Caffeine Consumption and Dementia: Are Lewy Bodies the Link?

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Objective: The objective of this study was to examine the association between caffeine intake and cognitive impairment. Caffeine-neuropathology correlations and interactions with lifestyle and genetic factors impacting caffeine metabolism and response were also tested.

Methods: We included 888 participants aged 59+ years from the Rush Memory and Aging Project (MAP) and 303,887 participants aged 55+ years from the UK Biobank (UKB). MAP participants took part in annual cognitive testing. Diagnosis of dementia was based on clinical neurological examination and standardized criteria. A subset provided postmortem tissue for neuropathologic evaluation for common age-related diseases (eg, Alzheimer's disease [AD], Lewy bodies, and vascular). For UKB, dementia was determined by linked hospital and death records. Self-reported caffeine intake was estimated using food-frequency questionnaires in both cohorts. Cox proportional hazard ratio (HR), regression, and mixed models were used to examine associations of caffeine intake with incident dementia, cognitive decline, and neuropathology.

Results: In MAP, compared to ≤100 mg/day, caffeine intake >100 mg/day was associated with a significantly higher HR (95% confidence interval [CI]) of all-cause (HR = 1.35, 95% CI = 1.03–1.76) and AD (HR = 1.41, 95% CI = 1.07–1.85) dementia. Caffeine intake was not associated with cognitive decline. In UKB, compared to ≤100 mg/day, the HRs (95% CI) of all-cause dementia for consuming 100 ≤ 200, 200 ≤ 300, 300 ≤ 400, and > 400 mg/day were 0.83 (95% CI = 0.72–0.94), 0.74 (95% CI = 0.64–0.85), 0.74 (95% CI = 0.64–0.85), and 0.92 (95% CI = 0.79–1.08), respectively. Similar results were observed for Alzheimer's dementia. In MAP, caffeine intake was inversely associated with postmortem Lewy bodies but no other age-related pathologies. Caffeine intake >100 mg/day was associated with lower neocortical type Lewy bodies (odds ratio (95% CI): 0.40 (95% CI = 0.21–0.75).

Interpretation: Caffeine intake was inconsistently associated with clinical dementia; potentially explained by cohort differences in underlying dementia etiology. Lewy bodies may link caffeine to lower risk in some persons.

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Caffeine is the most widely consumed psychoactive stimulant in the world; due largely to the popularity of coffee and tea, which are the major sources of dietary caffeine.[1] Acute intakes of caffeine enhance or maintain cognitive function.[2] Whether long-term, habitual, caffeine intake reduces or delays age-related cognitive impairment is unclear.[3] Most studies of cognitive decline or dementia present results separately for each dietary source of caffeine, thus separating beverage-specific associations from caffeine-specific associations is difficult. Meta-analyses of prospective studies of coffee consumption report no association with incident dementia or a nonlinear shaped association whereby light to

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moderate coffee drinking is protective, whereas none or very high intakes are relatively deleterious.[4,5] A linear positive association between tea consumption and incident dementia has been reported but meta-analyses are based on few studies.[4]

The Rush Memory and Aging Project (MAP) is an elderly community-based cohort study, free of known dementia at enrollment, and the participants agree to annual clinical neurological evaluations and organ donation at death. UK Biobank (UKB) is a large population cohort of adults who underwent a comprehensive assessment at clinical centers and whose health status is being tracked, in part, through linked death and health records. We used these 2 distinct cohorts to examine the association among habitual caffeine intake, incident cognitive impairment, and neuropathology in the MAP subset.

Methods

Rush Memory and Aging Project

MAP began in 1997 and is an ongoing open cohort of residents from over 40 retirement communities and senior public housing units in northeastern Illinois. As detailed previously,[6] participants are free of known dementia at enrollment and agree to annual clinical evaluations and organ donation at death. From 2004 to 2013, participants were invited to complete food frequency questionnaires (FFQs) at the time of their annual clinical evaluations. During that period, a total of 1,545 older persons had enrolled in the study, 90 died and 149 withdrew before the diet study began, leaving 1,306 participants eligible for these analyses. An Institutional Review Board of Rush University Medical Center approved the study, and all participants gave written informed consent, and signed an Anatomic Gift Act, and a repository consent to allow their resources to be shared.

Diet Assessment. Total caffeine intake (mg/day) based on coffee (not decaffeinated), tea (not herbal), soda, and chocolate was derived from responses to a modified Harvard semiquantitative FFQ administered at each annual clinical evaluation and that was validated for use in older Chicago area community residents.[7] Supplementary methods detail questionnaire items for dietary caffeine and the derivation of caffeine using US food composition tables. Responses from 15 food items were used to derive the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet pattern, as described previously.[8] Responses from all food items were used to derive total energy intake.[7] We used data from the first FFQ for the current analysis.

Annual Cognitive Assessments. In annual clinical examinations, MAP participants were administered a battery of 21 tests, 19 of which summarized cognition in 5 cognitive domains (episodic memory, working memory, semantic memory, visuospatial ability, and perceptual speed), as described previously.[9] For participants who completed their FFQ at their first visit (2004+) we considered assessment data from their next visit as baseline to minimize learning effects. Composite scores were computed for each cognitive domain and for a global measure of all 19 tests. Raw scores for each test were standardized using the mean and standard deviation from the baseline population scores, and the standardized scores were averaged.

Dementia Outcomes. Clinical diagnosis of dementia, and specifically that presumed due to Alzheimer's disease (AD), was determined at each annual evaluation, as previously described, and was based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[10] Clinical diagnosis of dementia due to AD requires a history of cognitive decline with impairment in memory and at least one other cognitive domain. The term "Alzheimer's dementia" refers to those with either probable or possible AD dementia. This designation was made without the use of biomarkers.

Genetic Data. MAP participants self-reporting as non-Hispanic white were genotyped on the Affymetrix 6.0, Illumina Human1M, and Illumina Global Screening Array platforms. The same quality control protocol was applied to each platform dataset, as described previously.[11] Genotype imputation was performed on the Michigan Imputation Server using 1000G version 3 and HRC version 1 reference panels. *APOE* genotyping was also performed using high throughput sequencing and was favored over array-based methods.

Neuropathological Outcomes. Brain autopsies were performed using standard procedures.[6] Neuropathological measures and methods have been described in detail previously[12,13] (Supplementary Methods). Neuritic plaques, diffuse plaques, and neurofibrillary tangles were quantified and used to derive a measure of global AD pathology, a pathological diagnosis of AD (NIA-Reagan) and Braak stage. Measures of the brain's load of amyloid-β and density of tau-labeled tangles were also computed. Cerebrovascular neuropathology included atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, and chronic gross infarcts and microinfarcts. Other neurodegenerative neuropathology included nigral predominant and limbic and neocortical types of Lewy body disease and limbic-predominant age-related transactive response DNA-binding protein

43 kDa encephalopathy neuropathologic changes (LATE-NC).

Other Covariates. Data for potential confounders and effect modifiers were obtained from structured interview questions and measurements at the participants' annual clinical evaluations. Baseline measures included self-reported years of regular schooling (education), income, and smoking history. Annually updated (time-varying) covariates included: frequency of participation in cognitively stimulating activities based on a 5-point scale[14]; depressive symptoms using the 10-item version of the Center for Epidemiologic Studies–Depression Scale (CESD); physical activity based on the sum of self-reported minutes spent over the previous 2 weeks on 5 activities; body mass index (BMI, weight in kg/m^2) computed from measured weight and height; history of hypertension based on self-reported medical diagnosis or current use of hypertensive medications, history of myocardial infarction based on self-reported medical diagnosis or interviewer recorded use of cardiac glycosides (eg, lanoxin and digitoxin); history of diabetes by self-reported medical diagnosis or current use of medications; and history of stroke based on self-reported questions, cognitive testing, interviews with participants, and neurological examination (when available).[15] Our primary analysis considered baseline covariates or covariates measured at the time of the first FFQ. Time-varying covariates were considered in cognitive decline analyses.

Current Study Sample. Of the 1,306 participants eligible for these analyses, 1,064 completed the FFQ and 1,047 of these had sufficient information to derive caffeine and energy intake. We excluded 112 participants with <1 follow-up assessment and 47 participants with prevalent clinical dementia leaving a maximal sample size of 888. The number of annual cognitive assessments analyzed for participants ranged from 2 to 18 with 70% of participants having 5 or more. Of the 888 participants 727 had genomewide data. Of the 1,047 with valid FFQ data, 579 died during follow-up and had neuropathological data (530 also with genetic data). The mean (SD) postmortem interval was 9.4 (8.3) hours.

UK Biobank

In the years 2006 to 2010, the UKB recruited over 502,633 participants aged 37 to 73 years at 22 centers across England, Wales, and Scotland.[16] This study was covered by the generic ethical approval for UKB studies from the National Research Ethics Service Committee North West–Haydock (approval letter dated June 17, 2011, Ref. #11/NW/0382), and all study procedures were performed in accordance with the World Medical Association Declaration of Helsinki ethical principles for medical research.

Diet Assessment. At the baseline visit, participants completed a touchscreen questionnaire that also included a dietary assessment of a range of common food and drink items. We estimated total caffeine (mg/day) from regular coffee and black/green tea. Supplementary methods detail coffee and tea questionnaire items and caffeine derivation. Other dietary sources of caffeine were not captured by the questionnaire.

Dementia Outcomes. A new diagnosis of all-cause dementia was derived by UKB a priori with hospital admission and death record data utilizing International Classification of Diseases version 10 (ICD-10 codes).[17] When possible, all-cause dementia was further specified as Alzheimer's, vascular, or frontotemporal dementia. Prevalent cases were defined as those whose date of diagnosis was before or at their UKB baseline visit or who self-reported dementia at the baseline visit. Details pertaining to whether cases were defined using biomarkers was not provided and thus we assume all were based on a clinical diagnosis without biomarkers.

Baseline Cognitive Function and Covariates. An episodic visual memory test (Pairs Matching) and a reaction time test were administered at baseline via the touchscreen, as described in detail previously.[18] For a global measure of cognitive function, scores for each test were standardized using the mean and standard deviation, and the standardized scores averaged; 95% of the analyzed sample had data for both tests. Other cognitive tests were discontinued or added part-way through the baseline assessment period and thus not included for the current analysis. Prevalent depression, diabetes, hypertension, cardiovascular disease, and stroke was defined using self-report, medication, and hospital admission data. Other covariate or confounder information was collected via self-report using the touchscreen, as described in detail previously[16] and included sex, race, Townsend deprivation index (higher scores and higher deprivation), education, income, employment status, smoking status, physical activity, BMI, and self-rated health and consumption of alcohol, fish, red meat, fruit, and vegetables.

Genetic Data. All UKB participants were genotyped using genomewide arrays. Quality control and imputation to the HRC version 1.1 and UK10K reference panels was performed centrally by the Wellcome Trust Centre for Human Genetics, as described elsewhere.[19] *APOE* carriers (ε4+) and non-carriers (ε4-) were defined using directly

genotyped single nucleotide polymorphisms (SNPs) rs429358 and rs7412. We limited other genetic analysis to unrelated individuals of British-European (EUR; approximately 96% of sample), African (AFR; approximately 1%), and Central/South Asian (CSA; approximately 2%) genetically inferred ancestry based on a recent principal component analysis (PCA) by Pan-UKB.[20]

Current Study Sample. The current analysis considered participants at least 55 years of age (n = 308,345) to avoid missing cases of clinical dementia that may occur among younger participants had follow-up been extended. Of these, 304,075 participants had information on coffee and tea intake to enable caffeine derivation. We also excluded 188 participants with a hospital diagnosis of dementia at baseline or who self-reported having "dementia, Alzheimer's disease, or cognitive impairment" at the baseline nurse interview; leaving 303,887 for analysis. Of these, 226,359 were included for the genetic analysis.

SNP Selection

We considered all SNPs previously associated with caffeine-traits in genomewide association study (GWAS) and large-scale studies (Table S1). We excluded SNPs with pleiotropic effects including those near *GCKR*, *MLXIPL*, *SEC16B*, *TMEM18*, *ALDH2*, and *MC4R* resulting in a final SNP list of 16.

Statistical Analysis

All statistical analyses were performed using the SAS statistical package (version 9.1; SAS Institute, Cary, NC). Cox proportional hazard regression models were used to examine the association between dietary caffeine intake and incident clinical all-cause or specific dementia. Sample size and caffeine distribution of each cohort largely dictated how caffeine intake was modeled in each cohort: ≤100 mg/day (reference) versus >100 for MAP and ≤100 mg/day (reference) versus 100 ≤ 200, 200 ≤ 300, 300 ≤ 400, and >400 for UKB. To test for linear trends, caffeine mg/day was entered into the model as a continuous term. A quadratic caffeine term was added to the test for nonlinear trends. MAP participants were considered at risk for dementia from baseline (participant-specific) and were followed up until the date of the first clinical diagnosis or last clinical examination; whichever came first. UKB participants were considered at risk for dementia from baseline (2006–2010) and were followed up until the date of the first clinical diagnosis, death, loss to follow-up, or January 1, 2019 (the last date of all-cause dementia reported), whichever came first. The proportionality of hazards assumption was assessed using time-dependent explanatory variables and Schoenfeld residuals techniques[21] and was satisfied for each cohort. A "Basic" model adjusted for age, sex, self-reported race, and study center (UKB only). To this model, we separately added sets of covariates capturing measures of cognitive reserve ("CogRes"), cardiovascular/metabolic health ("Disease"), and lifestyle ("Lifestyle"), which may confound or mediate the association between caffeine intake and cognitive impairment. A final model ("Full") included all covariates from previous models. Model covariates differed by cohort and are detailed in Table S2 and result table footers. Missing data were present in some covariates for MAP (up to 5%) and UKB (up to 2%) and were modeled as indictor variables (see Table S2) with the exception of baseline cognitive function in UKB; the 2,294 (0.8%) participants missing information on cognitive function were excluded in models (CogRes, Full) with that covariate. A preliminary imputation procedure for cognitive function yielded nearly identical results to those of a complete-data analyses. In sensitivity analysis, we (1) excluded incident dementia cases within the first 2 (MAP) or 5 (UKB) years of follow-up; (2) excluded participants with mild cognitive impairment (MCI) at baseline (MAP only), and (3) modeled individual dietary caffeine sources in the place of total caffeine. We also performed a competing risk analysis in UKB because death was a censoring event and plausibly competes with dementia onset.

For measures of cognitive decline in MAP, linear mixed models with random intercept and time (slope) estimated mean differences in rates of cognitive decline over each time point by caffeine intake. Models were constructed as described above but each additionally included a variable for time, and multiplicative terms between time and each model covariate; the latter providing the covariate estimated effect on cognitive change. Moreover, cognitive and physical activities, BMI, depressive symptoms, and cardiovascular conditions were modeled as time-varying variables.

For analysis of neuropathology in MAP, we performed logistic regression (NIA-Reagan AD diagnosis, chronic and microinfarcts, LATE-NC), ordinal logistic regression (Lewy body stage, Braak stage, arteriosclerosis, atherosclerosis, and amyloid angiopathy) or linear regression (global AD pathology amyloid and tangles) to examine the association of baseline caffeine consumption (exposure) with neuropathology (outcome). We used a square root transformation for continuous outcomes in linear regression due to the positively skewed distribution of data. Similar covariate models described above were evaluated but we replaced age at baseline with age at death (model 1) and added postmortem interval time (model 1). In post hoc analysis, we considered caffeine consumption closest to death.

For significant caffeine-outcome associations, we screened for effect modification (interaction) by sex,

smoking, history of diabetes, *APOE* ε4 carrier status, and caffeine-SNP (16 SNPs) by including in basic model regressions the modifying variable (main effect) and cross-product term of caffeine intake and the modifying variable. In light of nonlinear findings in UKB, we also tested models that included interactions with both the linear and quadratic terms of caffeine. Genetic interaction testing in UKB was performed stratified by EUR, AFR, and CSA ancestry. Statistical significance for analyses of clinical outcomes was defined as $p < 0.05$ whereas that for neuropathology outcomes was defined as $p < 0.004$; and reflects an α correction for 12 neuropathological indices tested. Significant interactions were defined as $p < 0.0025$, after applying a correction for testing 20 effect modifiers. In all UKB statistical models involving *APOE* ε4 and other genetic factors, we additionally adjusted for 20 principal components to further account for population stratification. Because results were similar, we present the unadjusted results to maximize the sample size.

Results

The mean (SD) caffeine intake among MAP and UKB participants at baseline was 74 (57) and 259 (153) mg/day, respectively. Table 1 presents characteristics of MAP and UKB participants by caffeine consumption. For both cohorts, higher caffeine consumers were more likely to be men, White, current smokers, they consumed more alcohol, coffee, and tea, and were less likely to report a history of diabetes compared with low caffeine consumers.

Caffeine Consumption and Cognitive Impairment in MAP

After a mean (SD) follow-up time of 7.4 (4.3) years, 266 MAP participants developed clinical dementia; 252 of these were Alzheimer's dementia. Mean (SD) age of onset was 89.8 (5.9) and 90.0 (5.9) years for all-cause and Alzheimer's dementia, respectively. Caffeine consumption as reported at baseline was not associated with incident all-cause or Alzheimer's dementia when adjusting for age, sex, and race (Table 2, basic model). However, in a fully adjusted model, consuming >100 mg/day was associated with a higher risk of both all-cause and Alzheimer's dementia compared to consuming <100 mg caffeine/day (full model). Upon further model exploration (Table S3), the covariate driving the difference between the basic and fully adjusted models was baseline cognitive function status. Excluding this covariate from the Full adjusted model the hazard ratios (HRs) 95% confidence interval (95% CI) associated with consuming >100 mg/day compared to ≤100 mg/day were reduced to 1.28 (95% CI = 0.98–1.67, $p = 0.07$) and 1.31 (95% CI = 1.00–1.71, $p = 0.048$) for all-cause and Alzheimer's dementia, respectively. Average global cognitive performances declined over time; −0.10 (−0.11, −0.09) standard units/year. Caffeine consumption was not associated with global cognitive function decline (see Table S3) nor any specific cognitive domain (data not shown).

Fully adjusted HR (95% CI) associated with consuming >100 mg/day compared to ≤100 mg/day were reduced to 1.23 (95% CI = 0.92–1.65) and 1.28 (95% CI = 0.95–1.73) for all-cause and Alzheimer's dementia, respectively, when excluding cases diagnosed within 2 years of follow-up, and 1.14 (95% CI = 0.80–1.63) and 1.24 (95% CI = 0.86–1.79), respectively, when excluding prevalent MCI. In a fully adjusted model replacing total caffeine with all individual dietary sources of caffeine as independent variables, only coffee was associated with dementia: HRs (95% CI) for all-cause and Alzheimer's dementia associated with consuming ≥1 cups of regular coffee/day compared to no coffee were 1.31 (95% CI = 0.97–1.79, $p = 0.08$) and 1.38 (95% CI = 1.01–1.89, $p = 0.045$), respectively.

Caffeine Consumption and Incident Dementia in UKB

After a mean (SD) follow-up time of 8.7 (1.6) years, 2,277 UKB participants developed clinical dementia; 863 of these had Alzheimer's dementia, 489 had vascular dementia, and 92 had frontotemporal dementia. Mean (SD) age of onset was 71.4 (4.3), 71.7 (3.9), 71.9 (4.1), and 69.6 (4.0) years for all-cause, Alzheimer's, vascular, and frontotemporal dementia, respectively. Caffeine intakes (derived from regular coffee and tea) up to 400 mg/day were significantly associated with a lower risk of dementia compared to ≤100 mg/day according to all statistical models tested (Table 3; Table S4). A similar but slightly lower risk pattern was observed for Alzheimer's dementia. A similar but nonsignificant nonlinear trend was observed for risk of vascular dementia (data not shown). Too few cases of frontotemporal dementia limited meaningful analysis. In the UKB subset with genetic data, further adjustment for *APOE* slightly attenuated dementia risk estimates but results remained significant. Excluding dementia cases diagnosed within 5 years of follow-up or accounting for the competing risk of death (N = 16,393) yielded similar results (data not shown). The protection attributable to moderate caffeine intake was not driven solely by regular coffee or by tea.

Caffeine Consumption and Postmortem Neuropathology in MAP

The mean (SD) time between the first FFQ and death of MAP participants with neuropathology measures was 7.3 (3.9) years. Caffeine consumption was not associated with AD-related (Table S5), cerebrovascular-related (Table S6) neuropathologies, or LATE-NC (data not shown).

Table 1. Baseline Characteristics of MAP and UKB Participants[a]

	MAP		UKB	
	≤100 mg/d	>100 mg/d	≤100 mg/d	>100 mg/d
Characteristic	**N = 572**	**N = 316**	**N = 37,351**	**N = 266,536**
Age, yr				
Mean ± SD	81.2 ± 7.2	81.2 ± 7.2	62.0 ± 4.1	62.1 ± 4.1
Range	60–100	58–98	55–72	55–73
Male, n (%)	137 (24)	81 (26)	14,602 (39)	126,111 (47)
White race/ethnicity, n (%)	534 (93)	305 (97)	34,342 (91)	258,233 (97)
Baseline cognitive function, Z-score	0.11 ± 0.53	0.12 ± 0.55	−0.15 ± 0.78	−0.15 ± 0.76
Mild cognitive impairment, n (%)	130 (23)	70 (22)	n/a	n/a
Education				
College or university degree, n (%)	n/a	n/a	10,670 (29)	76,420 (29)
Years of education	14.9 ± 2.9	15.1 ± 3.0	n/a	n/a
Hypertension, n (%)	417 (73)	232 (73)	8,405 (23)	54,977 (21)
Diabetes, n (%)	94 (16)	37 (12)	1718 (5)	9,857 (4)
Stroke, n (%)	65 (11)	33 (10)	839 (2)	5,292 (2)
Heart disease, n (%)	97 (17)	49 (16)	2,603 (7)	16,774 (6)
Current smoker, n (%)	16 (3)	7 (2)	2,392 (6)	25,733 (10)
BMI, kg/m^2	27.1 ± 5.1	27.5 ± 5.3	27.8 ± 5.0	27.5 ± 4.6
Moderate to vigorous physical activity, hr/week[b]	3.4 ± 3.7	3.1 ± 3.6	1.2 ± 1.6	1.3 ± 1.6
Depression/symptoms, n (%)[c]	23 (4)	11 (3)	1706 (5)	11,469 (4)
Alcohol				
Drinks/week	n/a	n/a	1.0 ± 1.5	1.2 ± 1.4
g/days	4.6 ± 11.2	6.3 ± 12.3	n/a	n/a
Caffeine intake, n (%)				
100 ≤ 200 mg/day	0 (0)	309 (98)	0 (0)	85,728 (32)
200 ≤ 300 mg/day	0 (0)	7 (2)	0 (0)	75,025 (28)
300 ≤ 400 mg/day	0 (0)	0 (0)	0 (0)	65,312 (25)
>400 mg/day	0 (0)	0 (0)	0 (0)	40,471 (15)
Coffee (regular) drinkers, n (%)	246 (43)	314 (99)	4,492 (12)	188,209 (71)
Tea (non-herbal) drinkers, n (%)	238 (42)	184 (58)	21,889 (59)	241,326 (91)
APOE ε4 carriers, n (%)[d]	125 (22)	64 (20)	8,632 (28)	60,796 (28)
Family history of dementia, n (%)	n/a	n/a	822 (2)	5,782 (2)

[a]Values are mean ± SD or n (%).
[b]For MAP, moderate activity also includes walking for exercise and gardening/yard work.
[c]CESD-10 ≥5 (MAP); hospital-records/self-report (UKB).
[d]UKB N = 226,359.
BMI = body mass index; CESD = Center for Epidemiologic Studies–Depression Scale; MAP = Rush Memory and Aging Project; n/a = information not available or not applicable; UKB = UK Biobank.

TABLE 2. Caffeine Consumption and Incident Dementia in MAP

Model	All-cause dementia		Alzheimer's Dementia	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Basic[a]				
≤ 100	Ref.		Ref.	
> 100	1.17 (0.91, 1.50)	0.21	1.21 (0.94, 1.56)	0.15
10 mg/day, trend	1.00 (0.98, 1.03)	0.68	1.01 (0.99, 1.03)	0.53
Nonlinear trend		0.20		0.14
Full[b]				
≤100	Ref.		Ref.	
>100	**1.35 (1.03, 1.76)**	**0.03**	**1.41 (1.07, 1.85)**	**0.01**
10 mg/day, trend	**1.03 (1.00, 1.05)**	**0.03**	**1.03 (1.01, 1.05)**	**0.02**
Nonlinear		0.58		0.48

[a]Results from Cox proportional hazard regression models adjusted for age, sex and race (N = 888). See Table S2 for additional covariate details.
[b]Basic + years of education, late-life cognitive activity, global cognition score, income, *APOE* carrier status, history of hypertension, diabetes, heart disease and stroke, smoking, alcohol intake, calorie intake, depressive symptoms, physical activity, MIND score, and BMI. See Table S3 for results from additional statistical models.
BMI = body mass index; CI = confidence interval; HR = hazard ratio; MAP = Rush Memory and Aging Project; MIND = Mediterranean-DASH Interventionfor Neurodegenerative Delay.

Table 4 presents an overall protective linear relationship between caffeine consumption and postmortem Lewy body; especially neocortical Lewy body disease (LBD). Too few participants limited analysis of nigral-predominant LBD disease (n = 9), specifically. Similar protection against neocortical LBD disease was observed for coffee (OR = 0.48, 95% CI = 0.25–0.92 for ≥1 cup/day vs none but not tea OR = 0.88, 95% CI = 0.36–2.16 for ≥1 cup/day vs none). When modeling self-reported caffeine intake closest to the time of death (mean [SD], time interval = 1.0 [1.2] years; caffeine intake = 64 [50] mg/day), directionally consistent associations were observed with postmortem Lewy body but all effect estimates were attenuated and no longer statistically significant (p >0.004). LBD are also features of Parkinson's disease (PD).[22] In posthoc analysis, excluding 24 participants with clinically diagnosed PD, the effect estimates decreased: ORs (95% CI) for the presence of limbic-type and neocortical-type LBD associated with consuming >100 mg/day compared to ≤100 mg/day were 0.47 (95% CI = 0.27–0.81, p = 0.007) and 0.30 95% CI = 0.14–0.62, p = 0.001), respectively.

Effect Modification by Sex, Smoking, Diabetes, and Genetic Factors

In UKB, we observed a nominally significant interaction between caffeine intake and smoking status for incident clinical all-cause dementia (nonlinear interaction p = 0.04). In stratified analyses, the protective relationship between caffeine intake and dementia was greatest among current smokers (HR = 0.61, 95% CI = 0.41–0.91; HR = 0.45, 95% CI = 0.29–0.69; HR = 0.48, 95% CI = 0.32–0.73; and HR = 0.49, 95% CI = 0.33–0.73 for 100 ≤ 200, 200 ≤ 300, 300 ≤ 400, and >400 mg/day compared to ≤100 mg/day) than among never smokers (HR = 0.80, 95% CI = 0.66–0.97; HR = 0.83, 95% CI = 0.68–1.02; HR = 0.70, 95% CI = 0.56–0.87; and HR = 1.04, 95% CI = 0.82–1.31 for 100 ≤ 200, 200 ≤ 300, 300 ≤ 400, and >400 mg/day vs ≤100 mg/day; Table S7). Differences were not explained by the competing risk of death (data not shown). A similar modifying effect by smoking was also observed for Alzheimer's dementia (see Table S7). Overall, UKB results were not significantly modified by sex (Table S8) or diabetes (data not shown; p >0.05 for interactions). Mean (SD) caffeine intakes among EUR, AFR, and CSA participants were 263 (153), 157 (1,331), and 164 (110) mg/day, respectively. Although moderate caffeine intake appeared protective against all-cause dementia across ancestry (Table S9), too few cases and narrow caffeine intake distributions in AFR and CSA participants limited robust ancestry-specific analysis. For this reason, caffeine-SNP interaction testing was limited to EUR

TABLE 3. Caffeine Consumption and Incident Dementia in UKB

Model	All-cause dementia		Alzheimer's dementia	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Basic[a]				
≤100	Ref		Ref	
100 ≤ 200	**0.81 (0.71, 0.92)**	**0.001**	**0.76 (0.62, 0.94)**	**0.01**
200 ≤ 300	**0.70 (0.61, 0.80)**	**<0.0001**	**0.64 (0.51, 0.80)**	**0.0001**
300 ≤ 400	**0.69 (0.59, 0.79)**	**<0.0001**	**0.64 (0.51, 0.81)**	**0.0002**
>400	0.95 (0.81, 1.10)	0.47	0.98 (0.78, 1.25)	0.89
10 mg/day, trend	1.00 (1.00, 1.00)	0.30	1.00 (1.00, 1.00)	0.58
Nonlinear trend		**<0.0001**		**<0.0001**
5. Full[b]				
≤100	Ref		Ref	
100 ≤ 200	**0.83 (0.72, 0.94)**	**0.005**	**0.76 (0.61, 0.94)**	**0.01**
200 ≤ 300	**0.74 (0.64, 0.85)**	**<0.0001**	**0.66 (0.53, 0.83)**	**0.0003**
300 ≤ 400	**0.74 (0.64, 0.85)**	**<0.0001**	**0.67 (0.53, 0.85)**	**0.0008**
>400	0.92 (0.79, 1.08)	0.30	0.96 (0.75, 1.23)	0.75
10 mg/day, trend	1.00 (1.00, 1.00)	0.88	1.00 (1.00, 1.00)	0.77
Nonlinear trend		**<0.0001**		**0.002**
5. Full + APOE[c]				
≤100	Ref		Ref	
100 ≤ 200	**0.85 (0.73, 0.99)**	**0.03**	**0.74 (0.58, 0.95)**	**0.02**
200 ≤ 300	**0.79 (0.68, 0.93)**	**0.004**	**0.71 (0.55, 0.92)**	**0.009**
300 ≤ 400	**0.78 (0.66, 0.92)**	**0.003**	**0.69 (0.53, 0.90)**	**0.007**
>400	0.97 (0.81, 1.16)	0.74	1.05 (0.80, 1.38)	0.74
10 mg/day, trend	1.00 (1.00, 1.00)	0.54	1.00 (1.00, 1.01)	0.19
Nonlinear trend		**0.0003**		**0.003**

[a]Results from Cox proportional hazard regression models adjusted for age, sex, race, and study center (N = 303,887). See Table S2 for additional covariate details.
[b]Basic + education (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications), Townsend deprivation index, global cognition score, income, employment status and family history of dementia; history of hypertension, diabetes, heart disease and stroke; smoking, history of depression, self-reported health, physical activity, BMI, and intakes of alcohol, fish, red meat, fruit, and vegetables (N = 301,593).
[c]Full + *APOE* carrier status (N = 244,672). See Table S4 for results from additional statistical models.
BMI = body mass index; CI = confidence interval: HR = hazard ratio; UKB = UK Biobank.

participants and these yielded no statistically significant interactions (p >0.0025). Table S10 and Table S11 present SNP-stratified analysis for nominally significant interactions (0.0025 < p < 0.05) involving SNPs near *CYP1A2*, *POR*, *ORM7P*, and *PDSS2*. The significant associations between caffeine intake and incident clinical dementia (see Table 2) or Lewy body pathology (see Table 4) observed in MAP were not significantly modified by smoking status, sex, diabetes, or genetic factors (p >0.05 for interactions, Tables S12–S15, or not shown).

TABLE 4. Caffeine Consumption and Postmortem Lewy Body Disease in MAP

Model	LBD stage[a]		Limbic LBD[b]		Neocortical LBD[c]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Basic[d]						
≤100	Ref.		Ref.			
>100	0.55 (0.36, 0.86)	0.009	0.53 (0.33, 0.84)	0.007	**0.41 (0.23, 0.73)**	**0.003**
10 mg/day, trend	0.95 (0.92, 0.99)	0.009	0.95 (0.91, 0.99)	0.006	**0.93 (0.89, 0.97)**	**0.002**
CogRes[e]						
≤100	Ref.		Ref.		Ref.	
>100	0.57 (0.36, 0.89)	0.01	0.54 (0.34, 0.87)	0.01	0.43 (0.24, 0.77)	0.005
10 mg/day, trend	0.96 (0.92, 0.99)	0.02	0.95 (0.91, 0.99)	0.01	0.94 (0.89, 0.98)	0.005
Disease[f]						
≤100	Ref.		Ref.		Ref.	
>100	0.56 (0.36, 0.87)	0.01	0.53 (0.34, 0.85)	0.008	**0.42 (0.24, 0.75)**	**0.003**
10 mg/day, trend	0.95 (0.92, 0.99)	0.01	0.95 (0.91, 0.99)	0.007	**0.93 (0.89, 0.98)**	**0.003**
Lifestyle[g]						
≤100	Ref.		Ref.		Ref.	
>100	**0.51 (0.32, 0.81)**	**0.004**	**0.46 (0.28, 0.75)**	**0.002**	**0.36 (0.19, 0.66)**	**0.001**
10 mg/day, trend	0.95 (0.91, 0.99)	0.006	**0.94 (0.90, 0.98)**	**0.003**	**0.92 (0.88, 0.97)**	**0.002**
Full[h]						
≤100	Ref.		Ref.		Ref.	
>100	0.55 (0.34, 0.89)	0.01	0.50 (0.30, 0.82)	0.007	**0.40 (0.21, 0.75)**	**0.004**
10 mg/day, trend	0.96 (0.92, 0.99)	0.02	0.95 (0.91, 0.99)	0.01	0.93 (0.89, 0.98)	0.008

[a]Results from ordinal regressions of LBD stage: none (n = 425), nigral (n = 9), limbic (n = 38), and neocortical (n = 82).
[b]Results from logistic regression: limbic Lewy body (n = 38) versus none (n = 425).
[c]Results from logistic regression: neocortical Lewy body (n = 82) versus none (n = 425).
[d]Adjusted for age at death, sex, race, and postmortem interval time.
[e]Basic + years of education, late-life cognitive activity, global cognition score, dementia status, income, and *APOE* carrier status.
[f]Basic + history of hypertension, diabetes, heart disease, and stroke.
[g]Basic + smoking, alcohol intake, calorie intake, depressive symptoms, physical activity, MIND score, and BMI.
[h]Adjusted for all covariates listed above. See Table S2 for additional covariate details.
BMI = body mass index; CI = confidence interval; CogRes = cognitive reserve; LBD = Lewy body disease; MAP = Rush Memory and Aging Project; MIND = Mediterranean-DASH Interventionfor Neurodegenerative Delay (MIND); OR = odds ratio.

Discussion

The current study leveraged the detailed clinical and postmortem measures of MAP and large sample size of UKB to investigate the association between dietary caffeine consumption and cognitive impairment. In MAP, caffeine consumption was inversely associated with Lewy body pathology despite absence of a protective association with incident clinical dementia and cognitive decline. In UKB, moderate caffeine consumption was associated with a lower risk of incident all-cause and Alzheimer's dementia. Based on our current findings and that of others discussed below, we propose that caffeine protects against dementia by inhibiting Lewy body pathology and that inconsistencies in the epidemiological literature on caffeine and clinically diagnosed dementia may be due, in part, to cross-cohort differences in underlying cause of dementia.

Dementia can result from a number of distinct diseases but overlap of some symptoms and neuropathological features of each present diagnostic challenges that, in turn, impact efforts to identify cause-specific risk factors.[23] LBD includes both Parkinson's disease dementia (PDD) and dementia with Lew body (DLB) and despite being a common degenerative dementia[24] has never been studied in prospective epidemiological studies of dietary caffeine. Lewy bodies are also a hallmark feature of PD[22] and strong epidemiological and experimental evidence support an inverse association between caffeine intake and PD.[25] DLB features more limbic- and neocortical-type LB compared to PDD and PD.[26–28] We and others report the presence of neocortical-type Lewy bodies, specifically, correlate with cognitive impairment.[29,30] Individuals with DLB often additionally also present with postmortem pathological hallmarks of AD and, given shared symptomology, are often misdiagnosed clinically as having AD dementia.[24,31] In a joint analysis of MAP and the Religious Order Study, 11% of Alzheimer's dementia cases were attributable to Lewy body pathology.[32] In the Honolulu-Asia Aging Study (HAAS, all men), 10% of clinical dementia cases were attributable to cortical Lewy body pathology.[33] Whereas caffeine intake was not associated with incident clinical dementia in HAAS, the subset of autopsy patients in the highest quartile of caffeine intake (≥411.0 mg/day) were less likely to have any neuropathologic lesions compared to those in the lowest quartile.[34] No specific lesion reached statistical significance, but associations with cortical LB presented with the lowest effect estimates. In the Mayo Clinic Study of Aging, individuals with clinically probable DLB were more likely to abstain from caffeine than were controls or individuals with probable AD[35]; caffeine behavior between controls and AD did not differ. To our knowledge, we are the first to report a significant association between habitual caffeine intake and Lewy body pathology. High coffee intake was also associated with low Lewy body pathology. Coffee is a major source of caffeine and thus we cannot dismiss the role of other bioactive compounds in coffee which also present with neuroprotective properties.[36]

If neuroprotective actions of caffeine (or coffee) are mediated by Lewy body pathology, a clinical benefit of caffeine might only be realized for dementias largely attributable to Lewy body. For UKB, we combined data from hospital and death records, which have been shown to improve sensitivity and specificity of detecting clinical dementia[17] but likely underestimated the number of incident dementia cases and misclassified the type of dementia. Primary care data are available for about 40% of UKB participants but were not included in our analysis to avoid case-ascertainment bias. MAP participants were older than UKB participants at baseline and the mean age of dementia onset in MAP and UKB was 90 and 71 years, respectively. Prevalence of postmortem Lewy body decreases with increasing age of cognitive impairment onset.[37] The age of DLB onset is also younger than that of Alzheimer's dementia.[38] More UKB than MAP participants may have presented with Lew body-related dementia and the unique enrollment criteria at baseline for MAP may have induced a selection bias towards later age-of-onset dementia, including Alzheimer's dementia. Placed in the context of our caffeine-Lewy body pathology findings, this may partly explain the inverse association between caffeine intake in dementia observed only in UKB.

Lewy body are intracellular inclusion bodies of proteinaceous aggregates comprised mainly of alpha-synuclein (α-Syn).[24,39] Native α-Syn form oligomers that aggregate and develop into mature fibrils which contribute to cytotoxicity and neurodegeneration.[39] It has been proposed that α-Syn (Lewy body) pathology begins in the enteric nervous system, travels to the dorsal motor nucleus of the vagus nerve, and then spreads in a caudal to rostral pattern from the brainstem nigra (nigra-predominant) to the limbic (limbic-type) and neocortex (neocortical-type Lewy body pathology).[27,40–42] Caffeine or other coffee bioactives may protect against limbic- and neocortical-type Lewy body pathology through actions on α-Syn aggregation and/or spread. Caffeine blocks adenosine 2A receptors (A_{2a}Rs) and caffeine treatment or the disruption of A_{2a}R attenuates the toxicity of α-Syn aggregates in vitro and improves synaptic and cognitive deficits in α-Syn mouse models.[43-47] Several other coffee-derived chemicals also present with beneficial impacts on α-Syn pathology in vitro but are difficult to interpret because the bioavailability of some is limited or doses tested are unlikely to accumulate in vivo.[48–51] For example, coffee is a unique and major contributor of chlorogenic acids (CGAs) in the diet but only the metabolites (ie, cinnamates) of CGA are efficiently absorbed in the human small intestine and only after hydrolysis by either digestive or microbial enzymes.[52] Moreover, human evidence that coffee-derived metabolites, besides caffeine, cross the blood–brain-barrier is inconclusive.[52–54] Nevertheless, a role of these coffee metabolites in α-Syn/LB pathology remains possible in light of emerging evidence that α-Syn pathology might initiate in peripheral sites, such as the gastrointestinal tract and propagate to the brain[55] and that gut microbiota plays a role in the process.[56,57] Indeed, coffee and coffee-derived metabolites are potent modulators of the human gut microbiome[58,59] and may thus alter α-Syn pathology both directly and indirectly.

In UKB, the protective association between caffeine and incident dementia was greater at every caffeine dose among smokers compared to associations among never

smokers. Whereas these results require replication a caffeine × smoking interaction in the context of the Lewy body pathological process is plausible. Heavy lifetime cigarette use was associated with reduced risk of Lewy body-related but not AD-related pathological changes in the Adult Changes in Thought study[60] and nicotine can slow or inhibit α-Syn fibrillization in vitro.[61] The opposing roles of smoking and caffeine on oxidative stress, implicated in dementia onset and progression,[62,63] may also underlie the interaction we observed. Caffeine reduces oxidative stress and this may be more evident under high oxidative stress conditions that result from smoking.[62–64] The current study provided no support for gene × caffeine interactions for all-cause dementia or Alzheimer's dementia. If our argument holds that caffeine impacts dementia development through Lewy body pathology, gene × caffeine interaction testing may be more informative in studies of Lewy body related dementia.

The strengths of the current study include the use of a community cohort with detailed neurological assessment and measures as well as a very large cohort with linked health and death records. The comprehensive and complementary diet and covariate data also enabled a harmonized approach to the analysis despite differences in study design, which is not possible in meta-analyses. Besides under- or misdiagnosis of dementia, other important limitations of the current study should be acknowledged. AD and other causes of dementia have long presymptomatic phases; individuals without dementia may be free of clinical symptoms, but may already have biomarkers for AD. Conversely, we also cannot discount the role of reverse causation. Pre-diagnostic symptoms of disease may have led to a reduction in caffeine prior to diagnosis. Incipient Lewy body pathology may also alter caffeine or coffee drinking behavior as a result of impaired sense of smell.[65] The time of caffeine collection in these cohorts may not have adequately reflected earlier exposures, which might have a greater impact on the disease process to influence outcomes. The lack of information collected on other caffeine sources in UKB is also a limitation. MAP participants reported very low caffeine intake, which may be due to the older age of the cohort or the FFQ which limited reporting of high coffee and tea intake. The narrow distribution of caffeine intake in MAP also limited our ability to further parse higher caffeine doses in this cohort. Finally, UKB and MAP are not representative of the sampling populations and thus extrapolation of our findings to a more general population is limited.

In summary, caffeine consumption was inconsistently associated with clinical dementia in a US community and UK biobank. Caffeine consumption was inversely associated with postmortem Lewy body but not associated with other neuropathologies. Inconsistencies in the broader epidemiological literature of caffeine and dementia may partly be due to cross-study differences in underlying dementia etiology. Despite supporting epidemiological and experimental evidence we acknowledge the speculative nature of hypotheses we propose in the current study. Whether caffeine intake benefits dementia's largely attributable to Lewy bodies merits further investigation. The use of pathology-specific biomarkers in future studies of caffeine and dementia is also recommended.

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Author Contributions

M.C.C. was responsible for the current study concept, design, and analysis, and also wrote the manuscript. All authors critically revised for important intellectual content and approved the final manuscript.

Potential Conflicts of Interest

The authors declared no conflict of interest.

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