

Caffeine and Alcohol Intakes and Overall Nutrient Adequacy Are Associated with Longitudinal Cognitive Performance among U.S. Adults^{1–3}

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Abstract

Among modifiable lifestyle factors, diet may affect cognitive health. Cross-sectional and longitudinal associations may exist between dietary exposures [e.g., caffeine (mg/d), alcohol (g/d), and nutrient adequacy] and cognitive performance and change over time. This was a prospective cohort study, the Baltimore Longitudinal Study of Aging ($n = 628$ – 1305 persons depending on the cognitive outcome; ~ 2 visits/person). Outcomes included 10 cognitive scores, spanning various domains of cognition. Caffeine and alcohol intakes and a nutrient adequacy score (NAS) were estimated from 7-d food diaries. Among key findings, caffeine intake was associated with better baseline global cognition among participants with a baseline age (Age_{base}) of ≥ 70 y. A higher NAS was associated with better baseline global cognition performance (overall, women, $Age_{\text{base}} < 70$ y), better baseline verbal memory (immediate and delayed recall, $Age_{\text{base}} \geq 70$ y), and slower rate of decline or faster improvement in the attention domain (women). For an Age_{base} of < 70 y, alcohol consumption was associated with slower improvement on letter fluency and global cognition over time. Conversely, for an Age_{base} of ≥ 70 y and among women, alcohol intake was related to better baseline attention and working memory. In sum, patterns of diet and cognition associations indicate stratum-specific associations by sex and baseline age. The general observed trend was that of putative beneficial effects of caffeine intake and nutrient adequacy on domains of global cognition, verbal memory, and attention, and mixed effects of alcohol on domains of letter fluency, attention, and working memory. Further longitudinal studies conducted on larger samples of adults are needed to determine whether dietary factors individually or in combination are modifiers of cognitive trajectories among adults. *J. Nutr.* 144: 890–901, 2014.

Introduction

Preventing age-related cognitive decline can help maintain quality of life (1). Dietary factors, such as the neuroactive compounds caffeine and alcohol, may affect cognitive health (2–4). Cognitive health benefits were also ascribed to healthy patterns of dietary intake and dietary quality (5). However, few studies with a prospective cohort design have examined all 3 predictors (i.e., caffeine and alcohol intakes and dietary quality)

simultaneously, covarying for the others. In fact, to our knowledge, research has to date restricted its aim to a single cognitive test score, thus failing to incorporate multiple domains of cognition. Consequently, well-designed cohort studies are needed to clarify independent associations of dietary quality and caffeine and alcohol intakes with cognition. Such studies would ascertain temporality, include multiple cognitive domains, and would account for potential confounding effects within the diet.

Caffeine, primarily obtained from coffee, is the most widely used neuroactive compound worldwide (6). Acting as a brain stimulant, it causes heightened alertness and arousal (6) and can improve perceptual speed, vigilance, and even memory (7,8). As a methylxanthine, caffeine blocks brain adenosine receptors, triggering cholinergic stimulation and potentially improving cognitive performance and slowing age-related cognitive decline (8). Caffeine's putative beneficial effects on cognition are domain-specific

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³ Supplemental Tables 1–3 and Supplemental Figures 1 and 2 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://jn.nutrition.org>.

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(9–17). However, several studies found no association (18–20), whereas others noted differential associations by gender (9,21).

Alcohol, on the other hand, is a well-known depressant drug widely consumed in Western diets. Although many large epidemiologic studies have examined cognition in relation to alcohol consumption, the direction of the association remains uncertain (22–51).

Importantly, caffeine- and alcohol-containing drinks are often consumed with other foods and with each other at different meals. Thus, intakes of caffeine and alcohol may be correlated with each other and with dietary quality or nutrient adequacy (i.e., an index of dietary quality based solely on nutrients). Furthermore, poor dietary quality has been associated with adverse cognitive outcomes, including decline and poor function (2,52–58). Thus, dietary quality may confound relations of caffeine and alcohol intakes with cognition. Previous studies failed to account for this potential confounding effect. In our present study, we evaluated the independent associations of caffeine and alcohol intake and nutrient adequacy with cross-sectional and longitudinal cognitive performance in a U.S. population of older adults. We hypothesized caffeine to have putative beneficial and sex-specific effects for certain domains (e.g., attention, perceptual speed, and memory), and alcohol to have both beneficial and deleterious effects, depending on the population subgroup (age group or gender) and the cognitive domain. In contrast, nutrient adequacy was hypothesized to affect a wide range of domains in a positive manner.

Based on previous evidence, particularly in the case of caffeine and alcohol intake (9,14,21,36,40), we presented sex-specific findings. In addition, variations in nutrient requirements by age at cut-points of 50 y and 70 y had been noted [e.g., fiber (lower at ≥ 50 y vs. < 50 y), sodium (lower at ≥ 70 y vs. < 70 y), calcium (different ranges for ≥ 50 y vs. < 50 y), iron (reduced with age), phosphorus [upper limit (UL)⁹ reduced at 70 y], vitamin B-6 (increases with age, including ≥ 50 y), and vitamin D (increases at age ≥ 70 y)] (59–62). Moreover, studies have commonly stratified by age associations of dietary components with cognition (15,17,40,57). Therefore, we stratified our results by sex and age accordingly, similar to previous studies (9,14,15,17,21,36,40,57).

Materials and Methods

Database and study population

The Baltimore Longitudinal Study of Aging (BLSA) is an ongoing prospective open cohort study of community-dwelling adults that was initiated in 1958 by the National Institute on Aging. BLSA participants were generally highly educated adults with a first-visit age of 17 to 97 y (median = 60.7; means \pm SDs = 58.9 \pm 18.0), and around 60% were men. Total enrollment included $n_1 = 3047$ participants ($n'_1 = 20,385$ visits, 1958–2009) (63). Exclusionary criteria are summarized elsewhere (64). Examinations were conducted at ~ 2 -y intervals, and the protocol was approved by the Medstar Research Institute's Institutional Review Board. Examinations included physical, neurocognitive, medical history, dietary assessment, laboratory, and radiologic tests and measurements. Participants completed a written informed consent form per visit (63).

Eligible participants (n), observations or visits (n'), and visits/participants (n'') were as follows: 1) had complete dietary intake data from 1961 to 2007 ($n_2 = 1821$ participants; $n'_2 = 4537$ visits; n''_2 range = 1–12 visits/participant, mean = 2.5 visits/participant); 2) had complete cognitive data from 1962 to 2008 ($n_{3a-3j} = 1199$ –2704 participants; $n'_{3a-3j} = 5111$ –10,704 visits depending on the cognitive test score; n''_3 range = 1–22 visits/participant; mean = 3.4–4.4 visits/participant); and 3) had ≥ 1 visits that were concurrent (i.e., during the same visit/year) between dietary and cognitive data ($n_{4a-4j} = 628$ –1305 participants; $n'_{4a-4j} = 1218$ –2528 visits; n''_4 range = 1–10 visits/participant; mean = 1.9–2.0 visits/participant). Moreover, the mean (range) first-visit age for final samples with cognitive and dietary data (4a-4j) was 62 to 69 y (17–99 y), depending on the cognitive test. However, a distinction was made between first-visit characteristics (including age) and baseline characteristics. The “baseline” (base) visit was the earliest visit/year (Year_{base}) with concurrent data on diet and cognition. Timing was similar for most tests, except for the Benton Visual Retention Test (BVRT), historically initiated earlier in the BLSA. In samples 4a-4j, Year_{base} ranged from 1961 to 2007 for BVRT and 1985 to 2007 for other cognitive tests. The baseline age (Age_{base}) range for samples 4a-4j was 18 to 93 y (mean: 62 y) for BVRT and 27 to 96 y (mean: 68–72 y) for other cognitive tests.

Dietary assessment: caffeine and alcohol intake and nutrient adequacy score

Dietary intake was assessed with 7-d dietary records. BLSA participants were instructed by trained dietitians to estimate portion size, weigh foods, and complete the records (65–67). Intake was assessed in a noncontinuous fashion: 1961 to 1965 (1.01% of $n'_2 = 4537$), 1968 to 1975 (31.10% of n'_2), 1984 to 1992 (23.46% of n'_2), and 1994 to 2007 (44.3% of n'_2). Overall ($n'_2 = 4537$, 1961–2007), the means \pm SDs of completed dietary records was 6.04 \pm 1.73 (IQR: 6–7). Food codes and amounts were recorded for each diary, with nutrient intakes [absolute and relative amounts (i.e., per 1000 kcal or % energy)] estimated using a revised and up-to-date nutrient database (68) and averaged over available diaries per individual visit. Specifically, caffeine (per 100 mg/d) and alcohol (g/d) intakes and the nutrient adequacy score (NAS) were of primary interest. Moderate alcohol consumption was defined as 14 to 28 g/d and was compared with lower and higher amounts of intake as a sensitivity analysis, based on previous studies (22–35,37–39).

To estimate the NAS, age/sex-specific DRIs for U.S. adults were used among others to categorize individuals according to adequacy of dietary intake for macronutrients (e.g., protein, carbohydrates, fat) and micronutrients (vitamins and minerals). Among DRI, adequate intake (AI) was used to reference an amount of vitamins and minerals above which a participant's intake was adequate without exceeding the UL. For carbohydrates, protein, and total fat (% energy), the acceptable macronutrient distribution range was used instead. Saturated fat (% energy) intake in moderation was estimated using the 2005 Healthy Eating Index complete score. Similarly, cholesterol (mg) intake was determined adequate based on the 1995 Healthy Eating Index complete score (60–62).

For all NAS components, AI or AI and UL in combination were used as follows: 1) AI only: total fiber, potassium, thiamin, riboflavin, and vitamin E; and 2) AI and UL: sodium, calcium, iron, magnesium, phosphorus, zinc, retinol, niacin, vitamin B-6, folate (UL applied only to synthetic folic acid), and vitamins C and D (59–62). Nutrient adequacy was determined for each nutrient in relation to its age/sex-specific recommended intake (0: inadequate; 1: adequate). The NAS (range: 0–22) was computed as the sum of 22 nutrient components, with a higher score reflecting better overall nutrient adequacy, similar to a previous study (69).

Cognitive assessment

A battery of 6 cognitive tests was used.

Mini Mental State Examination. Administered in the BLSA since the mid 1980s, the Mini Mental State Examination (MMSE) is a brief

⁹ Abbreviations used: AI, adequate intake; BLSA, Baltimore Longitudinal Study of Aging; BVRT, Benton Visual Retention Test; CVLT, California Verbal Learning Test; DS-B, digits span-backward; DS-F, digits span-forward; MMSE, Mini Mental State Examination; NAS, nutrient adequacy score; Trails A, Trail Making Test, part A; Trails B, Trail Making Test, part B; UL, upper limit; VFT-C, Verbal Fluency Test-Categorical; VFT-L, Verbal Fluency Test-Letter.

mental status test measuring orientation, concentration, immediate and delayed memory, language, and constructional praxis (70). Scores range from 0 to 30, with higher scores indicating better cognitive performance.

BVRT. The BVRT is a test of short-term visual memory and constructional abilities (71). Administration A has been used in the BLSA since 1960, with a modified error scoring system, based on the BVRT manual scoring, such that higher scores indicate poorer visual memory.

California Verbal Learning Test. Administered in the BLSA since 1993, the California Verbal Learning Test (CVLT) is a 16-item shopping list measuring verbal learning and memory. The variables of interest in this study were List A sum across 5 learning trials and long-delay free recall. Scores ranged from 0 to 80 for List A sum and 0 to 16 for long-delay free recall. Higher scores indicate better verbal memory (72).

Verbal Fluency Tests. Administered in the BLSA since the mid 1980s, the Verbal Fluency Test includes the letter (F, A, S) assessment measuring phonemic fluency (VFT-L) (73,74) and the categorical (fruits, animals, vegetables) assessment measuring semantic fluency (VFT-C) (75). Participants were required to generate as many words as possible for 60 s, starting with either a specific letter or category. Higher scores indicate better verbal fluency, with the total number of words, minus intrusions and perseverations, analyzed for each test.

Trail Making Tests. Trail Making Tests A and B are tests of attention (Trails A) and executive functioning (Trails B), specifically cognitive control and visuo-motor scanning (76). Participants corrected incident errors by returning to their last correct response and continuing from there. The stopwatch recorded the time while corrections were made. Scores reflected time to completion (in seconds) separately for Trails A and B. Higher scores indicate poorer performance.

Digits Span Forward and Backward. The Wechsler Adult Intelligence Scale-Revised, digits span-forward (DS-F) and digits span-backward (DS-B) (77), assesses attention and working memory, respectively. DS-F involves orally presenting a series of single-digit numbers at increasing digit span lengths for participants to repeat in the same order. The numbers' span length ranges from 3 to 9 digits. Two trials at each span are presented. The test is discontinued when participants incorrectly repeat both trials at a specified span. DS-B is similar to DS-F, except that participants repeat a series of increasingly longer spans of single digit numbers in reverse order. The numbers' span length ranges from 2 to 8 digits. The total score for both DS-F and DS-B is 14.

In sum, most cognitive test scores' direction was "better performance with a higher score"; the reverse was true for the BVRT and Trails A and B.

Covariates

Potentially confounding covariates were Age_{base}, Year_{base}, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, and other ethnicity), education (y), smoking_{base} ("never," "former", or "current smoker"), and measured baseline BMI [BMI_{base}, weight/(height)² in kg/m²]. First-visit measures (i.e., visit 1 of the BLSA) were also considered for the descriptive part of the analysis.

Statistical methods

Analyses were performed using Stata version 11.0 (78). Participant characteristics (fixed and at first-visit) were described and compared by data availability and by sex using a 1-factor ANOVA, *t* test, and χ^2 test.

Mixed-effects linear regression models were used to examine associations of baseline caffeine and alcohol intakes and NAS with baseline cognitive performance (cross-sectional effect) and their relations with cognitive change over time (longitudinal effect), controlling for Age_{base}, sex, and other "baseline" or fixed covariates, including race/ethnicity, education, baseline smoking status, and baseline BMI. These models, which we term time-interval, mixed-effects regression models, were adapted from a previously published study that described the methodology in detail (79). Time elapsed (y) was measured from Age_{base} (per cognitive test).

Equations 1.1–1.4

Multilevel models vs. composite models

$$\begin{aligned} Y_{ij} &= \pi_{0i} + \pi_{1i} \text{Time}_{ij} + \epsilon_{ij} \\ \pi_{0i} &= \gamma_{00} + \sum_{a=1}^3 \gamma_{0a} X_{aij} + \sum_{k=1}^l \gamma_{0k} Z_{ik} + \zeta_{0i} \\ \pi_{1i} &= \gamma_{10} + \sum_{a=1}^3 \gamma_{1a} X_{aij} + \sum_{m=1}^n \gamma_{1m} Z_{im} + \zeta_{1i} \\ Y_{ij} &= \gamma_{00} + \sum_{a=1}^3 \gamma_{0a} X_{aij} + \sum_{k=1}^l \gamma_{0k} Z_{ik} \\ &\quad + \gamma_{10} \text{Time}_{ij} + \sum_{a=1}^3 \gamma_{1a} X_{aij} \text{Time}_{ij} \\ &\quad + \sum_{m=1}^n \gamma_{1m} Z_{im} \text{Time}_{ij} \\ &\quad + (\zeta_{0i} + \zeta_{1i} \text{Time}_{ij} + \epsilon_{ij}) \end{aligned} \quad \text{Eq. 1.1 – 1.4}$$

where Y_{ij} represents cognitive test scores for individual "i" and visit "j"; π_{0i} , level-1 intercept for individual i; π_{1i} , level-1 slope for individual i; γ_{00} , level-2 intercept of the random intercept π_{0i} ; γ_{10} , level-2 intercept of the slope π_{1i} ; and Z_{ik} , a vector of individual-level fixed baseline covariates (including Age_{base}) predicting level-1 intercepts (π_{0i}) and level-1 slopes (π_{1i}). Among Z_{ik} covariates, education (y) was centered at 16y (approximate mean for BLSA), BMI at 25 kg/m², total energy intake at 2000 kcal/d, Age_{base} at 50 y, and Year_{base} at 2000. X_{ija} are the main predictor variables: "caffeine centered at 0 mg/d," "NAS centered at 10," and "alcohol centered at 10 g/d"; ζ_{0i} and ζ_{1i} are level-2 disturbances; and ϵ_{ij} is the within-person level-1 disturbance. In a sensitivity analysis, alcohol was entered as categorical variable and interacted as such with time elapsed: 0 = 14 to 28 g/d, 1 = <14 g/d, 2 = >28 g/d. Thus, having lower and higher than moderate consumption was compared with moderate consumption.

Estimated parameters with SE and *P* values reflected rate of cognitive change over time (γ_{10}), the effects of caffeine and alcohol intakes and NAS on baseline cognitive performance (time = 0) (γ_{01} , γ_{02} , and γ_{03} ; γ_{031} and γ_{032} for categorical alcohol), and effects of caffeine and alcohol intakes and NAS on annual rate of cognitive change over time (γ_{11} , γ_{12} , and γ_{13} ; γ_{131} and γ_{132} for categorical alcohol). Analysis was presented for the overall sample and was further stratified by sex and Age_{base} (<70 y vs. ≥ 70 y).

The effect modification by sex and Age_{base} was tested by including additional interaction terms in the "overall population" model (e.g., Age_{base} × caffeine and Age_{base} × caffeine × time, separately). We used a 2-stage Heckman selection model adjusting for bias because of nonrandom participant selection for final analyses (80,81).

We further estimated cognitive test scores and plotted their predicted means against time, with Age_{base} set alternatively at 50 y and 70 y. Each exposure was examined separately controlling for the other covariates. Caffeine intake was alternatively set at 0 mg/d vs. 300 mg/d; alcohol intake at 10 g/d vs. 50 g/d; and NAS at 5 vs. 15. Thus, cognitive performance trajectories for the hypothetical population with set covariate distribution was examined over time and compared by exposure level to illustrate direction and magnitude of fixed effects γ_{0a} and γ_{1a} .

Type I error was set at 0.05 for each of the 3 exposure variable-related hypotheses. Adjustment for multiple testing reduced the type I error to 0.05/3 = 0.017, and thus only *P* values <0.017 were considered statistically significant. However, type I error for 3-way interaction terms was set to 0.10 because of reduced power to detect significant associations (82).

Results

As shown in Table 1, compared with men, women were generally older and had more ethnic diversity, performed better on the MMSE, and had lower prevalence of current smoking. The distribution of study characteristics by sex and data completeness is presented in Supplemental Table 1 and Supplemental Figure 1.

Several key findings emerged from the time-interval, mixed-effects regression models. For most cognitive tests, younger participants at baseline performed better than older participants

TABLE 1 Baseline characteristics of participants included in the final analysis with the MMSE (global cognitive function) and dietary data available, stratified by sex, BLSA, 1962–2008¹

	<i>n</i> ²	<i>n</i> ³	Values
Men, <i>n</i>	415		
First-visit age, <i>y</i>	407		66.8 ± 13.9*
Race/ethnicity	407		
Non-Hispanic white	347		85.3*
Non-Hispanic black	50		12.3
Other	10		2.5
First-visit education, <i>y</i>	378		16.9 ± 2.7*
First-visit smoking	366		
Never smoker	120		32.8*
Former smoker	184		50.3
Current smoker	62		16.9
First-visit BMI, <i>kg/m</i> ²	393		26.3 ± 3.7
Energy intake, <i>kcal/d</i>		1458	2156 ± 565*
NAS		1458	11.10 ± 3.02*
>10 (above median), %		1458	56.5*
Caffeine, <i>mg/d</i>		1458	127.4 ± 211.0
100–300 <i>mg/d</i> (1–3 cups of coffee), %		1458	29.8*
Alcohol, <i>g/d</i>		1458	11.5 ± 0.4*
14–28 <i>g/d</i> (1–2 drinks), %		1458	18.2
MMSE total score		753	28.4 ± 2.2*
Women, <i>n</i>	312		
First-visit age, <i>y</i>	309		69.8 ± 12.1
Race/ethnicity	311		
Non-Hispanic white	234		75.2
Non-Hispanic black	62		19.9
Other	15		4.8
First-visit education, <i>y</i>	282		15.8 ± 2.6
First-visit smoking	251		
Never smoker	102		40.6
Former smoker	124		49.4
Current smoker	25		10.0
First-visit BMI, <i>kg/m</i> ²	301		25.9 ± 4.6
Energy intake, <i>kcal/d</i>		978	1697 ± 427
NAS		978	12.87 ± 3.16
>10 (above median), %		978	77.4
Caffeine, <i>mg/d</i>		978	138.7 ± 194.0
100–300 <i>mg/d</i> (1–3 cups of coffee), %		978	40.8
Alcohol, <i>g/d</i>		978	5.8 ± 0.3
14–28 <i>g/d</i> (1–2 drinks), %		978	9.8
MMSE total score		680	28.8 ± 2.1

¹ Values are means ± SDs or percentages. **P* < 0.05 for null hypothesis of no sex difference between means or proportions using the *t* test and χ^2 test, respectively, within each of the samples. BLSA, Baltimore Longitudinal Study of Aging; MMSE, Mini Mental State Examination; NAS, nutrient adequacy score.

² Number of participants in the analysis.

³ Total number of visits included in the analysis.

(γ_{Age} in the direction of poorer performance with higher age, **Table 2**). For a few tests, there was also an appreciable decline over time (γ_{10} in the direction of decline), controlling for Age_{base} , whereas for others there was a learning effect over time that was reduced or tapered off with increasing age (γ_{10} in the direction of improvement over time, *P* < 0.05, but with a $\gamma_{\text{Age} \times \text{Time}}$ in the direction of tapered-off learning and an eventual time-related decline at higher Age_{base} values).

Importantly, when examining associations of caffeine intake, NAS, and alcohol intake with cognitive performance at baseline (**Tables 2 and 3**; γ_{01} , γ_{02} , and γ_{03}), and change over time (γ_{11} , γ_{12} , and γ_{13}), there was apparent effect modification by Age_{base}

(<70 *y* vs. ≥ 70 *y*) and, occasionally, by sex. When testing interaction terms, sex and Age_{base} differentials in diet's association with cognition (cross-sectional and longitudinal) were significant for some but not all associations (*P* < 0.10).

Among key findings, caffeine intake was associated with better global cognitive function (MMSE) at baseline for those ≥ 70 *y* (*P* = 0.008), independently of potential confounding covariates. Second, the NAS was associated with better baseline performance on the MMSE overall (*P* = 0.004), in women (*P* = 0.003), and in those <70 *y* (*P* = 0.003). When Age_{base} was ≥ 70 *y*, the NAS was associated with better baseline performance on the CVLT-List A and CVLT-Delayed Recall. Similarly, the NAS was associated with slower decline or improvement over time on the DS-F test among women. Finally, alcohol intake was associated with faster decline or slower improvement on the MMSE (*P* = 0.008) and on the VFT-L test (*P* = 0.001) when Age_{base} was <70 *y*. However, when Age_{base} was ≥ 70 *y*, alcohol was related to better baseline performance on the DS-F and DS-B (**Tables 2 and 3**). There were no significant associations between any of the continuous dietary exposures and Trails A or B (**Supplemental Table 2**).

Our key findings are illustrated visually in **Supplemental Figure 2** if a population with fixed characteristics (listed in the footnote of the supplemental figures) was followed up from ages 50 *y* and 70 *y* for a period of ~9 *y* and was alternatively exposed to 2 different levels of each dietary exposure, keeping the other exposures and covariates constant.

In a sensitivity analysis (**Supplemental Table 3**), categorical alcohol intake was entered into time-interval, mixed-effects regression models. Compared with 14 to 28 *g/d* consumption, individuals with >28 *g/d* of alcohol intake had faster decline or slower improvement on the MMSE, particularly among women and in the older group ($\text{Age}_{\text{base}} \geq 70$ *y*, $\gamma_{132} = -0.59 \pm 0.22$, *P* = 0.009). This finding is at slight odds from our previous results with continuous alcohol intake where we found this relation in the younger group. Moreover, consuming <14 *g/d* was associated with slower decline or faster improvement in the VFT-L compared with a moderate intake of 14 to 28 *g/d* ($\text{Age}_{\text{base}} < 70$ *y*, $\gamma_{131} = +0.24 \pm 0.07$, *P* < 0.001). A similar pattern was noted also in the younger group for both Trails A ($\text{Age}_{\text{base}} < 70$ *y*, $\gamma_{131} = -1.40 \pm 0.53$, *P* = 0.009) and Trails B (<70 *y* at baseline, $\gamma_{131} = -3.41 \pm 1.23$, *P* = 0.006). Overall, among men, and for $\text{Age}_{\text{base}} \geq 70$ *y*, lower alcohol intake compared with moderate consumption was associated with poorer performance on the DS-B (overall, $\gamma_{031} = -0.76 \pm 0.28$, *P* = 0.008). However, and particularly among men, lower alcohol intake compared with moderate alcohol consumption was linked to slower decline on that test over time (men, $\gamma_{131} = +0.19 \pm 0.08$, *P* = 0.014).

Discussion

We examined cross-sectional and longitudinal relations of caffeine and alcohol intakes and nutrient adequacy with cognitive performance in the BLSA. Outcomes included 10 cognitive test scores spanning the domains of global cognition, verbal memory, visual memory/visuo-constructive ability, verbal fluency, attention, working memory, and executive function. Caffeine and alcohol intakes and the NAS were estimated from 7-d food diaries. Using time-interval, mixed-effect regression models, with baseline defined as the earliest available visit with dietary and cognitive data, caffeine intake was associated with better baseline global cognition (MMSE), particularly when baseline age was ≥ 70 *y*, independently of key potential confounders.

TABLE 2 Analysis of baseline caffeine intake (continuous, 100 mg/d), alcohol intake (g/d), and the NAS, and longitudinal change in cognitive performance (total and sex-stratified), time-interval mixed-effects linear regression analysis, BLSA, 1962–2008¹

	Total: model 1		Men: model 2		Women: model 3	
	$\gamma \pm \text{SEE}^2$	P^3	$\gamma \pm \text{SEE}^2$	P^3	$\gamma \pm \text{SEE}^2$	P^3
MMSE, total score ⁴	<i>n</i> = 555	<i>n'</i> = 1102	<i>n</i> = 328	<i>n'</i> = 595	<i>n</i> = 227	<i>n'</i> = 507
Fixed effects						
Intercept (γ_{00} for π_{0i})	+29.48 ± 0.27	<0.001	+29.76 ± 0.39	<0.001	+29.22 ± 0.36	<0.001
Time (γ_{10} for π_{1i})	+0.135 ± 0.106	0.201	+0.086 ± 0.148	0.559	+0.191 ± 0.182	0.294
Age _{base}	-0.052 ± 0.009	<0.001	-0.067 ± 0.013	<0.001	-0.032 ± 0.011	0.004
Age _{base} × time	-0.009 ± 0.004	0.014	-0.005 ± 0.006	0.386	-0.011 ± 0.006	0.044
Gender (women vs. men)	+0.182 ± 0.159	0.253	—	—	—	—
Gender × time	+0.020 ± 0.059	0.733	—	—	—	—
Caffeine (γ_{01} for π_{0i})	+0.094 ± 0.047	0.043	+0.001 ± 0.001	0.099	+0.060 ± 0.072	0.407
Caffeine × time (γ_{11} for π_{1i})	-0.004 ± 0.016	0.795	-0.000 ± 0.000	0.322	+0.008 ± 0.032	0.813
NAS (γ_{02} for π_{0i})	+0.072 ± 0.025	0.004	+0.058 ± 0.034	0.094	+0.104 ± 0.036	0.003
NAS × time (γ_{12} for π_{1i})	-0.004 ± 0.009	0.624	+0.003 ± 0.012	0.838	-0.013 ± 0.016	0.405
Alcohol (γ_{03} for π_{0i})	+0.006 ± 0.006	0.295	+0.008 ± 0.006	0.198*	-0.008 ± 0.011	0.432
Alcohol × time (γ_{13} for π_{1i})	-0.003 ± 0.002	0.095	-0.001 ± 0.002	0.692*	-0.008 ± 0.005	0.132
Random effects						
Level 1 residuals (R_{ij})	+0.79 ± 0.03	<0.001	+0.93 ± 0.05	<0.001	+0.622 ± 0.034	<0.001
Level 2 residuals						
Intercept (ξ_{0i})	+1.38 ± 0.05	<0.001	+1.36 ± 0.08	<0.001	+1.305 ± 0.034	<0.001
Linear slope (ξ_{1i})	+0.32 ± 0.02	<0.001	+0.30 ± 0.03	<0.001	+0.389 ± 0.037	<0.001
CVLT-List A, total score	<i>n</i> = 568	<i>n'</i> = 1111	<i>n</i> = 296	<i>n'</i> = 559	<i>n</i> = 272	<i>n'</i> = 552
Intercept (γ_{00} for π_{0i})	+58.32 ± 1.29	<0.001	+59.57 ± 1.85	<0.001	+63.18 ± 1.71	<0.001
Time (γ_{10} for π_{1i})	+0.060 ± 0.393	0.878	+0.191 ± 0.535	0.720	-0.175 ± 0.52	0.751
Age _{base}	-0.424 ± 0.036	<0.001	-0.472 ± 0.058	<0.001	-0.380 ± 0.046	<0.001
Age _{base} × time	-0.010 ± 0.010	0.317	-0.004 ± 0.015	0.789	-0.008 ± 0.014	0.554
Gender (women vs. men)	+6.547 ± 0.957	<0.001	—	—	—	—
Gender × time	-0.269 ± 0.249	0.280	—	—	—	—
Caffeine (γ_{01} for π_{0i})	+0.090 ± 0.276	0.745	-0.204 ± 0.348	0.559	+0.587 ± 0.480	0.222
Caffeine × time (γ_{11} for π_{1i})	+0.004 ± 0.064	0.944	-0.063 ± 0.078	0.419	+0.076 ± 0.109	0.484
NAS (γ_{02} for π_{0i})	+0.291 ± 0.152	0.055	+0.365 ± 0.231	0.114	+0.282 ± 0.203	0.164
NAS × time (γ_{12} for π_{1i})	+0.086 ± 0.040	0.031	+0.116 ± 0.056	0.040	+0.081 ± 0.059	0.169
Alcohol (γ_{03} for π_{0i})	+0.053 ± 0.031	0.088	+0.050 ± 0.038	0.191	+0.059 ± 0.057	0.295
Alcohol × time (γ_{13} for π_{1i})	-0.008 ± 0.007	0.208	-0.007 ± 0.007	0.298*	+0.016 ± 0.017	0.351
CVLT-delayed recall, total score	<i>n</i> = 568	<i>n'</i> = 1111	<i>n</i> = 296	<i>n'</i> = 559	<i>n</i> = 272	<i>n'</i> = 552
Intercept (γ_{00} for π_{0i})	+12.52 ± 0.40	<0.001	+12.94 ± 0.58	<0.001	+13.47 ± 0.52	<0.001
Time (γ_{10} for π_{1i})	-0.021 ± 0.113	0.850	+0.008 ± 0.159	0.959	-0.072 ± 0.151	0.631
Age _{base}	-0.112 ± 0.011	<0.001	-0.139 ± 0.018	<0.001	-0.089 ± 0.014	<0.001
Age _{base} × time	-0.004 ± 0.003	0.157	-0.004 ± 0.004	0.376	-0.003 ± 0.004	0.502
Gender (women vs. men)	+1.281 ± 0.299	<0.001	—	—	—	—
Gender × time	-0.024 ± 0.071	0.738	—	—	—	—
Caffeine (γ_{01} for π_{0i})	+0.015 ± 0.086	0.858	+0.006 ± 0.110	0.953	-0.017 ± 0.146	0.909
Caffeine × time (γ_{11} for π_{1i})	-0.083 ± 0.018	0.964	-0.033 ± 0.023	0.148*	+0.042 ± 0.030	0.157
NAS (γ_{02} for π_{0i})	+0.102 ± 0.047	0.030	+0.131 ± 0.073	0.071	+0.092 ± 0.062	0.140
NAS × time (γ_{12} for π_{1i})	+0.017 ± 0.011	0.131	+0.029 ± 0.017	0.081	+0.014 ± 0.016	0.373
Alcohol (γ_{03} for π_{0i})	+0.013 ± 0.010	0.174	+0.013 ± 0.012	0.550	+0.012 ± 0.017	0.477
Alcohol × time (γ_{13} for π_{1i})	-0.001 ± 0.002	0.498	-0.001 ± 0.002	0.550	+0.004 ± 0.005	0.366
BVRT, total errors	<i>n</i> = 1005	<i>n'</i> = 1975	<i>n</i> = 620	<i>n'</i> = 1152	<i>n</i> = 385	<i>n'</i> = 822
Intercept (γ_{00} for π_{0i})	+3.68 ± 0.31	<0.001	+4.03 ± 0.39	<0.001	+3.49 ± 0.43	<0.001
Time (γ_{10} for π_{1i})	+0.051 ± 0.048	0.288	+0.051 ± 0.058	0.384	-0.072 ± 0.082	0.377
Age _{base}	+0.112 ± 0.006	<0.001	+0.110 ± 0.008	<0.001	+0.111 ± 0.010	<0.001
Age _{base} × time	+0.005 ± 0.001	<0.001	+0.004 ± 0.001	<0.001	+0.005 ± 0.002	0.004
Gender (women vs. men)	-0.005 ± 0.244	0.985	—	—	—	—
Gender × time	-0.054 ± 0.035	0.128	—	—	—	—
Caffeine (γ_{01} for π_{0i})	-0.157 ± 0.070	0.024	-0.181 ± 0.092	0.050	-0.164 ± 0.112	0.144
Caffeine × time (γ_{11} for π_{1i})	+0.012 ± 0.005	0.031	+0.008 ± 0.012	0.507	+0.011 ± 0.007	0.138
NAS (γ_{02} for π_{0i})	-0.065 ± 0.037	0.076	-0.052 ± 0.051	0.311	-0.090 ± 0.054	0.099
NAS × time (γ_{12} for π_{1i})	-0.001 ± 0.005	0.878	+0.002 ± 0.007	0.795	-0.002 ± 0.008	0.776
Alcohol (γ_{03} for π_{0i})	-0.007 ± 0.007	0.307	-0.001 ± 0.007	0.933	-0.020 ± 0.016	0.220
Alcohol × time (γ_{13} for π_{1i})	-0.000 ± 0.001	0.851	-0.000 ± 0.001	0.539	+0.001 ± 0.002	0.718

(Continued)

TABLE 2 *Continued*

	Total: model 1		Men: model 2		Women: model 3	
	$\gamma \pm \text{SEE}^2$	P^3	$\gamma \pm \text{SEE}^2$	P^3	$\gamma \pm \text{SEE}^2$	P^3
VFT-C, total score	$n = 602$	$n' = 1236$	$n = 346$	$n' = 655$	$n = 256$	$n' = 581$
Intercept (γ_{00} for π_{0i})	+18.29 \pm 0.47	<0.001	+18.21 \pm 0.65	<0.001	+20.07 \pm 0.70	<0.001
Time (γ_{10} for π_{1i})	+0.167 \pm 0.093	0.073	+0.128 \pm 0.140	0.362	+0.314 \pm 0.138	0.022
Age _{base}	-0.169 \pm 0.015	<0.001	-0.173 \pm 0.022	<0.001	-0.165 \pm 0.023	<0.001
Age _{base} \times time	-0.014 \pm 0.003	<0.001	-0.012 \pm 0.005	0.030	-0.017 \pm 0.004	<0.001
Gender (women vs. men)	-0.341 \pm 0.460	0.458	—	—	—	—
Gender \times time	-0.084 \pm 0.139	0.545	—	—	—	—
Caffeine (γ_{01} for π_{0i})	-0.036 \pm 0.009	0.680	+0.002 \pm 0.108	0.985	-0.001 \pm 0.002	0.481
Caffeine \times time (γ_{11} for π_{1i})	+0.006 \pm 0.014	0.633	-0.003 \pm 0.018	0.871	+0.000 \pm 0.000	0.231
NAS (γ_{02} for π_{0i})	+0.051 \pm 0.047	0.279	+0.052 \pm 0.062	0.410	+0.056 \pm 0.074	0.443
NAS \times time (γ_{12} for π_{1i})	+0.003 \pm 0.008	0.741	+0.001 \pm 0.012	0.907	+0.004 \pm 0.012	0.739
Alcohol (γ_{03} for π_{0i})	+0.012 \pm 0.010	0.257	+0.006 \pm 0.011	0.576	+0.025 \pm 0.023	0.263
Alcohol \times time (γ_{13} for π_{1i})	-0.000 \pm 0.001	0.975	-0.000 \pm 0.002	0.967	+0.003 \pm 0.003	0.352
VFT-L, total score	$n = 601$	$n' = 1233$	$n = 346$	$n' = 645$	$n = 255$	$n' = 577$
Intercept (γ_{00} for π_{0i})	+15.13 \pm 0.60	<0.001	+14.43 \pm 0.87	<0.001	+16.25 \pm 0.84	<0.001
Time (γ_{10} for π_{1i})	+0.239 \pm 0.102	0.020	+0.273 \pm 0.140	0.052	+0.190 \pm 0.174	0.277
Age _{base}	-0.040 \pm 0.019	0.041	-0.019 \pm 0.029	0.515	-0.057 \pm 0.027	0.036
Age _{base} \times time	-0.012 \pm 0.003	0.001	-0.013 \pm 0.005	0.012	-0.012 \pm 0.005	0.026
Gender (women vs. men)	+0.729 \pm 0.387	0.059	—	—	—	—
Gender \times time	-0.001 \pm 0.055	0.987	—	—	—	—
Caffeine (γ_{01} for π_{0i})	+0.028 \pm 0.113	0.980	+0.097 \pm 0.145	0.502*	-0.116 \pm 0.187	0.533
Caffeine \times time (γ_{11} for π_{1i})	-0.023 \pm 0.015	0.121	-0.038 \pm 0.018	0.039	-0.000 \pm 0.000	0.994
NAS (γ_{02} for π_{0i})	-0.051 \pm 0.060	0.393	+0.033 \pm 0.084	0.687	-0.139 \pm 0.088	0.113
NAS \times time (γ_{12} for π_{1i})	+0.001 \pm 0.009	0.891	+0.006 \pm 0.012	0.586	+0.001 \pm 0.015	0.941
Alcohol (γ_{03} for π_{0i})	+0.021 \pm 0.013	0.107	+0.028 \pm 0.015	0.066	-0.006 \pm 0.027	0.827
Alcohol \times time (γ_{13} for π_{1i})	-0.002 \pm 0.002	0.141	-0.002 \pm 0.002	0.294	-0.002 \pm 0.004	0.652
DS-F, total score	$n = 541$	$n' = 1067$	$n = 285$	$n' = 544$	$n = 256$	$n' = 523$
Intercept (γ_{00} for π_{0i})	+9.50 \pm 0.30	<0.001	+10.04 \pm 0.43	<0.001	+8.74 \pm 0.40	<0.001
Time (γ_{10} for π_{1i})	-0.002 \pm 0.060	0.978	+0.015 \pm 0.093	0.869	+0.013 \pm 0.077	0.862
Age _{base}	-0.036 \pm 0.008	<0.001	-0.053 \pm 0.013	<0.001	-0.026 \pm 0.010	0.011
Age _{base} \times time	-0.002 \pm 0.001	0.237	-0.002 \pm 0.002	0.293	-0.001 \pm 0.002	0.588
Gender (women vs. men)	-0.493 \pm 0.215	0.022	—	—	—	—
Gender \times time	+0.012 \pm 0.034	0.729	—	—	—	—
Caffeine (γ_{01} for π_{0i})	-0.039 \pm 0.061	0.519	-0.077 \pm 0.076	0.312	+0.031 \pm 0.106	0.773
Caffeine \times time (γ_{11} for π_{1i})	-0.010 \pm 0.009	0.286	-0.005 \pm 0.013	0.706	-0.022 \pm 0.014	0.111
NAS (γ_{02} for π_{0i})	-0.003 \pm 0.035	0.934	-0.002 \pm 0.053	0.975	-0.010 \pm 0.047	0.835
NAS \times time (γ_{12} for π_{1i})	+0.010 \pm 0.006	0.085	+0.001 \pm 0.009	0.988	+0.022 \pm 0.008	0.005
Alcohol (γ_{03} for π_{0i})	+0.015 \pm 0.007	0.036	+0.022 \pm 0.009	0.012	+0.003 \pm 0.013	0.788
Alcohol \times time (γ_{13} for π_{1i})	+0.000 \pm 0.001	0.850	-0.001 \pm 0.001	0.406	+0.003 \pm 0.002	0.156
DS-B, total score	$n = 545$	$n' = 1066$	$n = 284$	$n' = 540$	$n = 261$	$n' = 526$
Intercept (γ_{00} for π_{0i})	+8.90 \pm 0.32	<0.001	+9.08 \pm 0.48	<0.001	+8.57 \pm 0.40	<0.001
Time (γ_{10} for π_{1i})	-0.367 \pm 0.098	<0.001	-0.383 \pm 0.143	0.008	-0.298 \pm 0.132	0.024
Age _{base}	-0.036 \pm 0.009	<0.001	-0.044 \pm 0.015	0.003	-0.032 \pm 0.011	0.002
Age _{base} \times time	+0.006 \pm 0.002	0.008	+0.008 \pm 0.004	0.041	+0.006 \pm 0.003	0.050
Gender (women vs. men)	-0.257 \pm 0.224	0.251	—	—	—	—
Gender \times time	+0.103 \pm 0.057	0.073	—	—	—	—
Caffeine (γ_{01} for π_{0i})	-0.040 \pm 0.064	0.533	-0.068 \pm 0.084	0.418	-0.034 \pm 0.111	0.759
Caffeine \times time (γ_{11} for π_{1i})	-0.008 \pm 0.015	0.576	-0.022 \pm 0.020	0.263	+0.014 \pm 0.024	0.558
NAS (γ_{02} for π_{0i})	-0.051 \pm 0.036	0.160	-0.052 \pm 0.058	0.373	-0.035 \pm 0.047	0.462
NAS \times time (γ_{12} for π_{1i})	+0.003 \pm 0.010	0.742	-0.003 \pm 0.015	0.849	+0.012 \pm 0.013	0.378
Alcohol (γ_{03} for π_{0i})	+0.021 \pm 0.007	0.004	+0.024 \pm 0.009	0.013	+0.018 \pm 0.013	0.171
Alcohol \times time (γ_{13} for π_{1i})	-0.002 \pm 0.002	0.106	-0.003 \pm 0.002	0.078	+0.001 \pm 0.004	0.788

¹ Models were further adjusted for baseline year of intake, race/ethnicity, education (y), baseline smoking status, and baseline BMI. See Materials and Methods for more details on covariate coding and model specifications. Random effects are presented only for the MMSE, for simplicity. * $P < 0.10$ for interaction with gender to test effect modification by gender for each of the 3 predictors' effects (i.e., caffeine intake, alcohol intake, and NAS) on cognitive performance at baseline and cognitive change over time. BLSA, Baltimore Longitudinal Study of Aging; BVRT, Benton Visual Retention Test; CVLT, California Verbal Learning Test; DS-B, digits span-backward; DS-F, digits span-forward; MMSE, Mini Mental State Examination; NAS, nutrient adequacy score; Trails A, Trail Making Test, part A; Trails B, Trail Making Test, part B; VFT-C, Verbal Fluency Test-Categorical; VFT-L, Verbal Fluency Test-Letter.

² n = number of participants in the analysis.

³ n' = total number of visits included in the analysis.

⁴ Cognitive scores were in the direction of higher score indicated better performance with the exception of the BVRT and Trails A and B.

A higher NAS was associated with slower decline or faster improvement on a test of attention (DS-F, for women), and with better baseline performance on immediate and delayed recall for verbal memory (CVLT-List A and DR for participants aged ≥ 70 y at baseline). A higher NAS was also associated with better baseline performance on global cognition overall among women and among participants aged < 70 y at baseline. Alcohol intake, on the other hand, was associated with slower improvement on letter fluency (VFT-L) and global cognition among those aged < 70 y at baseline. Conversely, alcohol intake was associated with better attention (DS-F) and working memory (DS-B) performance, particularly among men and individuals ≥ 70 y at baseline. Some nonlinear associations were found, with moderate alcohol consumption only showing a beneficial effect on baseline DS-B (a measure of working memory), specifically when compared with lower intakes. However, longitudinal associations indicated that alcohol has potentially deleterious effects over time with lower intake being a better choice than moderate intake.

Caffeine and alcohol consumption and the NAS have been associated with cognition in some studies, with mixed findings with respect to the associations' directionality. Although 2 cross-sectional studies found habitual caffeine intake to be linked with better cognitive or long-term memory performance (12,17), 2 others failed to detect an association (19,20). However, using data from the same cohort as in a previous study (12), after a 6-y follow-up no association was found (15). The Longitudinal Lothian Birth Cohort 1936 Study found a potential neuroprotective effect of caffeine intake, but only for coffee (83). Two other longitudinal studies reported such effects of caffeine intake in older women, but not men (9,21). In contrast, inverse J-shaped associations between coffee consumption and 10-y cognitive declines were seen in elderly men, with the least decline occurring for men consuming 3 cups of coffee per day in the Finland, Italy, and the Netherlands Elderly (FINE) cohort (16). However, among cohort studies, the Finnish Twin Cohort Study failed to detect an association after a 28-y follow-up (18). Protective associations between tea consumption, another source of caffeine, and cognitive decline have been demonstrated in Chinese adults (10,11). The results of our study suggest that there might be potential acute beneficial effects of caffeine on global cognition, but not other domains. Despite no sex differences, age differentials were significant whereby the putative beneficial effect on global cognition was more noticeable among older adults aged ≥ 70 y.

Among studies on alcohol intake and cognition (22–51), the Rotterdam Study (36) found that past alcohol consumption was predictive of speed and flexibility in a U-shaped manner, with the best performance among those drinking 1 to 4 glasses per day, particularly women, as was found in other studies (22–35,37–39). However, a linear dose-response relation has also been shown, sometimes with differences by sex (26). One cohort study found that overall, moderate consumption was protective against poor cognitive function, but that the reverse was true among ApoE4⁺ individuals (22). This effect modification was not found in another study (43). Slower memory decline with increased alcohol consumption in men was found in one study, although the opposite relation was found in the case of psychomotor speed among women (44). A cross-sectional positive relation between alcohol intake and memory was noted in one study with both men and women (45). However, heavy alcohol use has also been linked to poorer cognitive outcomes (34,46–48). Finally, few studies found no association between alcohol consumption and cognitive outcomes (49–51). Our

study detected an association between alcohol intake and faster decline in global cognition and letter fluency, as well as attention and executive function, when comparing moderate consumption with lower intake—findings that were not previously replicated. In contrast, an acutely beneficial effect of alcohol in domains of attention and working memory was found in our study, which shows that alcohol can potentially alter cognitive trajectories and cross-sectional performance differently across different domains.

Individual nutrients were shown to affect cognition with the most widely studied ones being n-3 fatty acids (84–86), some B vitamins (87–91), and antioxidants (92–94), all potentially protective against cognitive impairment. Recent studies are beginning to explore how complete dietary patterns may improve cognitive performance (52,54,58) and slow age-related cognitive decline (2,55,57), particularly diets high in fruits, vegetables, nuts, unsaturated fats from fish or olive oil, and whole grain breads/cereals, and low in red and processed meats, high fat dairy, and desserts. Consistent with previous studies, we observed that a nutrient-adequate diet was associated with better performance on global cognition, particularly among those aged < 70 y at baseline.

Among studies examining dietary quality or patterns in relation to cognition (2,52–58), limited research has explored specific cognitive domains (i.e., memory, executive function, attention). Nevertheless, some studies suggest that diets with adequate nutrients are associated with better verbal memory (58) and selective attention (52), which is consistent with our findings of better baseline performance on verbal memory and slower rates of decline on verbal memory and attention. In fact, rodent models suggest that higher intakes of saturated fats and simple carbohydrates are associated with neurophysiologic changes (i.e., insulin signaling, synaptic plasticity, and neurogenesis) in the hippocampus and hippocampal-dependent learning and memory (95).

Our investigation has many strengths, which include the use of a large and long-term prospective cohort study with repeated measurements on dietary intake and a comprehensive battery of cognitive performance, allowing us to assess effects of baseline diet on baseline cognitive performance and on cognitive change over time. Specifically, associations of caffeine and alcohol intake and NAS with cognitive performance over time were examined while controlling for key potential confounders, including each of those 3 exposures and socio-demographic and lifestyle factors. Moreover, use of advanced statistical techniques such as time-interval, mixed-effects linear regression models is a major study strength.

Our findings, however, should be interpreted with caution in light of several limitations. First, the BLSA is an open-cohort study of participants selected as a convenience sample, with continuous recruitment and dropout throughout the follow-up. Second, sample selectivity was noted whereby the final analytic sample differed from the original eligible BLSA cohort. To reduce selection biases, we used a 2-stage Heckman selection model (80). Third, although observation frequency for dietary intakes and cognitive function was adequate, data structure was largely unbalanced, given that first-visit age and duration between visits varied across participants. Consequently, we used time-interval, mixed-effects linear regression models, assuming missingness at random (79). Fourth, other covariates such as cardiovascular risk factors were not considered given their potential mediating effects between diet and cognition. Additionally, chance findings may be caused by the number of hypotheses being tested and the subgroup. However, for the

TABLE 3 Analysis of baseline caffeine intake (continuous, 100 mg/d), alcohol intake (g/d), and the NAS, and longitudinal change in cognitive performance (Age_{base}-stratified), time-interval, mixed-effects linear regression analysis, BLSA, 1962–2008¹

	Baseline age <70 y: model 4		Baseline age ≥70 y: model 5	
	$\gamma \pm \text{SEE}^2$	P^3	$\gamma \pm \text{SEE}^2$	P^3
MMSE, total score ⁴	<i>n</i> = 243	<i>n'</i> = 514	<i>n</i> = 312	<i>n'</i> = 588
Fixed effects				
Intercept (γ_{00} for π_{0i})	+29.07 ± 0.40	<0.001	+29.49 ± 0.62	<0.001
Time (γ_{10} for π_{1i})	+0.164 ± 0.099	0.097	+0.056 ± 0.363	0.878
Age _{base}	+0.001 ± 0.024	0.979	−0.064 ± 0.019	0.001
Age _{base} × time	−0.009 ± 0.005	0.087	−0.007 ± 0.011	0.532
Gender (women vs. men)	−0.149 ± 0.182	0.412	+0.512 ± 0.247	0.032
Gender × time	+0.050 ± 0.037	0.178	+0.017 ± 0.127	0.894
Caffeine (γ_{01} for π_{0i})	−0.004 ± 0.005	0.922*	+0.218 ± 0.083	0.008
Caffeine × time (γ_{11} for π_{1i})	−0.008 ± 0.010	0.377*	+0.016 ± 0.040	0.700
NAS (γ_{02} for π_{0i})	+0.084 ± 0.027	0.002	+0.077 ± 0.040	0.055
NAS × time (γ_{12} for π_{1i})	−0.014 ± 0.006	0.017	−0.007 ± 0.020	0.723
Alcohol (γ_{03} for π_{0i})	+0.005 ± 0.006	0.325	+0.010 ± 0.010	0.288
Alcohol × time (γ_{13} for π_{1i})	−0.002 ± 0.001	0.008	−0.008 ± 0.005	0.139
Random effects				
Level 1 residuals (R_{ij})	+0.80 ± 0.05	<0.001	+0.78 ± 0.04	<0.001
Level 2 residuals				
Intercept (ξ_{0i})	+0.91 ± 0.07	<0.001	+1.61 ± 0.08	<0.001
Linear slope (ξ_{1i})	+0.10 ± 0.02	<0.001	+0.49 ± 0.04	<0.001
CVLT-List A, total score	<i>n</i> = 321	<i>n'</i> = 579	<i>n</i> = 247	<i>n'</i> = 532
Intercept (γ_{00} for π_{0i})	+57.20 ± 1.49	<0.001	+68.51 ± 4.02	<0.001
Time (γ_{10} for π_{1i})	+0.215 ± 0.559	0.701	−0.672 ± 1.061	0.526
Age _{base}	−0.264 ± 0.070	<0.001	−0.747 ± 0.121	<0.001
Age _{base} × time	−0.010 ± 0.020	0.628	+0.006 ± 0.035	0.852
Gender (women vs. men)	+6.768 ± 1.230	<0.001	+7.449 ± 1.552	<0.001
Gender × time	−0.297 ± 0.347	0.392	−0.218 ± 0.457	0.633
Caffeine (γ_{01} for π_{0i})	+0.479 ± 0.323	0.138*	−0.796 ± 0.503	0.113
Caffeine × time (γ_{11} for π_{1i})	+0.005 ± 0.074	0.944	−0.043 ± 0.141	0.763
NAS (γ_{02} for π_{0i})	+0.018 ± 0.183	0.919	+0.630 ± 0.260	0.015
NAS × time (γ_{12} for π_{1i})	+0.128 ± 0.054	0.019	+0.030 ± 0.068	0.654
Alcohol (γ_{03} for π_{0i})	+0.035 ± 0.035	0.311	+0.098 ± 0.061	0.110
Alcohol × time (γ_{13} for π_{1i})	−0.009 ± 0.008	0.221	−0.010 ± 0.017	0.563
CVLT-delayed recall, total score	<i>n</i> = 321	<i>n'</i> = 579	<i>n</i> = 247	<i>n'</i> = 532
Intercept (γ_{00} for π_{0i})	+12.73 ± 0.45	<0.001	+14.97 ± 1.29	<0.001
Time (γ_{10} for π_{1i})	+0.060 ± 0.146	0.682	−0.344 ± 0.331	0.299
Age _{base}	−0.053 ± 0.021	0.011	−0.217 ± 0.039	<0.001
Age _{base} × time	−0.003 ± 0.005	0.521	+0.001 ± 0.011	0.899
Gender (women vs. men)	+1.091 ± 0.369	0.003	+1.921 ± 0.498	<0.001
Gender × time	−0.075 ± 0.090	0.407	−0.004 ± 0.498	0.975
Caffeine (γ_{01} for π_{0i})	+0.053 ± 0.097	0.580	−0.111 ± 0.161	0.490
Caffeine × time (γ_{11} for π_{1i})	+0.009 ± 0.019	0.656*	−0.051 ± 0.044	0.247
NAS (γ_{02} for π_{0i})	+0.005 ± 0.055	0.921*	+0.230 ± 0.083	0.006
NAS × time (γ_{12} for π_{1i})	+0.025 ± 0.014	0.077	+0.014 ± 0.021	0.489
Alcohol (γ_{03} for π_{0i})	+0.010 ± 0.010	0.336	+0.016 ± 0.019	0.410
Alcohol × time (γ_{13} for π_{1i})	−0.002 ± 0.002	0.242	−0.000 ± 0.005	0.967
BVRT, total errors	<i>n</i> = 667	<i>n'</i> = 1354	<i>n</i> = 338	<i>n'</i> = 620
Intercept (γ_{00} for π_{0i})	+3.13 ± 0.34	<0.001	+2.09 ± 1.25	<0.001
Time (γ_{10} for π_{1i})	+0.002 ± 0.041	0.956	+0.745 ± 0.408	0.068
Age _{base}	+0.073 ± 0.008	<0.001	0.183 ± 0.038	<0.001
Age _{base} × time	+0.003 ± 0.001	<0.001	−0.013 ± 0.013	0.292
Gender (women vs. men)	+0.263 ± 0.272	0.336	−0.341 ± 0.460	0.458
Gender × time	−0.043 ± 0.032	0.173	−0.084 ± 0.139	0.545
Caffeine (γ_{01} for π_{0i})	−0.096 ± 0.071	0.179	−0.082 ± 0.161	0.611
Caffeine × time (γ_{11} for π_{1i})	+0.005 ± 0.005	0.278	+0.073 ± 0.046	0.116
NAS (γ_{02} for π_{0i})	−0.073 ± 0.039	0.060	−0.013 ± 0.077	0.866
NAS × time (γ_{12} for π_{1i})	+0.009 ± 0.004	0.044	−0.037 ± 0.021	0.075
Alcohol (γ_{03} for π_{0i})	−0.008 ± 0.007	0.226	−0.004 ± 0.017	0.814
Alcohol × time (γ_{13} for π_{1i})	−0.000 ± 0.000	0.620	+0.003 ± 0.005	0.533

(Continued)

TABLE 3 Continued

	Baseline age <70 y: model 4		Baseline age ≥70 y: model 5	
	$\gamma \pm \text{SEE}^2$	P^3	$\gamma \pm \text{SEE}^2$	P^3
VFT-C, total score	$n = 275$	$n' = 561$	$n = 327$	$n' = 675$
Intercept (γ_{00} for π_{0i})	+17.32 ± 0.68	<0.001	+20.08 ± 1.06	<0.001
Time (γ_{10} for π_{1i})	+0.532 ± 0.177	0.003	+0.152 ± 0.242	0.528
Age _{base}	-0.149 ± 0.038	<0.001	-0.219 ± 0.032	<0.001
Age _{base} × time	-0.034 ± 0.010	<0.001	-0.018 ± 0.008	0.027
Gender (women vs. men)	+1.771 ± 0.458	<0.001	+1.780 ± 0.411	<0.001
Gender × time	+0.087 ± 0.072	0.230	+0.011 ± 0.081	0.896
Caffeine (γ_{01} for π_{0i})	+0.021 ± 0.116	0.853	-0.001 ± 0.001	0.553
Caffeine × time (γ_{11} for π_{1i})	-0.012 ± 0.017	0.462	+0.000 ± 0.000	0.213
NAS (γ_{02} for π_{0i})	+0.086 ± 0.066	0.193	+0.012 ± 0.067	0.857
NAS × time (γ_{12} for π_{1i})	-0.012 ± 0.011	0.260*	+0.019 ± 0.013	0.139
Alcohol (γ_{03} for π_{0i})	+0.002 ± 0.013	0.890	+0.030 ± 0.016	0.059
Alcohol × time (γ_{13} for π_{1i})	-0.001 ± 0.002	0.658	+0.002 ± 0.003	0.627
VFT-L, total score	$n = 275$	$n' = 561$	$n = 326$	$n' = 672$
Intercept (γ_{00} for π_{0i})	+14.74 ± 0.84	<0.001	+16.95 ± 1.44	<0.001
Time (γ_{10} for π_{1i})	+0.700 ± 0.185	<0.001	+0.111 ± 0.259	0.667
Age _{base}	-0.002 ± 0.047	0.973	-0.113 ± 0.044	0.008
Age _{base} × time	-0.036 ± 0.010	<0.001	-0.011 ± 0.009	0.212
Gender (women vs. men)	+0.792 ± 0.555	0.153	+0.896 ± 0.558	0.108
Gender × time	-0.018 ± 0.070	0.792	-0.077 ± 0.086	0.371
Caffeine (γ_{01} for π_{0i})	-0.147 ± 0.142	0.300	+0.241 ± 0.187	0.198
Caffeine × time (γ_{11} for π_{1i})	-0.026 ± 0.018	0.136	-0.016 ± 0.028	0.552
NAS (γ_{02} for π_{0i})	-0.084 ± 0.081	0.298	+0.006 ± 0.090	0.951
NAS × time (γ_{12} for π_{1i})	-0.012 ± 0.011	0.273	+0.013 ± 0.014	0.334
Alcohol (γ_{03} for π_{0i})	+0.027 ± 0.016	0.096	+0.018 ± 0.022	0.420
Alcohol × time (γ_{13} for π_{1i})	-0.006 ± 0.002	0.001	+0.003 ± 0.004	0.348
DS-F, total score	$n = 287$	$n' = 507$	$n = 254$	$n' = 560$
Intercept (γ_{00} for π_{0i})	+9.80 ± 0.39	<0.001	+10.00 ± 0.82	<0.001
Time (γ_{10} for π_{1i})	-0.021 ± 0.098	0.826	-0.095 ± 0.136	0.481
Age _{base}	-0.024 ± 0.018	0.181	-0.068 ± 0.024	0.006
Age _{base} × time	-0.001 ± 0.003	0.708	+0.004 ± 0.004	0.371
Gender (women vs. men)	-0.652 ± 0.313	0.037	-0.227 ± 0.316	0.472
Gender × time	-0.035 ± 0.053	0.514	+0.051 ± 0.048	0.283
Caffeine (γ_{01} for π_{0i})	-0.099 ± 0.080	0.994	+0.053 ± 0.101	0.600
Caffeine × time (γ_{11} for π_{1i})	-0.001 ± 0.001	0.994	-0.030 ± 0.016	0.062
NAS (γ_{02} for π_{0i})	-0.044 ± 0.048	0.357	+0.059 ± 0.053	0.264
NAS × time (γ_{12} for π_{1i})	+0.018 ± 0.009	0.040	-0.001 ± 0.008	0.930
Alcohol (γ_{03} for π_{0i})	+0.009 ± 0.009	0.291	+0.024 ± 0.012	0.045
Alcohol × time (γ_{13} for π_{1i})	-0.000 ± 0.001	0.694	-0.000 ± 0.002	0.962
DS-B, total score	$n = 289$	$n' = 511$	$n = 256$	$n' = 555$
Intercept (γ_{00} for π_{0i})	+8.93 ± 0.42	<0.001	+9.38 ± 0.86	<0.001
Time (γ_{10} for π_{1i})	-0.478 ± 0.148	0.001	-0.186 ± 0.242	0.444
Age _{base}	-0.036 ± 0.020	0.068	-0.054 ± 0.026	0.037
Age _{base} × time	+0.011 ± 0.004	0.018	+0.001 ± 0.008	0.849
Gender (women vs. men)	-0.251 ± 0.336	0.455	-0.213 ± 0.330	0.518
Gender × time	+0.141 ± 0.084	0.093	+0.126 ± 0.089	0.154
Caffeine (γ_{01} for π_{0i})	-0.027 ± 0.086	0.756	-0.052 ± 0.108	0.626
Caffeine × time (γ_{11} for π_{1i})	-0.004 ± 0.017	0.980	-0.030 ± 0.029	0.296
NAS (γ_{02} for π_{0i})	-0.075 ± 0.051	0.138	-0.024 ± 0.056	0.659
NAS × time (γ_{12} for π_{1i})	-0.062 ± 0.013	0.963	+0.06 ± 0.016	0.700
Alcohol (γ_{03} for π_{0i})	+0.015 ± 0.010	0.116	+0.030 ± 0.012	0.015
Alcohol × time (γ_{13} for π_{1i})	-0.002 ± 0.002	0.303	-0.006 ± 0.004	0.121

¹ Models were further adjusted for baseline year of intake, race/ethnicity, education (y), baseline smoking status and baseline BMI. See Materials and Methods for more details on covariate coding and model specifications. Random effects are presented only for the MMSE, for simplicity. * $P < 0.10$ for interaction with baseline age to test effect modification by age for each of the 3 predictors' effects (i.e., caffeine intake, alcohol intake, and NAS) on cognitive performance at baseline and cognitive change over time. BLSA, Baltimore Longitudinal Study of Aging; BVRT, Benton Visual Retention Test; CVLT, California Verbal Learning Test; DS-B, digits span-backward; DS-F, digits span-forward; MMSE, Mini Mental State Examination; NAS, nutrient adequacy score; Trails A, Trail Making Test, part A; Trails B, Trail Making Test, part B; VFT-C, Verbal Fluency Test-Categorical; VFT-L, Verbal Fluency Test-Letter.

² n = number of participants in the analysis.

³ n' = total number of visits included in the analysis.

⁴ Cognitive scores were in the direction of higher score indicated better performance with the exception of the BVRT and Trails A and B.

most part, we considered those hypotheses to be independent, given that cognitive domains included in each test were distinctive. Our analyses adjusted for multiple testing accounting for multiplicity of exposures. Finally, residual confounding and selection bias could explain some positive findings and low power may underlie some negative findings.

In conclusion, associations of caffeine and alcohol intake and nutrient adequacy with longitudinal cognitive performance are mixed in this sample of older adults. Consistent with prior studies, potential beneficial effects were found for some measures, but not others, with moderation by baseline age and sex. Although findings for alcohol consumption were mixed, the findings were generally supportive of the idea that a high-quality diet and higher caffeine intake may benefit cognition acutely and even prevent age-related declines in certain cognitive domains, including global cognition, verbal memory, and attention. Further longitudinal studies conducted on larger samples of adults are needed to determine whether dietary factors individually or in combination are modifiers of cognitive trajectories among adults.

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