2 p
Caffeine consumption per day			
0–1 unit	27.4	24.6	
1–2 units	32.4	31.5	0.0006
2–3 units	27.0	27.5	
>3 units	13.2	16.4	
Age, y			
65–69	26.0	25.1	
70–74	35.0	32.8	0.03
75–80	24.8	28.0	
80+	14.2	14.1	
Education, y			
5	21.7	24.8	
9	30.1	40.4	<0.0001
12	19.7	21.0	
12+	28.5	13.8	
CESD ≥ 16	13.8	28.1	<0.0001
Cardiovascular disease*	15.3	4.4	<0.0001
BMI			
Normal	38.0	53.7	
Overweight	49.4	33.0	<0.0001
Obese	12.6	13.3	
Diabetes†	12.8	6.7	<0.0001
Cancer‡	1.8	1.2	0.02
Hypertension§	64.2	57.4	<0.0001
LLA (statin or fibrate)	29.7	32.1	0.03
Hypercholesterolemia‖	78.7	60.2	<0.0001
Smoking			
Never	30.0	81.2	
Former	61.9	15.1	<0.0001
Current	8.1	3.7	
HRT			
Current		15.0	
Former		16.7	
Never		68.3	
Anticholinergic drugs	4.1	9.3	<0.0001
Mobility			
Confined home	1.2	1.8	
Confined neighborhood	2.0	4.4	<0.0001
Not confined	96.8	93.8	
Alcohol, g/d			
0	8.0	27.1	
1–12	31.8	54.0	<0.0001
13–36	41.2	17.3	
>36	19.0	1.6	
ApoE4	20.7	19.2	0.12
MMSE < 26¶	11.8	15.5	<0.0001
Isaacs test < 40¶	20.2	20.0	0.82
Benton test < 11¶	23.6	30.8	<0.0001

*History of stroke, myocardial infarction, angina pectoris, or arteritis.
†Diabetes defined as glucose ≥7.2 mmol/L or treated.
‡Cancer over the past 2 years.
§Systolic blood pressure ≥160 or diastolic blood pressure ≥95 mm Hg or intake of antihypertensive drugs.
‖Total cholesterol level ≥6.20 mmol/L.
¶Percent of subjects with lowest cognitive performances at baseline (lowest quintile).
CESD = Center for Epidemiologic Studies–Depression scale; BMI = body mass index; LLA = lipid-lowering agent; HRT = hormone replacement therapy; MMSE = Mini-Mental State Examination.

Table 2 Polytomous logistic regression: age, sex, and center-adjusted OR of taking caffeine (cross-sectional at baseline)

	1–2 units, OR (CI)	2–3 units, OR (CI)	>3 units, OR (CI)	Wald test, *p* value
Education, y				
5	1	1	1	
9	1.18 (1.01;	1.58 (1.33;	1.59 (1.28;	<0.0001
12	1.39)	1.87)	1.97)	
12+	1.07 (0.89; 1.28)	1.52 (1.25; 1.85)	1.78 (1.40; 2.25)	
	1.29 (1.06; 1.56)	1.88 (1.53; 2.30)	2.66 (2.09; 3.38)	
CESD ≥ 16	0.77 (0.66; 0.90)	0.78 (0.66; 0.91)	0.75 (0.62; 0.90)	0.001
Cardiovascular disease	0.81 (0.64; 1.02)	1.14 (0.91; 1.43)	1.12 (0.85; 1.48)	0.02
Hypertension	1.03 (0.90; 1.17)	0.96 (0.83; 1.09)	0.78 (0.66; 0.91)	0.003
Smoking				
Never	1	1	1	
Former	1.26 (1.08; 1.48)	1.44 (1.23; 1.70)	2.26 (1.87; 2.74)	<0.0001
Current	1.66 (1.22; 2.28)	1.66 (1.20; 2.30)	3.70 (2.63; 5.21)	
HRT (n = 4,197)				
Current	1.02 (0.79; 1.32)	1.24 (0.96; 1.61)	1.46 (1.10; 1.94)	0.03
Former	1.07 (0.86; 1.34)	1.07 (0.85; 1.35)	0.91 (0.69; 1.19)	
Never	1	1	1	
Anticholinergic drugs	0.77 (0.61; 0.97)	0.70 (0.55; 0.90)	0.81 (0.60; 1.08)	0.03
Alcohol, g/d				
0	1	1	1	
1–12	1.38 (1.17; 1.63)	2.06 (1.72; 2.46)	1.45 (1.18; 1.77)	<0.0001
13–36	1.60 (1.32; 1.94)	2.24 (1.82; 2.76)	1.60 (1.26; 2.03)	
>36	1.83 (1.39; 2.40)	2.51 (1.88; 3.35)	1.39 (0.98; 1.98)	

The polytomous logistic regression models the odds of being in one class of consumption vs being in the ≤1 unit class (reference category).
CESD = Center for Epidemiologic Studies–Depression scale; HRT = hormone replacement therapy.

of further study. No interactions were found between caffeine intake and alcohol ($p = 0.93$), anticholinergic drugs ($p = 0.85$), or HRT for women ($p = 0.26$). With regard to the Benton test, significant determinants of cognitive decline over time are age, education, study center, baseline cognitive performance, depressive symptoms, hypercholesterolemia, confinement to the neighborhood, with caffeine consumption of over three units approaching significance (OR = 0.82, $p = 0.09$). Examining coffee and tea consumption separately, decline on the Isaacs test is observed both for coffee (OR = 0.82, CI = 0.66 to 1.01, $p = 0.07$) and tea (OR = 0.81, CI = 0.65 to 1.02, $p = 0.07$) in women consuming three or more cups. In men, after adjustment no significant association was found between caffeine intake and cognitive decline on either cognitive test. Performing multivariate-adjusted random-effect models with the cognition score as the continuous variable led to the same results, the only significant association being found between caffeine intake and performance on the Isaacs test in women, for cross-sectional effect (p trend = 0.004) and longitudinal effect (p trend = 0.002) (table 5). With regard to dementia, a delayed-entry Cox model adjusted on sex, education, and center shows no relationship between baseline caffeine intake and incident dementia from all causes (n = 283, $p = 0.76$) or AD (n = 184, $p = 0.96$).

DISCUSSION This large prospective study estimates that around two thirds of elderly persons consume over 100 mg of caffeine per day, although there is a tendency for this rate to drop off in some subjects with age. The study has been able to examine the impact of caffeine use on cognitive functioning over time, taking into account multiple possible codeterminants of cognitive decline and thus clarifying previous small cross-sectional control studies. The principal findings of this study are first that caffeine consumption itself is significantly associated with a wide range of variables also associated with cognitive decline

Table 3 Age, education, baseline cognitive performance, and center-adjusted OR of cognitive decline according to baseline caffeine intake (longitudinal)

	Men, n = 2,820			Women, n = 4,197		
	OR (CI)	*p*	*p* Trend	OR (CI)	*p*	*p* Trend
ΔIsaacs ≤ −6						
1–2 units	0.92 (0.73; 1.17)	0.50		0.91 (0.75; 1.10)	0.33	
2–3 units	1.08 (0.85; 1.38)	0.51		0.82 (0.67; 1.00)	0.05	
>3 units	1.18 (0.87; 1.59)	0.29	0.19	0.66 (0.52; 0.83)	0.0005	0.0003
ΔBenton ≤ −2						
1–2 units	0.99 (0.80; 1.24)	0.96		0.95 (0.79; 1.14)	0.58	
2–3 units	1.11 (0.88; 1.40)	0.36	0.94	0.99 (0.82; 1.20)	0.92	0.21
>3 units	0.92 (0.69; 1.23)	0.57		0.83 (0.66; 1.04)	0.10	
ΔMMSE ≤ −2						
1–2 units	1.02 (0.81; 1.28)	0.87		0.97 (0.81; 1.17)	0.78	
2–3 units	1.00 (0.79; 1.27)	0.99		0.89 (0.73; 1.08)	0.23	
>3 units	1.19 (0.89; 1.59)	0.25	0.40	0.91 (0.73; 1.14)	0.42	0.24

Decrease of at least two points from the baseline for Mini-Mental State Examination and Benton test or of at least six points for the Isaacs test.
MMSE = Mini-Mental State Examination.

(age, education, gender, depressive symptoms, hypertension, cardiovascular disease, anticholinergic medication, HRT, smoking, and alcohol use), most of which have not been taken into account in previous studies. Secondly, prospective study of caffeine consumption and cognitive performance shows a significant protective effect in women which is maintained after adjustment for the other multiple factors contributing to cognitive decline and using two different models (logistic regression for incidence of cognitive impairment using categorical cognitive variables, and a random-effect model for mean changes over time using continuous cognitive variables).

Our observation that protective effects are observed in women only, and notably in the area of verbal skills, is consistent with most previous research, although a recent population study of Finnish men[23] found lower decline on the MMSE in men consuming three cups of coffee per day over a 10-year period. This study did not, however, adjust for the confounding effects of depressive symptoms, hypertension, cardiovascular disease, or anticholinergic medication. This difference could indicate that women are more sensitive to the effects of caffeine than men, perhaps due to pharmacodynamic or caffeine metabolism differences.[24,25] Another possibility could be that older women are more susceptible to the cholinergic properties of caffeine than men. However, we observed no interaction between caffeine intake and anticholinergic use. Steroid levels could also be involved. A positive association between caffeine intake and estrone, or sex hormone-binding globulin levels has been reported in postmenopausal women.[26] Previous work on PD suggests that the protective effect of caffeine in older women is diminished by HRT use,[27] but the mechanism remains unclear. In the present study we did not find an interactive effect on cognitive decline with the use of exogenous steroids (HRT).

A caffeine dose-effect was observed in our study, with women consuming over three units per day having greater protection than those consuming two to three units, and those with under two daily units no significant protective effect at all. The women in our study were also higher consumers of tea than men so that the protective effect may be attributable to components of tea other than the caffeine content (e.g., polyphenol antioxidants). We did not, however, find any difference in terms of protection between coffee and tea when these were considered separately, suggesting that any protective effect is principally attributable to the common component of caffeine. Finally the protective effect is observed principally in the performance of a verbal retrieval rather than a visuospatial task. The protective effect approached significance for the visuospatial task, perhaps because verbal mediating strategies often help subjects memorize nonverbal stimuli. No protective effect was found on the more global cognitive measure (MMSE), although in this latter case a ceiling effect is likely as the MMSE is designed to detect more serious cognitive disorder.

Table 4 Multivariate OR of a cognitive decline (longitudinal)

	Women (n = 4,197)			
	ΔIsaacs ≤ −6		ΔBenton ≤ −2	
	OR (CI)	*p*	OR (CI)	*p*
Age, y	1.06 (1.05; 1.08)	<0.0001	1.07 (1.05; 1.09)	<0.0001
Education, y				
5	1		1	
9	0.81 (0.67; 0.98)	0.03	0.73 (0.61; 0.88)	0.0009
12	0.52 (0.42; 0.66)	<0.0001	0.45 (0.36; 0.56)	<0.0001
12+	0.57 (0.44; 0.74)	<0.0001	0.46 (0.36; 0.58)	<0.0001
Center				
Montpellier	1	1	1	1
Bordeaux	1.02 (0.81; 1.29)	0.84	1.55 (1.24; 1.93)	0.0001
Dijon	1.17 (0.98; 1.41)	0.09	1.95 (1.63; 2.33)	<0.0001
Baseline cognitive test	1.08 (1.07; 1.09)	<0.0001	1.78 (1.70; 1.86)	<0.0001
CESD ≥ 16	1.17 (0.99; 1.37)	0.07	1.20 (1.02; 1.41)	0.03
Cardiovascular disease	1.25 (0.89; 1.75)	0.21	1.38 (0.98; 1.96)	0.07
BMI				
Normal	1		1	
Overweight	0.96 (0.81; 1.13)	0.59	1.14 (0.98; 1.34)	0.08
Obese	0.98 (0.78; 1.22)	0.83	1.14 (0.92; 1.43)	0.24
Diabetes*	1.19 (0.89; 1.58)	0.23	1.17 (0.88; 1.55)	0.30
Hypercholesterolemia	1.12 (0.96; 1.29)	0.15	0.86 (0.75; 1.00)	0.04
HRT				
Current	0.88 (0.70; 1.10)	0.25	1.04 (0.84; 1.28)	0.73
Former	0.95 (0.78; 1.17)	0.64	0.94 (0.78; 1.14)	0.54
Never	1		1	
Anticholinergic drugs	1.40 (1.10; 1.78)	0.007	1.08 (0.85; 1.38)	0.53
Mobility				
Confined home	1.77 (1.07; 2.95)	0.03	1.30 (0.77; 2.20)	0.32
Confined neighborhood	1.20 (0.85; 1.71)	0.30	1.51 (1.06; 2.16)	0.02
Not confined	1		1	
Alcohol, g/d				
0	1		1	
1–12	0.87 (0.73; 1.03)	0.11	1.09 (0.92; 1.28)	0.34
13–36	0.88 (0.70; 1.10)	0.26	1.01 (0.81; 1.25)	0.96
>36	1.17 (0.65; 2.11)	0.59	1.20 (0.66; 2.16)	0.55
Caffeine				
0–1 unit	1		1	
1–2 units	0.94 (0.77; 1.13)	0.49	0.96 (0.79; 1.16)	0.64
2–3 units	0.85 (0.70; 1.04)	0.12	1.00 (0.83; 1.22)	0.97
>3 units	0.67 (0.53; 0.85)	0.001	0.82 (0.65; 1.03)	0.09

*Diabetes defined as glucose ≥ 7.2 mmol/L or treated.
CESD = Center for Epidemiologic Studies–Depression scale; BMI = body mass index; HRT = hormone replacement therapy.

Thus from the present study we generally conclude that women with a high rate of caffeine consumption show significantly less decline in verbal cognitive functioning, and to a lesser extent in visuospatial memory over a 4-year period than women who are low or nonconsumers. We hypothesized a number of reasons for an apparent protective effect: that the presence or onset of

Table 5 Association between caffeine consumption at baseline and Isaacs score over time, random-effect models

	Men, n = 2,820			Women, n = 4,197		
	β estimate (SE)	p	p Trend	β estimate (SE)	p	p Trend
Univariate*						
Time, y	4.31 (0.58)	<0.0001		3.49 (0.46)	<0.0001	
Caffeine						
1–2 units	−0.25 (0.46)	0.59		0.14 (0.39)	0.72	
2–3 units	−0.35 (0.49)	0.48	0.19	0.56 (0.40)	0.16	0.004
>3 units	−0.82 (0.60)	0.17		1.31 (0.47)	0.005	
Caffeine × time						
1–2 units	0.06 (0.10)	0.60		0.07 (0.08)	0.40	
2–3 units	−0.01 (0.11)	0.91	0.85	0.14 (0.09)	0.10	0.002
>3 units	0.06 (0.13)	0.63		0.31 (0.10)	0.002	
Multivariate†						
Time, y	4.33 (0.58)	<0.0001		3.47 (0.46)	<0.0001	
Caffeine						
1–2 units	−0.37 (0.46)	0.43		−0.05 (0.39)	0.88	
2–3 units	−0.34 (0.48)	0.48	0.21	0.25 (0.40)	0.53	
>3 units	−0.82 (0.60)	0.17		1.10 (0.46)	0.02	0.02
Caffeine × time						
1–2 units	0.06 (0.10)	0.59		0.07 (0.09)	0.41	
2–3 units	−0.01 (0.11)	0.92	0.85	0.14 (0.09)	0.10	0.002
>3 units	0.06 (0.13)	0.64		0.31 (0.10)	0.002	

*Adjusted for age, age × time, educational level, center.
†Adjusted for age, age × time, educational level, center, Center for Epidemiologic Studies–Depression scale, cardiovascular disease, body mass index, diabetes, hypercholesterolemia, anticholinergic drugs, mobility, alcohol, hormone replacement therapy (for women only), and smoking (for men only).

chronic disease would constitute risk factors for cognitive decline and also lead to a decrease in coffee consumption; that persons with cognitive disorder would be confined to home and less likely to socialize or prepare coffee or tea; that persons taking medications with anticholinergic effects or with cerebrovascular disease would reduce their intake. We have taken into account all these scenarios in our analyses and despite the inclusion of a large range of potential confounding factors, we have been unable to attribute this protective effect to causes other than caffeine.

We observed a tendency for an age-by-caffeine intake interaction effect on verbal performance at follow-up, the oldest women (over 80 years) appearing to benefit most from a higher caffeine intake ($p = 0.11$), suggesting that caffeine intake could attenuate age-related cognitive decline in this group. Nevertheless, while caffeine appears to reduce rates of verbal cognitive decline in women, it does not appear on the other hand to significantly reduce rates of incident dementia within a 4-year follow-up period. The lack of a protective effect for caffeine in relation to dementia onset may, however, be due to a too short follow-up period. As the study is ongoing it will be possible to re-examine the question of whether the protective effect of caffeine is limited to subjects who have relatively stable cognitive deficits over a longer period of time.

Regarding the limitations of this study, selective attrition could have promoted a healthy survivor effect on the remaining sample, in which longstanding associations between a health-related habit and cognitive functioning may have been underestimated. Moreover, we did not consider type of consumption (filtered, instant, or brewed coffee, black or green tea). Habitual caffeine consumption was moreover based on actual intake thus assuming coffee/tea drinking habits are relatively stable over time. Finally, if caffeine slows the dementia process rather than preventing it, then a longer period than 4 years may be necessary to adequately evaluate risk. Conversely, one of the strengths of this study is its multicentric and longitudinal design and the size of the

sample including more than 7,000 elderly subjects from the general population. This study was able to take into account gender effects as well as preexisting and current clinical and sociodemographic factors which may independently contribute to cognitive decline. Finally, a standardized clinical protocol based on DSM-IV criteria was used to diagnose prevalent cases of dementia and all incident cases were validated by a panel of independent expert neurologists.

Can we on the basis of these findings recommend the therapeutic use of caffeine to reduce cognitive decline? On the one hand caffeine consumption is already widespread, has fewer contraindications than cholinesterase and memantine therapies, and requires only a relatively small dose (around three units per day) for a beneficial effect. This must be weighed against the potential hypertensive effects of caffeine (although this could probably be restricted to sugared or diet cola but not coffee[28]) and the risks of cognitive impairment due to cardio- and cerebrovascular disorders. From our study it appears that caffeine may only be useful in attenuating mild forms of cognitive decline, with no clear benefit in preventing AD. We previously observed the same pattern in relation to tobacco,[29] that is, that while stimulants increase performance in specific cognitive tests, they do not prevent neurodegenerative disease, although they may prolong the period to diagnosis. Furthermore, while our study has found that female caffeine consumers have diminished loss of cognitive functioning during the 4-year observation window provided by this study, we still do not know at what point caffeine may have construed its beneficial effects. It has been previously suggested[7] that the neuroprotective effect may be conveyed long before the onset of cognitive decline. Further biologic evidence clarifying the relationship between caffeine use and neural degeneration is required before the instigation of a public health program promoting caffeine intake may be recommended.

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