British Journal of Nutrition (2018), **119**, 552–558
doi:10.1017/S0007114517003804

Dietary inflammatory index and memory function: population-based national sample of elderly Americans

Emily Frith[1], Nitin Shivappa[2,3], Joshua R. Mann[4], James R. Hébert[2,3], Michael D. Wirth[2,3,5] and Paul D. Loprinzi[1]*

[1]*Physical Activity Epidemiology Laboratory, Exercise Psychology Laboratory, Department of Health, Exercise Science and Recreation Management, University of Mississippi, Oxford, MS 38677, USA*
[2]*Department of Epidemiology and Biostatistics and the Cancer Prevention and Control Program, University of South Carolina, Columbia, SC 29208, USA*
[3]*Connecting Health Innovations, LLC, Columbia, SC 29201, USA*
[4]*Department of Preventive Medicine, School of Medicine and John D. Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS 39216, USA*
[5]*College of Nursing, University of South Carolina, Columbia, SC 29208, USA*

(Submitted 9 October 2017 – Final revision received 21 November 2017 – Accepted 11 December 2017 – First published online 24 January 2018)

Abstract

The objective of this study was to examine the association between dietary inflammatory potential and memory and cognitive functioning among a representative sample of the US older adult population. Cross-sectional data from the 2011–2012 and 2013–2014 National Health and Nutrition Examination Survey were utilised to identify an aggregate sample of adults 60–85 years of age (n 1723). Dietary inflammatory index (DII®) scores were calculated using 24-h dietary recall interviews. Three memory-related assessments were employed, including the Consortium to Establish a Registry for Alzheimer's disease (CERAD) Word Learning subset, the Animal Fluency test and the Digit Symbol Substitution Test (DSST). Inverse associations were observed between DII scores and the different memory parameters. Episodic memory (CERAD) ($b_{adjusted}$ = −0·39; 95 % CI −0·79, 0·00), semantic-based memory (Animal Fluency Test) ($b_{adjusted}$ = −1·18; 95 % CI −2·17, −0·20) and executive function and working-memory (DSST) ($b_{adjusted}$ = −2·80; 95 % CI −5·58, −0·02) performances were lowest among those with the highest mean DII score. Though inverse relationships were observed between DII scores and memory and cognitive functioning, future work is needed to further explore the neurobiological mechanisms underlying the complex relationship between inflammation-related dietary behaviour and memory and cognition.

Key words: Dietary inflammatory index: Cognition: Executive functioning: Neuroscience: Nutrition: Obesity: Population health

Memory is an important constituent of higher-level cognition. Specifically, executive functioning is suggested to mechanistically influence, and be influenced by, numerous dimensions of memory, including episodic, working and semantic memory[1,2]. In terms of short- and long-term memory, episodic memory refers to the memory of an event or an 'episode'. Working memory capacity and executive function share a common underlying executive attention that is strongly predictive of higher-level cognitive function, including episodic memory[3]. Executive function includes subcomponents of cognition, such as cognitive-related inhibition and reasoning. These parameters may help to facilitate basic cognitive functioning required to perform goal-directed behaviours (e.g. inhibiting and filtering distractive stimuli). Further, individuals with enhanced levels of executive function generally have the ability to maintain an appropriate mental state to fulfil a future goal[4], which may include cognitive processes such as planning, filtering competing information, maintaining efforts despite distractions and inhibiting goal-inconsistent responses[5]. Lastly, semantic memory involves retrieval of factual information that is learned over a period of time (e.g. the definition of a word)[6] and is not bound to any specific experience in which the memory was acquired[7]. Evaluation of factors influencing semantic memory is of particular importance as semantic functional MRI (fMRI) activation has been shown to serve as a better predictor of cognitive change when compared with episodic fMRI tasks[8].

Emerging work suggests that obesity is associated with worse memory function. For example, chronic obesity may detrimentally influence memory function through morphological brain changes, insulin resistance, neuroinflammation, TAG metabolism, circulating levels of glucocorticoids and cerebral metabolite concentrations[9]. In addition to obesity, research

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's disease; DII, dietary inflammatory index; DSST, Digit Symbol Substitution Test; NHANES, National Health and Nutrition Examination Survey.

* **Corresponding author:** P. D. Loprinzi, fax +1 662 915 5525, email pdloprin@olemiss.edu

demonstrates that obesity-related diets, such as the 'Western diet' (high in saturated fats and simple sugars), has been shown to correlate with impairments in learning and memory[10–14]. Further, some work suggests that such memory impairments may be diet-induced, as opposed to be driven by changes in adiposity[15]. For example, results from recent animal studies demonstrate that spatial and working memory deficits are observable after only a few days of consuming a Western diet[16]. Human studies also indicate diets high in vegetables, fruit, fish, soya products may benefit cognitive functioning in older individuals[17].

Existing observational work examined dietary inflammatory index (DII®) scores and cognitive function over time. This includes evidence for pro-inflammatory diets to correlate with incident cognitive impairment and dementia among older women[18], as well as middle-aged men and women evaluated 13 years following initial cognitive assessment[19]. Related work[19] has examined the association of DII on semantic memory and working memory, although episodic memory performance was not included as an outcome of interest[19], which is a novel addition of our present study. We evaluated this topic further, by extending the investigation to include a nationally representative sample of US older adults, as this population is susceptible to age-related memory impairment[20]. Thus, the main purpose of this study was to examine the association between DII scores and a test battery of specific memory functions. In addition, to comprehensively evaluate the association between DII and memory, we examined this potential association while considering various memory parameters, including episodic memory, working memory and semantic memory.

Methods

Study design and participants

The National Health and Nutrition Examination Survey (NHANES) is an ongoing survey conducted by the Center for Disease Control and Prevention. NHANES employs a nationally represented sample of U.S. adults evaluated through a multistage, clustered probability design. Participants are initially interviewed in their homes and then, within 1–2 weeks, examined in a mobile examination centre (MEC). Details of the NHANES methodology is available on the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

NHANES procedures were approved by the National Center for Health Statistics institutional review board. Consent was obtained from all participants before data collection. Participant data from the 2011–2012 and 2013–2014 NHANES cycles were utilised, as these are the latest NHANES cycles with memory function data. The NHANES analytic sample included 1723 older adults 60–85 years (only those in this age range were eligible for memory assessment) of age who did not have one or more of the following chronic diseases: congestive heart failure, coronary artery disease, heart attack, stroke or physician-diagnosed diabetes.

Dietary inflammatory index

Dietary intake was assessed using the 24-h dietary recall interviews (24HR) that were validated by the Nutrition Methodology Working Group[21]. A single 24HR was used to calculate DII scores. The details of development of DII are described by Shivappa *et al.*[22]. High sensitivity C-reactive protein (CRP) measurements were used to examine construct validity of the DII in a longitudinal cohort using 24HR and 7-d dietary recalls. Subsequently, the new DII also was validated in four studies among different populations with an extended number of inflammatory biomarkers (e.g. IL, IL-6, high-sensitivity C-reactive protein and TNF-α)[23–27].

The DII consists of forty-five food parameters which include various macro- and micronutrients, flavonoids, spices and food items, each associated with an inflammatory effect score[22]. These forty-five food parameters were based on findings contained in a total of 1943 articles that were reviewed and scored for their associations with these inflammatory biomarkers (CRP, IL-1β, IL-4, IL-6, IL-10 and TNF-α). A global database (food consumption from eleven populations globally) representing global daily intake for each of the forty-five parameters (i.e. foods, nutrients and other food components) was used as standard dietary intake to calculate the DII. A standard mean for each parameter from the representative world database was subtracted from the actual individual exposure and divided by its standard deviation to generate z scores. These z scores were converted to proportions (minimising effects of outliers/right-skewing). This value was then doubled and 1 was subtracted to achieve symmetrical distribution with values centred on 0. The resulting value was then multiplied by the corresponding inflammatory score derived from scoring the 1943 research articles for each food parameter and summed across all food parameters, to obtain the overall DII. To control for the effect of total energy intake, the DII was calculated per 1000 energy content of food consumed, which requires using the energy-standardised version of the world database. For the present study, twenty-six of the forty-five food parameters were available for DII calculation. Previous work indicated that there is no change in predictive ability of the DII in predicting inflammation when fewer food parameters are available (e.g. 26) compared with the full list of forty-five. In fact, rarely, if ever, do datasets have all available food parameters[22]. These foods included carbohydrate, protein, fat, alcohol, fibre, cholesterol, SFA, MUFA, PUFA, niacin, thiamin, riboflavin, vitamin B_{12}, vitamin B_6, Fe, Mg, Zn, Se, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, β-carotene, n-6 and n-3.

Memory function

Several memory function assessments (episodic, semantic, and working memory/executive function) were employed, including the Consortium to Establish a Registry for Alzheimer's disease[28] (CERAD) Word Learning subset, the Animal Fluency test and the Digit Symbol Substitution Test (DSST).

The CERAD Word Learning subset has been used in several major epidemiological studies with diverse racial and cultural communities[29–32]. This test specifically assesses episodic memory and consists of three learning trials, along with a delay trial (i.e. fourth trial). For the learning trials, participants read aloud ten unrelated words, one at a time, as they are presented on a computer screen. Following the tenth word, participants recalled as

British Journal of Nutrition

many words as possible. The order of the words changed across the three trials. The delayed trial occurred approximately 10 min after trial 1. The maximum score for each trial is 10.

The Animal Fluency test also has been employed in various epidemiologic cohorts[33–37], assessing verbal fluency[38] and semantic-based memory function. In this task, participants are asked to name as many animals as possible in 1 min. One point was given for each named animal.

The DSST is a component of the Wechsler Adult Intelligence Test[39], and has been used in large epidemiological and clinical studies[40–42]. The DSST relies on processing speed, sustained attention and working memory, and is frequently used as a sensitive measure of frontal lobe executive function[43,44]. The DSST was assessed using a paper-and-pencil format. At the top of the paper was a key containing nine numbers paired with symbols. Participants had two minutes to copy the corresponding symbols in 133 boxes that adjoin the numbers. A score was given for each correct match, with maximum score of 133.

Statistical analysis and covariates

Analyses (Stata®, version 12) accounted for the complex survey design employed in NHANES by utilising sample weights, primary sampling units and strata via the Taylor series (linearisation) method. Sample weights were re-weighted to account for the use of combined NHANES cycles. This was done by multiplying the 2-year cycles by 0·5. Information on the use of sample weights to generate population weighted estimates is available elsewhere[50].

Multivariable linear regression analyses were fit. Analytical assumptions of linear regression were checked and confirmed not to be violated. Models were computed separately for each memory outcome. In each model, DII was categorised into quartiles (lowest quartile as referent; see Table 1 for the mean DII values across the quartiles), with covariates including: age (years; continuous), sex (male/female), race-ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black and other), measured BMI (kg/m^2; continuous), self-reported smoking status (never, former, current), self-reported average hours of sleep each night (h/night; continuous), self-reported engagement in leisure-time moderate-to-vigorous physical activity (min/week) assessed from the Global Physical Activity Questionnaire[45,46], and Patient Health Questionnaire (PHQ-9) assessed depression symptomology (range = 0–27; continuous). Statistical significance was established as a nominal α of 0·05.

Results

Table 1 displays the demographic characteristics of the study variables. Participants, on average, were 68·4 years, with the sample similarly distributed across sex (58 % female). Participants with a higher DII (i.e. 4th quartile) were more likely to be male, be a smoker, had a higher BMI score, and engaged in less physical activity.

In an adjusted model, and when DII was expressed as a continuous variable, DII was not statistically significantly associated with trial 1 ($\beta = -0{\cdot}02$; 95 % CI −0·09, 0·03), trial 3 ($\beta = -0{\cdot}01$; 95 % CI −0·07, 0·05) or the delay trial ($\beta = -0{\cdot}06$; 95 % CI −0·15, 0·01) of the CERAD, but was significantly associated with Trial 2 of the CERAD ($\beta = -0{\cdot}08$; 95 % CI −0·13, −0·01), the Animal Fluency test ($\beta = -0{\cdot}24$; 95 % CI −0·42, −0·06) and the DSST ($\beta = -0{\cdot}64$; 95 % CI −1·16, −0·13).

Table 2 displays the regression results examining the association between DII scores (categorised into quartiles) and

Table 1. Weighed characteristics of the study variables (*n* 1723), National Health and Nutrition Examination Survey, 2011–2014 (Mean values with their standard errors)

	Point estimate									
	Entire sample		1st quartile		2nd quartile		3rd quartile		4th quartile	
Variables	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age (years)	68·4	0·2	69·3	0·4	68·7	0·3	67·5	0·4	68·2	0·5
Sex (% female)	58·4		67·4		57·6		56·2		51·9	
Race-ethnicity (% non-Hispanic white)	81·8		82·6		81·9		81·4		81·4	
Smoking status (%)										
Every day	8·2		2·9		5·9		8·3		15·3	
Some days	1·3		0·3		1·8		0·8		2·2	
Former smoker	37·1		40·7		38·1		35·4		33·8	
Never smoker	53·6		55·9		54·0		55·3		48·5	
BMI (kg/m^2)	28·3	0·2	27·1	0·2	28·3	0·3	28·8	0·4	28·9	0·3
Sleep (h/night)	7·2	0·03	7·2	0·1	7·1	0·1	7·2	0·1	7·1	0·1
Depression (PHQ-9)	2·4	0·1	2·3	0·2	2·1	0·1	2·2	0·1	2·8	0·2
Moderate-to-vigorous physical activity (min/week)	138·1	8·7	170·9	15·8	151·1	16·5	128·8	15·2	98·4	10·6
Dietary inflammatory index	−0·25	0·07	−2·79	0·05	−0·78	0·02	0·56	0·02	2·21	0·03
CERAD word learning										
Trial 1	5·2	0·1	5·2	0·1	5·1	0·1	5·3	0·1	5·0	0·1
Trial 2	7·2	0·1	7·3	0·1	7·2	0·1	7·2	0·1	6·9	0·1
Trial 3	8·0	0·1	7·9	0·1	8·0	0·1	7·9	0·1	7·9	0·1
Delay trial	6·6	0·1	6·7	0·1	6·5	0·2	6·6	0·1	6·3	0·1
Animal fluency (number of animals)	18·9	0·2	19·4	0·4	19·1	0·3	18·7	0·3	18·1	0·3
Digit symbol substitution test	55·9	0·6	57·2	1·1	56·4	1·1	56·1	1·2	53·3	1·0

PHQ-9, Patient Health Questionnaire; CERAD, Consortium to Establish a Registry for Alzheimer's disease.

British Journal of Nutrition

Table 2. Regression results examining association between dietary inflammatory index (DII) and memory function (*n* 1723), National Health and Nutrition Examination Survey, 2011–2014*
(Regression coefficients (*b*) and 95 % confidence intervals)

	Unadjusted		Adjusted	
CERAD word learning	*b*	95 % CI	*b*	95 % CI
Trial 1				
DII Q2 *v.* Q1	−0·03	−0·34, 0·27	−0·03	−0·30, 0·24
DII Q3 *v.* Q1	0·09	−0·26, 0·44	0·01	−0·26, 0·29
DII Q4 *v.* Q1	−0·16	−0·50, 0·18	−0·11	−0·44, 0·21
Trial 2				
DII Q2 *v.* Q1	−0·10	−0·42, 0·20	−0·09	−0·37, 0·17
DII Q3 *v.* Q1	−0·08	−0·42, 0·25	−0·16	−0·43, 0·10
DII Q4 *v.* Q1	−0·34†	−0·67, −0·01	−0·30	−0·66, 0·05
Trial 3				
DII Q2 *v.* Q1	0·16	−0·20, 0·54	0·18	−0·18, 0·55
DII Q3 *v.* Q1	0·01	−0·31, 0·34	−0·04	−0·32, 0·23
DII Q4 *v.* Q1	0·03	−0·36, 0·42	0·07	−0·32, 0·46
Sum of trials 1–3				
DII Q2 *v.* Q1	0·01	−0·88, 0·92	0·05	−0·76, 0·88
DII Q3 *v.* Q1	0·02	−0·87, 0·92	−0·19	−0·87, 0·48
DII Q4 *v.* Q1	−0·47	−1·40, 0·46	−0·34	−1·28, 0·59
Delay trial				
DII Q2 *v.* Q1	−0·17	−0·65, 0·29	−0·18	−0·59, 0·22
DII Q3 *v.* Q1	−0·02	−0·43, 0·39	−0·16	−0·53, 0·20
DII Q4 v. Q1	−0·39†	−0·76, −0·03	−0·39†	−0·79, 0·00
Animal Fluency				
DII Q2 *v.* Q1	−0·23	−1·36, 0·90	−0·33	−1·21, 0·54
DII Q3 *v.* Q1	−0·66	−1·68, 0·35	−1·00†	−1·89, −0·12
DII Q4 *v.* Q1	−1·22†	−2·34, −0·10	−1·18†	−2·17, −0·20
DSST				
DII Q2 *v.* Q1	−0·80	−3·88, 2·27	−0·66	−3·15, 1·82
DII Q3 *v.* Q1	−1·16	−4·73, 2·40	−1·84	−4·68, 0·99
DII Q4 *v.* Q1	−3·93†	−6·86, −1·01	−2·80†	−5·58, −0·02

CERAD, Consortium to Establish a Registry for Alzheimer's disease; Q, quartile; DSST, Digit Symbol Substitution Test; PHQ-9, Patient Health Questionnaire.
* In the adjusted model, covariates included age (years; continuous), sex (male/female), race-ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black and other), measured BMI (kg/m^2; continuous), self-reported smoking status (never, former, current), self-reported average hours of sleep each night (h/night; continuous), self-reported engagement in leisure-time moderate-to-vigorous physical activity (min/week) assessed from the Global Physical Activity Questionnaire and PHQ-9 assessed depression symptomology (range = 0–27; continuous).
† Statistical significance ($P < 0·05$).

memory function. Results were similar for the unadjusted and adjusted models. In addition, there was evidence of consistent inverse associations between DII scores and the different memory parameters. For episodic memory (CERAD Word Learning), those in the 4th (i.e. more pro-inflammatory) *v.* 1st (i.e. more anti-inflammatory) DII quartile recalled fewer words during the 10-min delay assessment ($b_{adjusted} = -0·39$; 95 % CI −0·79, 0·00). Similarly, for semantic-based memory (Animal Fluency Test), those in the 4th *v.* 1st DII quartile listed fewer animal names ($b_{adjusted} = -1·18$; 95 % CI −2·17, −0·20). Lastly, for the executive function and working-memory assessment (DSST), those in the 4th *v.* 1st DII quartile correctly matched fewer paired symbols ($b_{adjusted} = -2·80$; 95 % CI −5·58, −0·02). Notably, there was no evidence of an interaction effect of sex and DII on any of the memory outcomes (results not shown).

Discussion

The purpose of this study was to examine the association between DII scores and a test battery of specific memory functions. The main finding of our study was that higher DII scores were associated with worse episodic memory, working memory, and semantic memory. Notably, however, DII was not consistently associated with the first three learning trials of the CERAD, but was significantly associated with the delayed trial of the CERAD. This suggests that dietary inflammation, as measured by the DII, may be less related to memory encoding, but may have a stronger influence on memory consolidation. Of course, future work is needed to evaluate this speculation.

Reduced cognitive performance has been evidenced in rats consuming an energy-dense, Western-style diet[10]. Notably, cognitive functioning diminished following only 3 d of this high-fat dietary regimen, highlighting the plausible risk for deleterious cognitive outcomes to precede weight gain. This is a meaningful outcome, as not only are weight gain and chronic obesity associated with cognitive impairment, but acute deleterious changes in dietary practices may accelerate this risk of decline[10].

Although energetic requirements can be met by consuming a variety of healthful nutrients, Americans often consume foods high in refined carbohydrates and saturated fat[47,48]. These foods are known to trigger dopaminergic reward pathways, strengthening learned associations between pleasurable food stimuli and immediate reinforcement[48,49]. Initially, ingestion of fatty and/or sugary meals increases the rate of dopaminergic firing, governed by the ventral tegmental area, along with dopamine release from the nucleus accumbens. Habitual intake of foods common to the Western diet, habituates the dopamine reward response to manifest even during the anticipation of experiencing food rewards[50]. The hippocampus, an important subcortical memory structure, is also a key neuromodulator involved in the regulation of energy intake. Studies evaluating the influence of amnesic pathology in humans have shown that excessive eating behaviours may be accelerated following damage to the hippocampus[51–53]. Other animal research suggests that hippocampal-dependent, episodic memory (including flexible memory) impairment may be attenuated by engaging in regular physical activity, despite concurrent consumption of a high-fat diet[54]. This finding lends further credence to the potential efficacy of physical activity to preserve memory functioning, counteracting diet-associated deficits in acute and delayed recall, attention, and processing speed[16,55,56]. Our findings, however, demonstrate an association between DII and memory function, independent of self-reported physical activity behaviour.

It has been suggested that consumption of inflammatory-related, high-fat, high-sugar diets may induce both transient and sustained neurological deficits, particularly dependent upon hippocampal and prefrontal cortex (PFC) function[57]. Inhibitory control and global memory function may suffer as a result of neural disturbances within these regions. Coupled with a heightened dopamine response, impaired inhibition and memory functioning contribute to poor appetite regulation via incongruous hunger cues[58], which may lead to overeating and continuation of negative dietary behaviours. This cyclical response has been observed directly in rats that demonstrate an inability to regulate hunger signals, becoming hyperphagic following hippocampal lesions[53,59–61].

Regarding the crucial importance for adequate functioning of the hippocampus and PFC to remain intact, the hemispheric

encoding retrieval asymmetry model posits these structures are responsible for distinct roles within the complex domain of memory mechanisms. Retrieval of semantic information is governed by the left PFC, whereas the right PFC directs retrieval of episodic memory[62]. The Trace Transformation theory proposes acute memory processes are encoded and organised in the hippocampus, reach neocortical storage, and may then be transformed into shared, hippocampal-neocortical representations[63,64]. Taken together, the differential impact of dietary behaviours on these (and other) highly-integrated structures warrants continued scientific exploration. Dietary inflammation must be regarded as a preventable function of poor diet. Therefore, increasing the quality and quantity of reputable research on this topic, will do much to expand empirical knowledge of the downstream impact of the obesity epidemic. High-fat, high-sugar diets may impart neural and systemic risks associated with weight gain, memory impairment, and cognitive dysfunction[48,65]. However, recent work admonishes scientists to consider variable inflammatory-induced metabolic and cognitive responses specific to white, beige, and brown adipose tissue[66] when attempting to explain the specific correlates of body weight and cognition, as the relationship may be more nuanced than expected[67]. Nevertheless, our findings that higher DII scores (i.e. consistent with greater diet-related inflammation) were associated with worse episodic memory, working memory and semantic memory are noteworthy, and should prompt continued research on this exigent health concern. Such work should continue to explore the specific dietary-related neuro-inflammatory effects on key cellular pathways (e.g. long-term potentiation) that subserve memory function. For example, emerging work suggests reduced synaptic potentiation, long-term potentiation, and glutamate release are suggested to be associated with IL-1 mediated inflammatory responses[68]. Pro-inflammatory cytokines, such as IL-1, are found in high concentrations in the hippocampus[69], and may exert profound negative effects on memory and cognition. Exogenously applied IL-1 can inhibit calcium influx[70], protein kinase A (PKA)[70], and release of acetylcholine[71] and glutamate[72,73] in the hippocampus, all of which play a key role in the cellular basis of episodic memory.

Memory deficits, impaired neuronal growth and proliferation, and inhibited brain-derived neurotrophic factor activity also are driven by diet-induced endothelial cell dysfunction, and subsequent IL-1 release across the blood-brain barrier. Further, neuroinflammation linked with microglial phenotypic changes engendered by chronic systemic inflammation may limit the efficiency of long-term hippocampal potentiation[47,74].

Diet-induced obesity also has been shown to impair dopaminergic signalling[75]. Diet-associated adiposity may impair memory as dopamine plays an important role in memory function[76]. For example, dopamine receptor-mediated signals (e.g. via D1 and D2 receptors) are important in facilitating long-term potentiation[77,78], a critical cellular basis of memory function (particularly episodic memory)[79]. Dopamine regulation of long-term potentiation may occur via the D1/cAMP/PKA pathway, where the D1 receptor coupled to adenylate cyclase (AC) increases AC activity[76]. This leads to the formation of cAMP that activates PKA, which in turn can phosphorylate transcription factors (e.g. CREB) as well as phosphorylate both AMPA and NMDA receptors[76], key receptors in memory-related long-term potentiation.

A limitation of this investigation was our use of a single measure of dietary intake, assessed across a time-period of 24 h. However, this measure has been validated (i.e. correlated with other markers of inflammation) in previous research in large populations[23–27], and, thus, was an appropriate method to estimate DII for the purposes of the present study. Another limitation is that the NHANES memory assessments, particularly the DSST, does not exclusively measure memory function, as it also evaluates other sub-cognitive parameters such as cognitive processing speed and executive function. However, the consistent findings of an association between DII and the three memory-related assessments provides credence to these observations. In addition, NHANES did not collect data on cognitive impairment or neurocognitive disorders; thus, we were unable to take this into account when interpreting our findings. Further, like all epidemiological studies, it is not possible to fully discount the potential effects of residual confounding bias. We are also not able to infer causality of our observed associations given the cross-sectional design of our study. Thus, we cannot discount the potential reverse causality, or possible bi-directionally of DII and memory function. Lastly, based on the available NHANES data, we were only able to include twenty-six of the original forty-five parameters when calculating DII. Thus, our calculated DII may be an underestimate of the participant's true DII, and as a result, our observed association between DII and memory may be underestimated. To our knowledge, this is the first study assessing older US men and women ages 60+ from a nationally representative sample. In addition, as no studies have explored the specific relationship between DII on a multitude of memory parameters, this paper is a robust first step to more comprehensive research. Future work should track dietary behaviour over multiple days to provide a more inclusive representation of changes in dietary behaviour across time.

In conclusion, we observed a consistent inverse association between DII and various memory types. Future experimental work confirming our findings are warranted. Our findings underscore the importance of eating an anti-inflammatory diet, not only for cardiovascular reasons, but for cognitive purposes as well. Future work investigating potential molecular mediators of the DII-memory relationship is also warranted.

Acknowledgements

Drs M. D. W., N. S. and J. R. H. were supported by grant no. R44DK103377 from the National Institutes of Health's (NIH's) National Institute of Diabetes and Digestive and Kidney Diseases. The NIH had no role in the design, analysis or writing of this article.

E. F. prepared part of the initial draft of the manuscript. N. S. assisted in the calculation of the DII. P. D. L. computed the analyses. E. F., N. S., J. R. M., J. R. H., M. D. W. and P. D. L. helped conceptualize the study and provided feedback on various drafts of the manuscript.

Dr J. R. H. owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right

to his invention of the DII from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Drs M. D. W. and N. S. are employees of CHI.

References

1. Carpenter PA, Just MA & Reichle ED (2000) Working memory and executive function: evidence from neuroimaging. *Curr Opin Neurobiol* **10**, 195–199.
2. Mazoyer B, Zago L, Mellet E, *et al.* (2001) Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res Bull* **54**, 287–298.
3. McCabe DP, Roediger HL, McDaniel MA, *et al.* (2010) The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. *Neuropsychology* **24**, 222–243.
4. Posner MI & DiGirolamo GJ (1998) Executive attention: conflict, target detection, and cognitive control. In *The Attentive Brain*, pp. 401–423 [R Parasuraman, editor]. Cambridge, MA: MIT Press.
5. Glass JM, Buu A, Adams KM, *et al.* (2009) Effects of alcoholism severity and smoking on executive neurocognitive function. *Addiction* **104**, 38–48.
6. Slotnick SD (2017) Types of memory and brain regions of interest. In *Cognitive Neuroscience of Memory*, p. 5 [SD Slotnick, editor]. New York: Cambridge University Press.
7. Eichenbaum H (2012) *The Cognitive Neuroscience of Memory: An Introduction*. New York: Oxford University Press.
8. Hantke N, Nielson KA, Woodard JL, *et al.* (2013) Comparison of semantic and episodic memory BOLD fMRI activation in predicting cognitive decline in older adults. *J Int Neuropsychol Soc* **19**, 11–21.
9. Bruce-Keller AJ, Keller JN & Morrison CD (2009) Obesity and vulnerability of the CNS. *Biochim Biophys Acta* **1792**, 395–400.
10. Kanoski SE & Davidson TL (2011) Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol Behav* **103**, 59–68.
11. Okubo H, Inagaki H, Gondo Y, *et al.* (2017) Association between dietary patterns and cognitive function among 70-year-old Japanese elderly: a cross-sectional analysis of the SONIC study. *Nutr J* **16**, 56.
12. Chan R, Chan D & Woo J (2013) A cross sectional study to examine the association between dietary patterns and cognitive impairment in older Chinese people in Hong Kong. *J Nutr Health Aging* **17**, 757–765.
13. Anastasiou CA, Yannakoulia M, Kosmidis MH, *et al.* (2017) Mediterranean diet and cognitive health: initial results from the Hellenic Longitudinal Investigation of Ageing and Diet. *PLOS ONE* **12**, e0182048.
14. Titova OE, Ax E, Brooks SJ, *et al.* (2013) Mediterranean diet habits in older individuals: associations with cognitive functioning and brain volumes. *Exp Gerontol* **48**, 1443–1448.
15. Coppin G, Nolan-Poupart S, Jones-Gotman M, *et al.* (2014) Working memory and reward association learning impairments in obesity. *Neuropsychologia* **65**, 146–155.
16. Kanoski SE & Davidson TL (2010) Different patterns of memory impairments accompany short- and longer-term maintenance on a high-energy diet. *J Exp Psychol Anim Behav Process* **36**, 313–319.
17. Jiang X, Huang J, Song D, *et al.* (2017) Increased consumption of fruit and vegetables is related to a reduced risk of cognitive impairment and dementia: meta-analysis. *Front Aging Neurosci* **9**, 18.
18. Hayden KM, Beavers DP, Steck SE, *et al.* (2017) The association between an inflammatory diet and global cognitive function and incident dementia in older women: The Women's Health Initiative Memory Study. *Alzheimer's Dement* **13**, 1187–1196.
19. Kesse-Guyot E, Assmann KE, Andreeva VA, *et al.* (2017) Long-term association between the dietary inflammatory index and cognitive functioning: findings from the SU.VI.MAX study. *Eur J Nutr* **56**, 1647–1655.
20. Nyberg L, Backman L, Erngrund K, *et al.* (1996) Age differences in episodic memory, semantic memory, and priming: relationships to demographic, intellectual, and biological factors. *J Gerontol Series B Psychol Sci Soc Sci* **51**, P234–P240.
21. US National Center for Health Statistics (1994) *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94*. Hyattsville, MD, Washington, DC: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention.
22. Shivappa N, Steck SE, Hurley TG, *et al.* (2014) Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* **17**, 1689–1696.
23. Shivappa N, Steck SE, Hurley TG, *et al.* (2014) A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr* **17**, 1825–1833.
24. Tabung FK, Steck SE, Zhang J, *et al.* (2015) Construct validation of the dietary inflammatory index among postmenopausal women. *Ann Epidemiol* **25**, 398–405.
25. Wirth MD, Shivappa N., Davis L, *et al.* (2017) Construct validation of the dietary inflammatory index among African Americans. *J Nutr Health Aging* **21**, 487–491.
26. Wirth MD, Burch J, Shivappa N, *et al.* (2014) Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. *J Occup Environ Med* **56**, 986–989.
27. Ramallal R, Toledo E, Martinez-Gonzalez MA, *et al.* (2015) Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the SUN Cohort. *PLOS ONE* **10**, e0135221.
28. Morris JC, Heyman A, Mohs RC, *et al.* (1989) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* **39**, 1159–1165.
29. Fillenbaum GG, van Belle G, Morris JC, *et al.* (2008) Consortium to Establish a Registry for Alzheimer's Disease (CERAD): the first twenty years. *Alzheimers Dement* **4**, 96–109.
30. Gao S, Jin Y, Unverzagt FW, *et al.* (2009) Hypertension and cognitive decline in rural elderly Chinese. *J Am Geriatr Soc* **57**, 1051–1057.
31. Lee DY, Lee KU, Lee JH, *et al.* (2004) A normative study of the CERAD neuropsychological assessment battery in the Korean elderly. *J Int Neuropsychol Soc* **10**, 72–81.
32. Prince M, Acosta D, Chiu H, *et al.* (2003) Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet* **361**, 909–917.
33. Ramirez-Gomez L, Zheng L, Reed B, *et al.* (2017) Neuropsychological profiles differentiate Alzheimer disease from subcortical ischemic vascular dementia in an autopsy-defined cohort. *Dement Geriatr Cogn Disord* **44**, 1–11.
34. Tuokko H, Griffith LE, Simard M, *et al.* (2017) Cognitive measures in the Canadian Longitudinal Study on Aging. *Clin Neuropsychol* **31**, 233–250.
35. Clark LJ, Gatz M, Zheng L, *et al.* (2009) Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **24**, 461–468.
36. Canning SJ, Leach L, Stuss D, *et al.* (2004) Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. *Neurology* **62**, 556–562.

37. Grundman M, Petersen RC, Ferris SH, *et al.* (2004) Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol* **61**, 59–66.
38. Duff K, Schoenberg MR, Scott JG, *et al.* (2005) The relationship between executive functioning and verbal and visual learning and memory. *Arch Clin Neuropsychol* **20**, 111–122.
39. Wechsler D (1958) *The Measurement and Appraisal of Adult Intelligence*, vol. 33. Baltimore, MD: Williams & Wilkins Co.
40. Bienias JL, Beckett LA, Bennett DA, *et al.* (2003) Design of the Chicago Health and Aging Project (CHAP). *J Alzheimers Dis* **5**, 349–355.
41. Plassman BL, Langa KM, Fisher GG, *et al.* (2007) Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* **29**, 125–132.
42. Proust-Lima C, Amieva H, Dartigues JF, *et al.* (2007) Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. *Am J Epidemiol* **165**, 344–350.
43. Vilkki J & Holst P (1991) Mental programming after frontal lobe lesions: results on digit symbol performance with self-selected goals. *Cortex* **27**, 203–211.
44. Parkin AJ & Java RI (1999) Deterioration of frontal lobe function in normal aging: influences of fluid intelligence versus perceptual speed. *Neuropsychology* **13**, 539–545.
45. Cleland CL, Hunter RF, Kee F, *et al.* (2014) Validity of the global physical activity questionnaire (GPAQ) in assessing levels and change in moderate-vigorous physical activity and sedentary behaviour. *BMC Public Health* **14**, 1255.
46. Bull FC, Maslin TS & Armstrong T (2009) Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* **6**, 790–804.
47. Freeman LR, Haley-Zitlin V, Rosenberger DS, *et al.* (2014) Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. *Nutr Neurosci* **17**, 241–251.
48. Volkow ND, Wang GJ & Baler RD (2011) Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci* **15**, 37–46.
49. Higgs S (2016) Cognitive processing of food rewards. *Appetite* **104**, 10–17.
50. Epstein LH, Temple JL, Roemmich JN, *et al.* (2009) Habituation as a determinant of human food intake. *Psychol Rev* **116**, 384–407.
51. Hebben N, Corkin S, Eichenbaum H, *et al.* (1985) Diminished ability to interpret and report internal states after bilateral medial temporal resection: case H.M. *Behav Neurosci* **99**, 1031–1039.
52. Scoville WB & Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* **20**, 11–21.
53. Higgs S (2008) Cognitive influences on food intake: the effects of manipulating memory for recent eating. *Physiol Behav* **94**, 734–739.
54. Klein C, Jonas W, Iggena D, *et al.* (2016) Exercise prevents high-fat diet-induced impairment of flexible memory expression in the water maze and modulates adult hippocampal neurogenesis in mice. *Neurobiol Learn Mem* **131**, 26–35.
55. Francis H & Stevenson R (2013) The longer-term impacts of Western diet on human cognition and the brain. *Appetite* **63**, 119–128.
56. Holloway CJ, Cochlin LE, Emmanuel Y, *et al.* (2011) A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. *Am J Clin Nutr* **93**, 748–755.
57. Volkow ND, Wang GJ, Telang F, *et al.* (2009) Inverse association between BMI and prefrontal metabolic activity in healthy adults. *Obesity* **17**, 60–65.
58. Francis HM & Stevenson RJ (2011) Higher reported saturated fat and refined sugar intake is associated with reduced hippocampal-dependent memory and sensitivity to interoceptive signals. *Behav Neurosci* **125**, 943–955.
59. Davidson TL (1993) The nature and function of interoceptive signals to feed: toward integration of physiological and learning perspectives. *Psychol Rev* **100**, 640–657.
60. Kennedy PJ & Shapiro ML (2004) Retrieving memories via internal context requires the hippocampus. *J Neurosci* **24**, 6979–6985.
61. Davidson TL, Kanoski SE, Walls EK, *et al.* (2005) Memory inhibition and energy regulation. *Physiol Behav* **86**, 731–746.
62. Nyberg L, Cabeza R & Tulving E (1996) PET studies of encoding and retrieval: The HERA model. *Psychon Bull Rev* **3**, 135–148.
63. Nader K (2003) Memory traces unbound. *Trends Neurosci* **26**, 65–72.
64. Loprinzi PD, Edwards MK & Frith E (2017) Potential avenues for exercise to activate episodic memory-related pathways: a narrative review. *Eur J Neurosci* **46**, 2067–2077.
65. Gunstad J, Paul RH, Cohen RA, *et al.* (2007) Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr Psychiatry* **48**, 57–61.
66. Cohen P, Levy JD, Zhang Y, *et al.* (2014) Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch. *Cell* **156**, 304–316.
67. Hao S, Dey A, Yu X, *et al.* (2016) Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. *Brain Behav Immun* **51**, 230–239.
68. Murray CA & Lynch MA (1998) Evidence that increased hippocampal expression of the cytokine interleukin-1 beta is a common trigger for age- and stress-induced impairments in long-term potentiation. *J Neurosci* **18**, 2974–2981.
69. Cunningham ET Jr., Wada E, Carter DB, *et al.* (1992) In situ histochemical localization of type I interleukin-1 receptor messenger RNA in the central nervous system, pituitary, and adrenal gland of the mouse. *J Neurosci* **12**, 1101–1114.
70. Plata-Salaman CR & ffrench-Mullen JM (1994) Interleukin-1 beta inhibits Ca2+ channel currents in hippocampal neurons through protein kinase C. *Eur J Pharmacol* **266**, 1–10.
71. Rada P, Mark GP, Vitek MP, *et al.* (1991) Interleukin-1 beta decreases acetylcholine measured by microdialysis in the hippocampus of freely moving rats. *Brain Res* **550**, 287–290.
72. Huang KF, Huang WT, Lin KC, *et al.* (2010) Interleukin-1 receptor antagonist inhibits the release of glutamate, hydroxyl radicals, and prostaglandin E(2) in the hypothalamus during pyrogen-induced fever in rabbits. *Eur J Pharmacol* **629**, 125–131.
73. Murray CA, McGahon B, McBennett S, *et al.* (1997) Interleukin-1 beta inhibits glutamate release in hippocampus of young, but not aged, rats. *Neurobiol Aging* **18**, 343–348.
74. Liu X, Wu Z, Hayashi Y, *et al.* (2012) Age-dependent neuroinflammatory responses and deficits in long-term potentiation in the hippocampus during systemic inflammation. *Neuroscience* **216**, 133–142.
75. Johnson PM & Kenny PJ (2010) Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci* **13**, 635–641.
76. Jay TM (2003) Dopamine: a potential substrate for synaptic plasticity and memory mechanisms. *Prog Neurobiol* **69**, 375–390.
77. Frey U, Matthies H, Reymann KG, *et al.* (1991) The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region in vitro. *Neurosci Lett* **129**, 111–114.
78. Frey U, Schroeder H & Matthies H (1990) Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. *Brain Res* **522**, 69–75.
79. Lynch MA (2004) Long-term potentiation and memory. *Physiol Rev* **84**, 87–136.

British Journal of Nutrition