THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. XX, No. XX, 1–6
doi:10.1093/gerona/gly090
Advance Access publication July 6, 2018

OXFORD

Research Article

Age Modulates the Association of Caffeine Intake With Cognition and With Gray Matter in Elderly Diabetics

Rebecca K. West, PhD,[1] Ramit Ravona-Springer, MD,[2,3] Abigail Livny, PhD,[2,4] Anthony Heymann, MD,[5] Danit Shahar, RD,[6] Derek Leroith, MD, PhD,[7] Rachel Preiss, NP,[2] Ruth Zukran, MA,[2] Jeremy M. Silverman, PhD,[1,8] and Michal Schnaider-Beeri, PhD[1,2]

[1]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York. [2]Sheba Medical Center, The Joseph Sagol Neuroscience Center, Tel Aviv University, Tel Aviv, Israel. [3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. [4]Sheba Medical Center, Diagnostic Imaging Department, affiliated to Sackler Facility of Medicine, Tel Aviv University, Tel Aviv, Israel. [5]Maccabi Healthcare Services, Tel Aviv, Israel. [6]The S. Daniel Abraham International Center for Health and Nutrition, Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel. [7]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York. [8]James J. Peters Veterans Affairs Medical Center, Bronx, NY.

Address correspondence to: Rebecca K. West, PhD, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, Box 1230 One Gustave L Levy Place, New York, NY 10029. E-mail: rebecca.west@mssm.edu

Received: October 7, 2017; Editorial Decision Date: March 21, 2018

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: The association between caffeine and cognitive performance has not been tested in older individuals with type 2 diabetes (T2D). Its association with brain volume in T2D has been tested only in animals.
Methods: We examined the association of caffeine with cognitive function and brain volume in a sample of elderly diabetics participating in the Israel Diabetes and Cognitive Decline Study (n = 638) and the moderating effect of age on this association. In a subsample (n = 185) with magnetic resonance imaging, we also examined these associations with gray and white matter volumes (GM/WM).
Results: Using linear regression adjusting for cognition-related covariates, we found that higher caffeine intake was associated with better function in overall cognition (p = .018), attention/working memory (p = .002), executive functioning (p = .047), and semantic categorization (p = .026). Interaction analyses of caffeine intake with age were significant for semantic categorization (p = .025), and approached significance for overall cognition (p = .066). This association was driven by the older group (above-median) for whom the association of caffeine intake with semantic categorization (p = .001), attention/working memory (p = .007), executive functioning (p = .005), and overall cognition (p = .002) were significant. In the magnetic resonance imaging subsample, there was an interaction (p = .034) of caffeine intake with age for GM volume; in the older group, higher caffeine intake was associated with greater GM volume (β = .198, p = .033).
Conclusions: Caffeine intake may have a beneficial role in cognitive functioning of elderly adults with T2D, which may be moderated by age. Greater GM volume may be a mechanism underlying the association of higher caffeine intake with better cognitive function.

Keywords: Cognitive aging, Alzheimer's, Neuroimaging, Type 2 diabetes

Caffeine is among the most commonly ingested stimulants worldwide (1), naturally occurring in coffee, cocoa, and tea, among other foodstuffs. It is generally considered safe, with numerous potential benefits such as improved alertness, but also potential dangers, including anxiety and impaired sleep (2). Acute caffeine consumption has been linked to temporary improvements in cognitive functioning, especially in reaction time and focused attention (2). Habitual or longer-term caffeine use has also been linked to better global and specific cognitive performance and cognitive maintenance (3,4). However, caffeine may not be beneficial for all cognitive domains, may be more beneficial for women (5), and may not be dose-dependent (6,7). Similarly, caffeine has been associated with lower risk of dementia and Alzheimer's disease (AD) (5,8,9) but see (6,10) and in AD mouse models, caffeine has been shown to reverse memory

impairment (11), and with lower risk of other neurodegenerative disorders, including Parkinson's disease (12). Finally, there is evidence indicating its association with hippocampal volume (13), more white matter (WM) lesions in the elderly adults (14), changes in cerebral blood flow (1), functional connectivity (1), and with fewer AD and vascular neuropathologic lesions (15).

Age is the strongest risk factor for cognitive decline and dementia. Age has been shown to modify the relationship of caffeine intake with cognition (3,4), so that the potential advantage provided by caffeine to the brain is stronger with advancing age. The causes for this moderating effect of age are unknown but longer accumulating effects of caffeine (16), a stronger physiological reaction to caffeine in older individuals (17) are potential explanations. Age is also associated with decreased gray matter (GM) volume (18), as is T2D (19), however very little is known about the relationship between caffeine and GM.

Elderly adults with type 2 diabetes (T2D) are at particularly high risk of developing cognitive impairment and dementia (20). However, despite the potential neuroprotective effects of caffeine, its relationship with cognition has not been investigated in this high-risk population. Caffeine may be especially beneficial for T2D; it has been found to reverse T2D-related neurological damage and prevent memory loss in T2D model mice. Thus, we examined the relationships of caffeine intake with cognition and the impact of age on this relationship in a large cohort of T2D elderly adults participating in the Israel Diabetes and Cognitive Decline (IDCD) study. The IDCD study is an investigation of the relationships of long-term T2D-related characteristics with cognitive decline. In a subsample of the cohort that had a magnetic resonance imaging (MRI), we examined the relationship of caffeine with gray and WM volume. The study is a collaboration between the Icahn School of Medicine at Mount Sinai (ISMMS), NY, the Sheba Medical Center, Israel, and the Maccabi Healthcare Services, Israel.

Method

Study Population

The IDCD study enrolls subjects with T2D, aged 65+ years, and living in the area of Tel-Aviv. They are randomly selected from the approximately 11,000 T2D individuals that are in the Maccabi Health Services diabetes registry. The IDCD study is approved by the ISMMS, Sheba, and Maccabi IRB committees. Inclusion criteria requires that participants are nondemented at the time of enrollment, have at least three hemoglobin A1c (HbA1c) assessments, have an informant, and are fluent in Hebrew. Exclusion criteria prohibit an ICD code for dementia or dementia subtypes, prescribed cholinesterase inhibitors, or a major psychiatric or neurological condition that could affect cognitive performance. The IDCD has recruited 1,288 subjects of whom 897 were eligible (8.5% refused participation and 21.9% were excluded by eligibility criteria) and 744 had caffeine intake information; 638 had complete data on all relevant variables (caffeine, full cognitive testing, and covariates).

Maccabi Health Services Diabetes Registry

The Maccabi Diabetes Registry is an electronic patient record system that includes diagnoses, medications, and blood exam values for any Maccabi client with diabetes. In order to be listed in the Maccabi registry, patients must have one of the following: (i) HbA1c >7.25%, (ii) Glucose >200 mg/dL on two exams more than 3 months apart, (iii) purchase of diabetic medication twice within 3 months, and (iv) diagnosis of diabetes (ICD9 code) by a general practitioner, internist, endocrinologist, ophthalmologist, or diabetes advisor, supported by a HbA1c>6.5% or Glucose>125 mg/dL within half a year.

Dementia Evaluation and Diagnostic Consensus Conference

Each participant in the IDCD completes a demographic, medical and psychiatric history, neuropsychological testing, and physical testing. Laboratory results are received from the Maccabi registry. For each participant, a diagnostic consensus conference is jointly conducted by neurologists, psychiatrists, geriatricians, and neuropsychologists (at least two types of expertise). Only subjects deemed as cognitively normal are included in the IDCD study.

Neuropsychological battery

The outcome measures of this study are derived from a neuropsychological test battery and have been adapted to Hebrew and the Israeli culture (21). It is administered by a neuropsychologist. All test scores were transformed into Z scores, reversed if necessary, so positive values represented good cognition. Factor analysis summarized the neuropsychological measures into four factors: episodic memory (immediate recall, delayed recall, and recognition), executive functioning (Trails A and Trails B, constructional praxis, and digit symbol), semantic categorization (similarities, letter fluency, category fluency), and attention/working memory (diamond cancellation, digit span forward, and digit span backwards). The score for each domain was the sum of its z-scores; an overall cognition score was the sum of all z-scores.

Caffeine Intake

Daily caffeine intake was assessed using the Food Frequency Questionnaire (FFQ), a questionnaire specifically developed and validated for the elderly population in Israel (22,23). Instant coffee, coffee, tea, and soft drinks were considered sources of caffeine (with coffee accounting for 84% of the caffeine consumed). Beverage portion sizes were based on the standard portion sizes, as published by the Israeli Ministry of Health. Daily caffeine intake was calculated by multiplying portion by the values of caffeine per 100 mL and by frequency of intake per month, and dividing by 30.5 (an estimate of days/month) in order to get an estimation of caffeine intake per day.

Estimation of Gray and White Matter Volume

Randomly selected participants from the IDCD cohort (n = 897, n = 744 with caffeine intake information) underwent a MRI scan. MRI scans were performed in the diagnostic imaging department, at Sheba Medical Center with a 3 Tesla scanner (GE, Signa HDxt, v16VO2). High-resolution (1 mm^3) images were acquired using a 3D inversion recovery prepared spoiled gradient-echo (FSPGR) T1-weighted sequence (TR/TE = 7.3/2.7s, 20° flip angle, TI 450 ms). T1-weighted anatomical images for each subject were processed using the Voxel Based Morphometry (VBM) toolbox, developed by Gaser (http://www.fil.ion.ucl.ac.uk/spm/ext/#VBMtools) and implemented in Statistical Parametric Mapping (SPM8) software. This procedure included automated iterative skull stripping, segmentation of the images into GM, WM, and cerebrospinal fluid probability images, and spatial normalization of the GM images to a customized GM template in standard MNI (Montreal Neurological Institute) space. In order to optimize signal to noise, the GM maps were smoothed using an 8 mm Gaussian kernel. GM probability maps were held at the threshold of 0.1 to minimize inclusion of

incorrect tissue types. Total intracranial volume (ICV) was calculated using the segmented and thresholded images (ICV = GM + WM + CSF).

Measurement of Covariates

Sociodemographic covariates were age, sex, and years of education. Cardiovascular covariates were low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) cholesterol, and systolic and diastolic blood pressure. Inflammation covariates were IL-6 and C-reactive protein (CRP). T2D-related covariates were duration of T2D (calculated as the time from the first date the subject was identified by the Diabetes Registry as having T2D, and the date of the baseline cognitive assessment), and hemoglobin A1c [HbA1c] the gold standard measure of glycemic control. APOE genotype (dichotomized as having or not having an APOE4 allele), serum albumin, and serum thyroid-stimulating hormone, each associated with cognitive functioning (24–26), were also covariates, as was smoking (never, previously, current) Cardiovascular covariates were each calculated by averaging all measurements available for each subject in the Maccabi Diabetes Registry since its inception in 1998 or since the participant entered the Registry. The first two HbA1c measurements in the Diabetes Registry were not included in the analyses to avoid residual effects from the time before the diagnosis.

Statistical Analysis

Regression analyses, controlling for sociodemographic, caloric intake, cardiovascular, albumin, thyroid-stimulating hormone, and T2D characteristics, were performed to examine the associations of caffeine intake with the four cognitive domains and overall cognition.

To examine modulation by age of the relationship of caffeine with cognitive outcomes, regression analyses examined the relationship of cognitive outcomes with an interaction variable comprised of the product of age and caffeine. For a concrete description of the change in the association of caffeine with cognition as age increases, regression analyses examined the relationships of caffeine with cognitive outcomes split by the median age (which was similar for the whole sample [71.50] and the MRI subsample [71.08]). Median age was used because it was similar for both the whole sample and the MRI subsample, allowing for comparisons of two groups of similar size.

Finally, to identify the relationship between age, caffeine, and brain volume, regression analyses were used to examine (i) the association of caffeine with GM and WM in $N = 183$ participants with MRI, (ii) the interaction of age and caffeine on MRI outcomes, and (iii) the correlations between caffeine and MRI outcomes within younger and older participants.

Results

Participant Characteristics

Participant characteristics, for the entire sample, and above and below median of age are presented in Table 1. The younger age group had higher caffeine intake, systolic blood pressure and albumin levels, grater GM volume, shorter duration of diabetes, and lower thyroid-stimulating hormone. There were no significant differences among the groups in years of education, caloric intake, total intracranial volume, WM volume, HDL and LDL cholesterols, diastolic blood pressure, hemoglobin A1C, smoking, ApoE4, CRP, or IL-6.

Caffeine and Cognition

Adjusting for the covariates, regression analyses showed that higher caffeine intake was significantly associated with better attention/working memory ($R^2 = .211$, $\beta = .117$, $t(619) = 3.108$, $p = .002$), overall cognition ($R^2 = .372$, $\beta = .080$, $t(619) = 2.372$, $p = .018$), semantic categorization ($R^2 = .286$, $\beta = .080$, $t(619) = 2.229$, $p = .026$), and executive functioning ($R^2 = .342$, $\beta = .069$, $t(618) = 1.992$, $p = .047$), but not episodic memory ($R^2 = .129$, $\beta = -.030$, $t(619) = -.753$, $p = .452$).

Age modified the relationship of caffeine with semantic categorization ($R^2 = .292$, $\beta = 1.272$, $t(618) = 2.245$, p for interaction = .025), and at trend level for overall cognition ($R^2 = .375$, $\beta = .980$, $t(618) = 1.841$, $p = .066$), but not executive functioning ($R^2 = .344$, $\beta = .759$, $t(617) = 1.391$, $p = .165$), attention/working memory ($R^2 = .212$, $\beta = .305$, $t(618) = .511$, $p = .610$), or episodic memory ($R^2 = .130$, $\beta = .573$, $t(618) = .914$, $p = .316$).

To describe the direction of the interaction, linear regression analysis of caffeine with the cognitive outcomes was performed on subgroups above and below median, and showed that the relationship was strongest in the older age group (see Table 2), where caffeine was significantly associated with overall cognition ($R^2 = .399$, $\beta = .151$, $t(302) = 3.176$, $p = .002$), semantic organization ($R^2 = .326$, $\beta = .163$ $t(302) = 3.250$, $p = .001$), attention/working memory ($R^2 = .220$, $\beta = .148$, $t(302) = 2.733$, $p = .007$), and executive functioning ($R^2 = .402$, $\beta = .135$, $t(301) = 2.860$, $p = .005$), but not with episodic memory ($R^2 = .142$, $\beta = .004$, $t(302) = .078$, $p = .938$. There were no significant associations between caffeine and any cognitive factor in the younger age group.

We also assessed the association of caffeine with GM and WM in the participants with MRI (see Table 3). In this subsample, caffeine was neither associated with GM nor WM volumes. However, there was an interaction between age and caffeine for GM ($R^2 = .716$, $\beta = 1.694$, $t(164) = 2.135$, $p = .034$) such that in those below median age, higher caffeine intake was not associated with GM ($R^2 = .743$, $\beta = -.064$, $t(66) = -1.024$, $p = .309$) but in those above median age, higher caffeine intake was associated with greater GM ($R^2 = .580$, $\beta = .198$, $t(65) = 2.177$, $p = .033$). There was no interaction of caffeine intake with age on WM ($R^2 = .861$, $\beta = -.422$, $t(164) = -.760$, $p = .448$).

To investigate whether T2D-related characteristics affected the results, we repeated the analyses controlling only for age, sex, and education and all results were very similar.

Discussion

In this sample of elderly individuals with T2D, age moderated the relationships of caffeine both with cognition and with GM, such that higher caffeine intake levels were significantly associated with better cognitive performance and greater GM volume in older T2D individuals but not in younger, after controlling for numerous relevant covariates. Caffeine intake had a small but significant association with overall cognition, working memory/attention, semantic categorization, and approached significance for executive functioning. No associations were found with WM.

Older age is associated with worsening cognitive functioning and greater risk of all dementia types (27). Our results are consistent with those of others showing an age-related association between caffeine and cognitive performance, such that the relationship was strongest in older individuals (3,4). Longer exposure to and accumulating benefits of caffeine (16), and higher sensitivity to caffeine in older

Table 1. Characteristics of the Study Population

	Entire Sample (*N* = 638)	Entire Sample by Age Split		
Mean (*SD*)	All Participants	Younger Group (age 64–71.5) *N* = 317	Older Group Age (age 71.5–86) *N* = 321	*p*-value Difference
Overall cognition	0.68 (7.3)	2.4 (6.9)	−1.02 (7.3)	
Semantic categorization	0.21 (2.4)	0.67 (2.3)	−0.25 (2.3)	
Attention/working memory	0.08 (2.2)	0.30 (2.2)	−0.14 (2.1)	
Executive functioning	0.23 (2.9)	0.91 (2.8)	−0.43 (3.0)	
Episodic memory	0.15 (2.2)	0.52 (2.1)	−0.21 (2.2)	
Female (%)	38.2%	36.6%	39.9%	.220
Years of education	13.3 (3.5)	13.5 (3.3)	13.0 (3.6)	.306
Caloric intake (Kcal)	2,066.7 (703.37)	2,091.18 (745.48)	2,042.56 (659.41)	.383
Caffeine (mg)	204.2 (114.5)	214.94 (125.4)	193.64 (101.7)	.025
HDL cholesterol (mg/dL)	47.5 (10.7)	46.9 (10.4)	48.0 (10.9)	.195
LDL cholesterol (mg/dL)	101.7 (19.0)	103.1 (19.7)	100.3 (18.3)	.070
Diastolic blood pressure	84.0 (14.9)	84.9 (14.5)	83.2 (15.1)	.160
Systolic blood pressure	165.9 (9.7)	166.8 (9.6)	165.1 (9.8)	.027
Albumin	4.31 (.2)	4.33 (.2)	4.28 (.2)	<.001
TSH	2.5 (1.5)	2.3 (1.4)	2.6 (1.6)	.015
Duration of diabetes	8.7 (2.6)	8.5 (2.7)	8.9 (2.5)	.042
HbA1c	6.8 (.80)	6.8 (.86)	6.7 (.73)	.224
Apoe4	13.5%	12.3%	14.6%	.227
T2D medication	75.9% hypoglycemic only 0.8% insulin only 9.9% insulin and hypoglycemic 13.5% none	76.3% hypoglycemic only 0.6% insulin only 9.1% insulin and hypoglycemic 13.9% none	75.4% hypoglycemic only 0.9% insulin only 10.6% insulin and hypoglycemic 13.1% none	.892
Smoker	Never 39.7% Previously 48.7% Current 11.6%	Never 37.9% Previously 49.2% Current 12.9%	Never 41.4% Previously 48.3% Current 10.3%	.470
Il-6 (pg/mL)	2.81 (2.4)	2.77 (2.7)	2.85 (2.2)	.205
CRP (mg/mL)	1.14 (1.9)	1.19 (2.2)	1.09 (1.5)	.464
Gray matter (*N* = 185)	514.21 (50.8)	532.04 (50.6) (*N* = 101)	492.78 (43.34) (*N* = 84)	<.001
White matter (*N* = 185)	515.72 (66.8)	521.5 (71.9) (*N* = 101)	508.8 (59.7) (*N* = 84)	.196
Total intracranial volume (*N* = 185)	1,335.82 (135.91)	1,350.04 (146.4) (*N* = 101)	1,318.72 (120.7) (*N* = 84)	.119

Note: CRP = C-reactive protein; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; TSH = Thyroid-stimulating hormone.

Table 2. Interactions of Caffeine and Age on Cognitive Functions, for All Participants, and Linear Associations of Caffeine With Cognition Median Age, Controlling for Demographic, Cardiovascular, Diabetes, Smoking, and ApoE Variables (linear contrast *p* values)

	Interaction of Caffeine With Age on Cognition	Entire Sample by Age Group	
	All Participants *N* = 638	Youngest Group (age 64–71.5) *N* = 101	Oldest Group (age 71.5–84) *N* = 84
Overall cognition	R^2 = .375, β = .980, *p* = .066*	R^2 = .312, β = .033, *p* = .517	R^2 = .399, β = .151, *p* = .002**
Semantic categorization	R^2 = .292, β = 1.272, *p* = .025**	R^2 = .270, β = .015, *p* = .783	R^2 = .326, β = .163, *p* .001**
Attention/working memory	R^2 = .212, β = .305, *p* = .610	R^2 = .224, β = .101, *p* = .065	R^2 = .220, β = .148, *p* = .007**
Executive functioning	R^2 = .344, β = .759, *p* = .165	R^2 = .234, β = .034, *p* = .520	R^2 = .402, β = .135, *p* = .005**
Episodic memory	R^2 = .130, β = .573, *p* = .361	R^2 = .103, β = −.059, *p* = .311	R^2 = .142, β = .004, *p* = .938

Note: * trend level at >.10. **significant at .05 level.

individuals (17) have been proposed as potential underlying mechanisms behind the moderating effect of age on the association of caffeine with cognition. Finally, hypotension, associated with cognitive decline, is common among older individuals (28) and individuals with T2D (29). Caffeine may provide a slight rise in blood pressure without the risk of hypertension (30), thereby mitigating the impact of hypotension on cognition; this study included the mean of blood pressure measurements over several years as a covariate, and its inclusion did not alter the results. However, we do not have information on daily fluctuations of blood pressure. Finally, though all participants are nondemented, those in the older group do have lower cognitive functioning compared to the younger group. Within the older group, higher caffeine is associated with better cognitive functioning, however, this relationship does not exist in the younger

Table 3. Interactions of Caffeine and Age on Brain Volume, for MRI Sample, and Linear Associations of Caffeine With Brain Volume by Median Age, Controlling for Demographic, Cardiovascular, Diabetes, Smoking, and ApoE Variables

	Interaction of Caffeine With Age on Brain Volume	MRI Sample by Median Age	
	MRI Sample *N* = 185	Youngest Group (age 64–71.5) *N* = 101	Oldest Group (age 71.5–84) *N* = 84
Gray matter	R^2 = .716, β = 1.694, *p* = .034*	R^2 = .550, β = –.064, *p* = .309	R^2 = .580, β = .198, *p* = .033*
White matter	R^2 = .861, β = –.422, *p* = .448	R^2 = .865, β = .014, *p* = .745	R^2 = .866, β = –.032, *p* = .536

Note: MRI = Magnetic resonance imaging.
*Significant at .05 level.

group. It is possible that, due to stronger cognitive functioning in the younger group, a difference between those who use larger amounts of caffeine and those who do not cannot yet be seen.

The result of an association between caffeine and cognitive outcomes in this sample of individuals with T2D is strengthened by our finding of an interaction between age and caffeine on GM (such that higher levels of caffeine are associated with more GM volume in the older group of participants). Caffeine consumption has been found to reverse T2D-related neurological damage and prevent T2D-related memory impairment in mice (31) suggesting that long-term use of caffeine is potentially beneficial in reducing T2D- related neuropathology and cognitive loss. Our results of greater volume of GM in older subjects who have higher intake of caffeine are consistent with the reduction of neuronal loss with age by chlorogenic acids and polyphenols (8,32). As longer duration of T2D is associated with brain volume loss, particularly in the GM (19), the moderation of age on the relationship of caffeine with GM may suggest that as individuals with T2D age, caffeine may protect against T2D-related GM loss and therefore also against cognitive decline. Finally, it is important to recognize that caffeine is associated with cerebral blood flow (33). In this study, caffeine intake was not associated with WM volume, in line with findings of no relationship between WM loss and T2D (34).

Several mechanisms by which caffeine and coffee (one of the most popular caffeine-providing beverages) may be neuroprotective have been suggested. Caffeine appears to reduce beta-amyloid deposits in mice (35), potentially due to caffeine's role as an adenosine antagonist (36). Caffeine also protects the blood brain barrier, improving efflux of beta-amyloid and thereby reducing the risk of AD (as well as Parkinson's disease) (12,37). Finally, coffee contains polyphenols, specifically chlorogenic acid, an antioxidant, which may reduce inflammation and protect against dementia (32).

Caffeine has been shown to be associated with lower risk of dementia, AD, and cognitive decline (8,16,17) and with better cognitive functioning (32). Here, we show that the association between caffeine and cognition is relevant to T2D elderly adults, specifically older elderly adults. This study was limited by its cross-sectional outcomes. Longitudinal outcomes of the IDCD study are ongoing. We do not have information on whether caffeine intake was a constant habit for the participants. This is especially important in light of a recent longitudinal analysis of caffeine consumption, in which a constant, moderate caffeine consumption was associated with reduced risk of MCI, but an increase in caffeine consumption was associated with an increased risk (7). We cannot rule out that persons with incipient, preclinical dementia, decrease their caffeine intake (38), leading to an apparent association of higher caffeine intake with better cognition. Although there is often a decline in caloric intake prior to the onset of dementia (39), which might include caffeine intake, caloric intake was controlled for in this study. This study is strengthened by a large sample, strong validity for T2D diagnosis and cardiovascular variables, and a broad cognitive assessment, permitting examination of global and specific cognitive domains as well as by a subsample who had MRI so brain markers related to the potential neuroprotective role of caffeine could be examined. The study innovates by focusing on a sample of T2D patients, who are at high dementia risk. Further, we could not find studies examining the association of caffeine with GM volume. Our study did not include a non-T2D sample impeding conclusions regarding specific effects of T2D. However, results were similar with and without inclusion of T2D-related covariates, possibly suggesting that elderly adults without T2D might benefit from caffeine. The range of caffeine intake in the IDCD sample was from 0 to 626.5 mg, averaging 205.2 mg, with very few participants' intake above recommended values. These levels are consistent with those of U.S. samples of comparable ages (40). There were few participants with very high caffeine intake levels; this impeded testing of whether very high levels may deleteriously (or beneficially) affect cognition, however, a study investigating different levels of caffeine found a "lack of a distinct dose-response association (6)". Based on Fulgoni, Keasit, and Lieberman (2015) (40), a high caffeine intake dose was defined in our paper as 439 mg/d (90th percentile, (40)). Twenty-seven participants in this study reported a daily intake of caffeine above 439 mg/d. Caffeine is an inexpensive, readily available drug, so understanding its potential role in cognition and GM volume, and how age moderates it, may suggest preventive strategies against dementia.

Funding

This study was supported by the National Institutes of Health (Grant/Award Number: R01 AG034087/AG/NIA NIH HHS), Alzheimer's Association (Grant/Award Number: NIRG-11-205083 2012), the American Federation for Aging Research, The Bader Philanthropies, and the LeRoy Schecter Foundation.

Author contributions

R.K.W. conducted statistical analysis and wrote manuscript. R.R-S. researched data, reviewed/edited manuscript. A.L. reviewed/edited manuscript. A.H. researched data, reviewed/edited manuscript. D.S. extracted caffeine intake data, reviewed the manuscript. D.L. reviewed/edited manuscript and contributed to discussion. R.P. collected data and reviewed the manuscript. R.Z. collected data and reviewed the manuscript. J.M.S. reviewed/edited manuscript. M.S-B. designed the study, performed the experiments, analyzed and researched data, and reviewed/edited the manuscript.

Conflict of Interest

None reported.

References

1. Haller S, Montandon ML, Rodriguez C, et al. Caffeine impact on working memory-related network activation patterns in early stages of cognitive decline. *Neuroradiology*. 2017;59:387–395. doi:10.1007/s00234-017-1803-5
2. Smith A. Effects of caffeine on human behavior. *Food Chem Toxicol*. 2002;40:1243–1255. doi:10.1016/S0278-6915(02)00096-0
3. Ritchie K, Carrière I, de Mendonca A, et al. The neuroprotective effects of caffeine: a prospective population study (the three city study). *Neurology*. 2007;69:536–545. doi:10.1212/01.wnl.0000266670.35219.0c
4. Johnson-Kozlow M, Kritz-Silverstein D, Barrett-Connor E, Morton D. Coffee consumption and cognitive function among older adults. *Am J Epidemiol*. 2002;156:842–850. doi:10.1093/aje/kwf119
5. Driscoll I, Shumaker SA, Snively BM, et al. Relationships between caffeine intake and risk for probable dementia or global cognitive impairment : the women's health initiative memory study. *J Gerontol Med Sci*. 2017;71:1596–1602. doi:10.1093/gerona/glw078
6. Panza F, Solfrizzi V, Barulli MR, et al. Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. *J Nutr Health Aging*. 2015;19:313–328. doi:10.1007/s12603-014-0563-8
7. Solfrizzi V, Custodero C, Lozupone M, et al. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. *J Alzheimers Dis*. 2017;59:815–849. doi:10.3233/JAD-170248
8. Cao C, Loewenstein DA, Lin X, et al. High blood caffeine levels in MCI linked to lack of progression to dementia. *J Alzheimers Dis*. 2012;30:559–572. doi:10.3233/JAD-2012-111781
9. Eskelinen MH, Kivipelto M. Caffeine as a protective factor in dementia and Alzheimer's disease. *J Alzheimers Dis*. 2010;20 (Suppl 1):S167–S174. doi:10.3233/JAD-2010-1404
10. Carman AJ, Dacks PA, Lane RF, Shineman DW, Fillit HM. Current evidence for the use of coffee and caffeine to prevent age-related cognitive decline and Alzheimer's disease. *J Nutr Health Aging*. 2014;18:383–392. doi:10.1007/s12603-014-0021-7
11. Han K, Jia N, Li J, Yang L, Min LQ. Chronic caffeine treatment reverses memory impairment and the expression of brain BNDF and TrkB in the PS1/APP double transgenic mouse model of Alzheimer's disease. *Mol Med Rep*. 2013;8:737–740. doi:10.3892/mmr.2013.1601
12. Chen X, Ghribi O, Geiger JD. Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's diseases. *J Alzheimers Dis*. 2010;20 (Suppl 1):S127–S141. doi:10.3233/JAD-2010-1376
13. Perlaki G, Orsi G, Kovacs N, et al. Coffee consumption may influence hippocampal volume in young women. *Brain Imaging Behav*. 2011;5:274–284. doi:10.1007/s11682-011-9131-6
14. Ritchie K, Artero S, Portet F, et al. Caffeine, cognitive functioning, and white matter lesions in the elderly: establishing causality from epidemiological evidence. *J Alzheimers Dis*. 2010;20 (Suppl 1):S161–S166. doi:10.3233/JAD-2010-1387
15. Gelber RP, Petrovitch H, Masaki KH, Ross GW, White LR. Coffee intake in midlife and risk of dementia and its neuropathologic correlates. *J Alzheimers Dis*. 2011;23:607–615. doi:10.3233/JAD-2010-101428
16. Rosso A, Mossey J, Lippa CF. Caffeine: neuroprotective functions in cognition and Alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2008;23:417–422. doi:10.1177/1533317508320083
17. Massey LK. Caffeine and the elderly. *Drugs Aging*. 1998;13:43–50. doi:10.2165/00002512-199813010-00005
18. Courchesne E, Chisum HJ, Townsend J, et al. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology*. 2000;216:672–682. doi:10.1148/radiology.216.3.r00au37672
19. Bryan RN, Bilello M, Davatzikos C, et al. Effect of diabetes on brain structure: the action to control cardiovascular risk in diabetes MR imaging baseline data. *Radiology*. 2014;272:210–216. doi:10.1148/radiol.14131494
20. Biessels GJ. Caffeine, diabetes, cognition, and dementia. *J Alzheimers Dis*. 2010;20 (Suppl 1):S143–S150. doi:10.3233/JAD-2010-091228
21. Guerrero-Berroa E, Ravona-Springer R, Schmeidler J, et al. Age, gender, and education are associated with cognitive performance in an older Israeli sample with type 2 diabetes. *Int J Geriatr Psychiatry*. 2014;29:299–309. doi:10.1002/gps.4008
22. Shahar D, Fraser D, Shai I, Vardi H. Development of a food frequency questionnaire (FFQ) for an elderly population based on a population survey. *J Nutr*. 2003;133:3625–3629. doi:10.1093/jn/133.11.3625
23. Shai I, Rosner BA, Shahar DR, et al.; DEARR study. Dietary evaluation and attenuation of relative risk: multiple comparisons between blood and urinary biomarkers, food frequency, and 24-hour recall questionnaires: the DEARR study. *J Nutr*. 2005;135:573–579. doi:10.1093/jn/135.3.573
24. Llewellyn DJ, Langa KM, Friedland RP, Lang IA. Serum albumin concentration and cognitive impairment. *Curr Alzheimer Res*. 2010;7:91–96. doi:10.2174/187220919747156312 8
25. Raber J, Wong D, Yu GQ, et al. Apolipoprotein E and cognitive performance. *Nature*. 2000;404:352–354. doi:10.1038/35006165
26. Wahlin A, Bunce D, Wahlin TB. Longitudinal evidence of the impact of normal thyroid stimulating hormone variations on cognitive functioning in very old age. *Psychoneuroendocrinology*. 2005;30:625–637. doi:10.1016/j.psyneuen.2005.01.010
27. Hall CB, Verghese J, Sliwinski M, et al. Dementia incidence may increase more slowly after age 90: results from the Bronx Aging Study. *Neurology*. 2005;65:882–886. doi:10.1212/01.wnl.0000176053.98907.3f
28. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. *Nat Rev Cardiol*. 2010;7:686–698. doi:10.1038/nrcardio.2010.161
29. Van Hateren KJ, Kleefstra N, Blanker MH, Ubink-veltmaat LJ, Groenier KH. Orthostatic hypotension, diabetes, and falling in older patients: a cross-sectional study. *Br J Gen Pr*. 2012;62:696–702. doi:10.3399/bjgp12X656838
30. Geleijnse JM. Habitual coffee consumption and blood pressure: an epidemiological perspective. *Vasc Health Risk Manag*. 2008;4:963–970. doi:10.2147/VHRM.S3055
31. Duarte JM, Agostinho PM, Carvalho RA, Cunha RA. Caffeine consumption prevents diabetes-induced memory impairment and synaptotoxicity in the hippocampus of NONcZNO10/LTJ mice. *PLoS One*. 2012;7:e21899. doi:10.1371/journal.pone.0021899
32. Cropley V, Croft R, Silber B, et al. Does coffee enriched with chlorogenic acids improve mood and cognition after acute administration in healthy elderly? A pilot study. *Psychopharmacology (Berl)*. 2012;219:737–749. doi:10.1007/s00213-011-2395-0
33. Dager SR, Friedman SD. Brain imaging and the effects of caffeine and nicotine. *Ann Med*. 2000;32:592–599. doi:10.3109/07853890009002029
34. Espeland MA, Erickson K, Neiberg RH, et al. Brain and white matter hyperintensity volumes after 10 years of random assignment to lifestyle intervention. *Diabetes Care*. 2016;39:764–771. doi:10.2337/dc15-2230
35. Arendash GW, Mori T, Cao C, Mamcarz M. Caffeine reverses cognitive impairment and decreases brain amyloid-β levels in aged Alzheimer's disease mice. *J Alzheimer's Dis*. 2009;17:661–680. doi:10.3233/JAD-2009-1087
36. Ritchie K, Ancelin ML, Amieva H, Rouaud O, Carrière I. The association between caffeine and cognitive decline: examining alternative causal hypotheses. *Int Psychogeriatr*. 2014;26:581–590. doi:10.1017/S1041610213002469
37. Qosa H, Abuznait AH, Hill RA, Kaddoumi A. Enhanced brain amyloid-β clearance by rifampicin and caffeine as a possible protective mechanism against Alzheimer's disease. *J Alzheimers Dis*. 2012;31:151–165. doi:10.3233/JAD-2012-120319
38. Maia L, de Mendonça A. Does caffeine intake protect from Alzheimer's disease? *Eur J Neurol*. 2002;9:377–382. doi:10.1046/j.1468-1331.2002.00421.x
39. Grundman M. Weight loss in the elderly may be a sign of impending dementia. *Arch Neurol*. 2005;62:20–22. doi:10.1001/archneur.62.1.20
40. Fulgoni VL, Keast DR, Lieberman HR. Trends in intake and sources of caffeine in the diets of US adults: 2001–2010. *Am J Clin Nutr*. 2015;101:1081–1087. doi:10.3945/ajcn.113.080077