

5-1-2016

Chocolate intake is associated with better cognitive function: The Maine-Syracuse Longitudinal Study

Georgina E. Crichton

Merrill F. Elias

University of Maine - Main, mfelias@maine.edu

Ala'a Alkerwi

Follow this and additional works at: https://digitalcommons.library.umaine.edu/longitudinal_papers

 Part of the [Cognition and Perception Commons](#), [Cognitive Psychology Commons](#), and the [Health Psychology Commons](#)

Repository Citation

Crichton, Georgina E.; Elias, Merrill F.; and Alkerwi, Ala'a, "Chocolate intake is associated with better cognitive function: The Maine-Syracuse Longitudinal Study" (2016). *Maine-Syracuse Longitudinal Papers*. 22.
https://digitalcommons.library.umaine.edu/longitudinal_papers/22

This Article is brought to you for free and open access by DigitalCommons@UMaine. It has been accepted for inclusion in Maine-Syracuse Longitudinal Papers by an authorized administrator of DigitalCommons@UMaine. For more information, please contact um.library.technical.services@maine.edu.



Chocolate intake is associated with better cognitive function: The Maine-Syracuse Longitudinal Study



Georgina E. Crichton ^{a,*}, Merrill F. Elias ^{b,c}, Ala'a Alkerwi ^d

^a Nutritional Physiology Research Centre, University of South Australia, Adelaide, Australia

^b Department of Psychology, University of Maine, Orono, ME, USA

^c Graduate School of Biomedical Sciences and Engineering, University of Maine, Orono, ME, USA

^d Luxembourg Institute of Health L.I.H. (formerly Centre de Recherche Public-Santé), Epidemiology and Public Health Research Unit EPHRU, Strassen, Luxembourg

ARTICLE INFO

Article history:

Received 16 August 2015

Received in revised form

7 February 2016

Accepted 8 February 2016

Available online 10 February 2016

Keywords:

Cognitive function

Chocolate

Cocoa flavanols

ABSTRACT

Chocolate and cocoa flavanols have been associated with improvements in a range of health complaints dating from ancient times, and has established cardiovascular benefits. Less is known about the effects of chocolate on neurocognition and behaviour. The aim of this study was to investigate whether chocolate intake was associated with cognitive function, with adjustment for cardiovascular, lifestyle and dietary factors. Cross-sectional analyses were undertaken on 968 community-dwelling participants, aged 23–98 years, from the Maine-Syracuse Longitudinal Study (MSLS). Habitual chocolate intake was related to cognitive performance, measured with an extensive battery of neuropsychological tests. More frequent chocolate consumption was significantly associated with better performance on the Global Composite score, Visual-Spatial Memory and Organization, Working Memory, Scanning and Tracking, Abstract Reasoning, and the Mini-Mental State Examination. With the exception of Working Memory, these relations were not attenuated with statistical control for cardiovascular, lifestyle and dietary factors. Prospective analyses revealed no association between cognitive function and chocolate intake measured up to 18 years later. Further intervention trials and longitudinal studies are needed to explore relations between chocolate, cocoa flavanols and cognition, and the underlying causal mechanisms.

© 2016 Elsevier Ltd. All rights reserved.

1. Introduction

Chocolate consumption is widespread throughout the world. In 2009, 7.2 million tons of chocolate was consumed worldwide (Statista, 2015). Commonly associated with pleasure and enjoyment, chocolate is a frequently ‘craved’ food (Macht & Dettmer, 2006; Macht & Mueller, 2007; Parker, Parker, & Brotchie, 2006), possibly due to its rich natural complexity (Wilson, 2010). The sweet taste, high carbohydrate and fat content and highly palatable orosensory qualities, obtained from its specific constituents, may all contribute to its appeal as a ‘comfort’ food. Few other natural products have been purported to have as many medicinal benefits as chocolate. From very early times to the present day, chocolate has been used to reduce fever, treat childhood diarrhoea, promote strength before sexual conquests, decrease ‘female complaints’,

increase breast-milk production, encourage sleep and to clean teeth (Wilson, 2010). More recent scientific interest has been directed at the cardiovascular (Heiss, Keen, & Kelm, 2010; Hooper et al., 2012) and neurocognitive benefits (Scholey & Owen, 2013; Sokolov, Pavlova, Klosterhalfen, & Enck, 2013) derived from chocolate and cocoa consumption. The cardiovascular benefits have been well established from dietary intervention trials showing improvements in insulin sensitivity (Grassi, Lippi, Necozione, Desideri, & Ferri, 2005), blood pressure (Grassi et al., 2005), endothelial function (Engler et al., 2004; Heiss et al., 2007) and cerebral blood flow (Sorond, Lipsitz, Hollenberg, & Fisher, 2008). In contrast to the evidenced-based benefits from cocoa and chocolate consumption on cardiovascular health, the precise impact of chocolate on human cognitive function is less clear.

Ageing is usually accompanied by declines in multiple domains of cognitive function, including memory and processing speed. In the absence of effective treatments for neurodegenerative disorders, nutritional practises targeted at preventing or slowing cognitive decline may contribute significantly towards optimising cognitive functioning across the adult life-span (Bryan, 2004;

* Corresponding author. Nutritional Physiology Research Centre, University of South Australia, GPO Box 2471, Adelaide, South Australia 5001, Australia.

E-mail addresses: georgina.crichton@unisa.edu.au (G.E. Crichton), mfelias@maine.edu (M.F. Elias), Alaa.Alkerwi@lih.lu (A. Alkerwi).

Solfrizzi, Panza, & Capurso, 2003; Van Dyk & Sano, 2007; Crichton, Bryan, Murphy, & Buckley, 2010; Crichton et al., 2012; Haider et al., 2011). The ability of flavonoid-rich foods to improve cognitive function has been demonstrated in both epidemiological studies (Letenneur, Proust-Lima, Le Gouge, Dartigues, & Barberger-Gateau, 2007; Nurk et al., 2009) and clinical trials (Macready et al., 2009).

Chocolate and cocoa products are a rich source of flavonoids. Flavonoids, naturally occurring polyphenolic compounds present in plant-based foods, represent up to 20% of the compounds present in cocoa beans (Sokolov et al., 2013). Flavanols, and in particular epicatechin, are a subgroup of flavonoids, and are the most common cocoa flavonoids (Sokolov et al., 2013). High levels of flavanols are also found in tea, red wine, and fruits such as grapes and apples (Gu et al., 2004). In addition to cocoa flavanols, other psychoactive components of chocolate include the methylxanthines, caffeine and theobromine, both of which have been associated with improving alertness and cognitive function (Smit, Gaffan, & Rogers, 2004; Mitchell et al., 2011). The amount of cocoa in chocolate ranges from approximately 7–15% in milk chocolate, to 30–70% in dark chocolate. One hundred grams of dark chocolate contains approximately 100 mg of flavanols, while 100 g of unsweetened cocoa powder without methylxanthines can contain up to 250 mg of flavanols (Bhagwat, Haytowitz, Holden).

Two randomized trials have demonstrated improvements in cognitive function following a single dose of chocolate or cocoa flavanols (Scholey et al., 2010; Field, Williams, & Butler, 2011). Benefits to information processing speed and working memory were observed in these studies within hours of consuming cocoa flavanols or dark chocolate. Less research has examined the effects from the longer-term consumption of chocolate or cocoa. One recent randomized controlled trial, the Cocoa, Cognition, and Aging (CoCoA) Study, has provided evidence that daily consumption of cocoa flavanols can improve cognitive function in healthy, elderly individuals (Mastroiacovo et al., 2015). Consistent with the immediate effect studies (Field et al., 2011; Scholey et al., 2010), improvements in processing speed and attentional tasks were seen following 8-weeks of consuming an intermediate to high daily dose of cocoa flavanols (Mastroiacovo et al., 2015).

In contrast to the aforementioned research, some studies using a more chronic administration of chocolate or cocoa flavanols, ranging from 5 days to 6 weeks, have failed to find any positive effects on cognition (Crews, Harrison, & Wright, 2008; Camfield et al., 2012; Francis, Head, Morris, & Macdonald, 2006). It is possible that the variability in the flavanol content in chocolate, which may vary according to the bean variety, origin and manufacturing processes, may contribute to the mixed outcomes observed in studies to date on the effects of cocoa flavanols on cognition (Sokolov et al., 2013).

We have not identified any cohort studies that have examined associations between longer-term habitual chocolate consumption over a number of years, with cognitive functioning measures. The existing evidence remains limited and inconclusive. Using data collected from participants in the Maine-Syracuse Longitudinal Study (MSLS), the aim of the present study was to determine whether habitual chocolate intake is associated with improved cognitive function, with consideration given to cardiovascular, lifestyle and dietary factors.

2. Materials and methods

2.1. Participants

The MSLS was a community-based study of cardiovascular risk factors and cognitive functioning in adults (Dore, Elias, Robbins, Budge, & Elias, 2008; Elias, Robbins et al., 2009; Elias et al., 2006;

Robbins, Elias, Elias, & Budge, 2005). The MSLS consists of five cohorts defined by time of entry into the study (1975–2000, see Appendix 1). At initial recruitment, participants were living independently in Syracuse, New York State. Participants in the present study were those returning for the sixth study wave (2001–2006), as dietary intake measures and extensive data on risk factors for CVD were first obtained at wave 6. From a sample of 1049 individuals, participants were excluded for the following reasons: missing dietary or cognitive data ($n = 38$), acute stroke ($n = 28$), probable dementia ($n = 8$), undertaking dialysis treatment ($n = 5$), inability to read English ($n = 1$), and prior alcohol abuse ($n = 1$), leaving 968 participants. Dementia cases were excluded as we were interested in examining relationships between diet and cognitive performance in those without severe cognitive impairment because poorer cognitive performance in such individuals is a major risk factor for dementia (Elias et al., 2000; Tierney, Moineddin, & McDowell, 2010) and Alzheimer's Disease (Tierney, Yao, Kiss, & McDowell, 2005). The clinical diagnosis of dementia was determined by committee using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, MSLS cognition data, diagnostic records and medical interview data (McKhann et al., 1984). Stroke was defined as a focal neurological deficit of acute onset persisting for more than 24 h, and was based on self-report or medical records.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the University of Maine Institutional Review Board. Written informed consent was obtained from all subjects.

2.2. Procedure and assessment

Dietary Intake Dietary intake was also assessed using the Nutrition and Health Questionnaire (Kaaks & Riboli, 1997; Riboli & Kaaks, 1997). Participants were required to stipulate how frequently they consume a list of foods, including meat, fish, eggs, breads, cereals, rice and pasta, fruit, vegetables, dairy foods, chocolate, nuts, other snack-type foods and beverages, including tea, coffee, water, fruit juice and alcohol. Participants were required to stipulate how frequently they consumed each food, from six response options: never, seldom, once/week, 2–4 times/week, 5–6 times/week, and once or more per day. Chocolate was not differentiated according to type, i.e. milk, dark or white chocolate.

In order to estimate mean intake of the major food groups and total energy intake, the median score within each response option was used to estimate total intake per week; for example, 2–3 times per week was estimated at 2.5. The mean number of times each food was consumed on a weekly and then daily basis was calculated for all foods in the questionnaire. Because portion sizes were not stipulated to participants, these totals are an estimate of the number of times each food was consumed on a daily basis. Individual foods were categorised into five major food groups – grains, fruits, vegetables, protein foods, and dairy foods – based on the USDA Food Guide Pyramid (United States Department of Agriculture, 2011). Intake of individual foods and beverages within each food group were summed to give an estimate of total intake for each group. An estimation of total energy intake was calculated by adding intake of all food groups, and was used to control for energy intake in subsequent analyses.

Cognitive Function Cognitive function was assessed using the MSLS neuropsychological test battery, which has been used in numerous health and cognition studies (Dore et al., 2008; Elias, Robbins et al., 2009, 2006; Robbins et al., 2005; Elias, Elias et al., 2009). The following composite scores have been previously derived using factor analysis from 20 individual tests designed to

measure a wide range of cognitive domains: visual-spatial memory and organization, scanning and tracking, verbal episodic memory, and working memory. The WAIS Similarities Test (Lezak, Howieson, & Loring, 2004), a measure of abstract reasoning, loaded on all composite scores (factors) and was thus employed separately. A global cognition composite score was derived by averaging the z-scores for all individual tests and then re-standardizing these scores to obtain a z-score with a mean of zero and SD of 1.00. In addition, the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), a global measure of mental status widely used in the literature, was included in the MSLS battery. The derivation of these composites has been described previously (Elias et al., 2006) and they have been repeatedly utilized in MSLS studies. All cognitive performance measures are expressed in the same unit of measurement (SD units), i.e. z-scores, with higher scores indicating better performance.

Demographics and Physical Health Assessment Demographic, socioeconomic and lifestyle characteristics were obtained from the Nutrition and Health Questionnaire (Kaaks & Riboli, 1997; Riboli & Kaaks, 1997). Data obtained included smoking history, marital status and medical history. Physical activity was measured with the Nurses' Health Study Activity Questionnaire, a validated measure of time spent engaging in various physical activities (Wolf et al., 1994). The Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977) was used to assess depressive symptoms. Education level was obtained through self-report (mean = 14.7 ± 2.7 years, range 4–20 years).

Standard assay methods were employed (Elias et al., 2006) to obtain fasting plasma glucose (mg/dL), total cholesterol (TC, mg/dL), low-density lipoprotein cholesterol (LDL, mg/dL), high-density lipoprotein cholesterol (HDL, mg/dL), triglycerides (mg/dL) and C-reactive protein (CRP, mg/L), following an overnight fast. Body weight was measured with participants wearing light clothing to the nearest 0.1 kg, and height was measured with a vertical ruler to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Waist circumference (in centimetres) was taken over light clothing, using a non-extendable measuring tape, at the level of the iliac crest. Automated blood pressure measures (GE DINAMAP 100DPC-120XEN, GE Healthcare) were taken in the right arm five times each in recumbent, standing and sitting position after a supine rest for 15 min, and averaged for systolic and diastolic blood pressure. Obesity was defined as having BMI of at least 30 kg/m².

3. Statistical analyses

Participant demographics, health and dietary variables, and cognitive scores were compared according to chocolate consumption (never/rarely vs. at least once/week). Independent samples *t*-tests were used for continuous variables and Chi-square for categorical variables.

For the primary analyse, chocolate intake was further classified into three intake groups based on self-reported frequency of consumption: less than once per week, once per week, and more than once per week. Multivariate analysis of variance (MANOVA) (a step-down protection procedure) (van der Laan, Dudoit, & Pollard, 2004) was used to examine relationships between chocolate intake and cognitive performance (Visual-Spatial Memory and Organization, Scanning and Tracking, Verbal Episodic Memory, Working Memory, Similarities, MMSE). All cognitive outcomes were entered into the analyses simultaneously as dependent variables except for the Global Composite score, as the Global Composite is co-dependent on all the measures other than the MMSE. Multivariate ANOVA was used to examine relationships between chocolate intake and the Global Composite. In addition to MANOVA, the Bonferroni

procedure was used to protect against multiple comparisons.

Potential confounding factors were identified on the basis of two criteria: (1) had to be theoretically relevant (Jaccard & Jacoby, 2010) and, (2) had to show a statistically significant association ($p < 0.05$) with both chocolate intake and the Global Composite. Three covariate sets were used:

- (1) Covariate set 1: age, sex.
- (2) Covariate set 2: age, sex, education, total cholesterol, glucose, LDL-cholesterol, hypertension, estimated energy intake (total daily intake of all food groups as previously described).
- (3) Covariate set 3: covariate sets 1 and 2, plus dietary intake of alcohol, meats, vegetables, and dairy foods.

The other risk factors measured as potential covariates did not correlate significantly with chocolate consumption (predictor) or an outcome measure and therefore were not included in the statistical models.

All statistical analyses were performed with PASW for Windows[®] version 21.0 software (formerly SPSS Statistics Inc. Chicago, IL, USA); $p < 0.05$ was considered statistically significant.

4. Results

4.1. Participant characteristics and chocolate consumption

Table 1 shows the demographic and health-related variables, cognitive scores, and dietary intake for MSLS participants ($n = 968$), according to chocolate consumption (those who consume chocolate never or rarely, compared with at least once per week). Effect sizes are shown for those variables where there were significant differences between groups ($p < 0.05$). Women ate chocolate more frequently than men. Compared to those who never or rarely ate chocolate, those who ate chocolate on a weekly basis, had higher total and LDL-cholesterol, but lower glucose levels. Hypertension and type 2 diabetes were lower in regular chocolate consumers than in non-consumers. From a dietary perspective, those who ate chocolate also consumed more energy overall, and more daily serves of meat, vegetables and dairy foods, but significantly less alcohol. All cognitive scores were significantly higher in those who consumed chocolate at least once per week, than in those who never/rarely consumed chocolate.

4.2. Chocolate Consumption and Cognitive Performance in the MSLS.

The multivariate tests performed as protection against multiple contrasts for multiple outcome variables were statistically significant for all three models (covariate set 1: F [Wilks' lambda] = 2.93, $p < 0.001$; covariate set 2: $F = 2.43$, $p = 0.004$; covariate set 3: $F = 2.21$, $p = 0.009$). Therefore we report the results of the univariate analyses for each cognitive outcome.

Table 2 shows the adjusted mean z-scores (and SE) for each cognitive outcome across increasing categories of chocolate intake (all three models). *P*-values are adjusted via the Bonferroni procedure. Chocolate intake was significantly and positively associated with the Global Composite, Visual-Spatial Memory and Organization, Working Memory, Scanning and Tracking, the Similarities test (abstract reasoning), and the MMSE (covariate set 1, all $p < 0.05$).

With full adjustment for demographic variables, cardiovascular risk factors, and a number of dietary variables including total energy intake, significant positive associations remained between chocolate intake and the Global Composite, Visual-Spatial Memory and Organization, Scanning and Tracking, Similarities and the

Table 1
Participant characteristics according to baseline chocolate consumption in MSLS, N = 968.

Characteristic	Chocolate consumption				Cohen's <i>d</i> ^e
	Never or rarely <i>n</i> = 337 (34.8%)		At least once/week <i>n</i> = 631 (65.2%)		
	Mean	SD	Mean	SD	
Age (years)	61.8	13.0	62.1	12.8	
Sex (%)					
Men	46.6		38.2*		
Women	53.4		61.8*		
Education (years)	14.5	2.8	14.7	2.7	
CES-D	7.6	7.2	7.6	6.6	
C-reactive protein (mg/L)	0.4	0.5	0.4	0.5	
Smoking (cigarettes/day)	1.5	5.4	1.3	5.2	
Body mass index (kg/m ²)	29.6	6.6	29.2	5.5	
Waist circumference (cm)	96.3	16.5	94.9	14.2	
Physical activity (MET hours)	19.3	25.9	21.3	28.4	
Systolic blood pressure (mm Hg)	132	22	130	21	
Diastolic blood pressure (mm Hg)	70.7	10.7	70.3	9.7	
Total cholesterol (mg/dL)	197	40	204*	40	0.16
HDL cholesterol (mg/dL)	53.9	16.1	53.3	14.9	
LDL cholesterol (mg/dL)	116	34	123**	33	0.21
Triglycerides (mg/dL)	145	128	142	103	
Glucose (mg/dL)	103	37	97**	21	0.27
Obesity ^a , %	39.5		38.4		
Hypertension ^b , %	67.7		58.3**		
Diabetes ^c , %	17.5		9.8**		
Dietary (serves per day)					
Total all food groups	13.8	4.7	15.4***	4.4	0.36
Total grains	3.6	2.8	3.8	1.9	
Total meats	1.9	0.8	2.1**	0.9	0.24
Total fruit	1.5	0.9	1.7	1.0	
Total vegetables	2.6	1.1	2.8**	1.1	0.24
Total dairy foods	1.8	1.1	2.1**	1.1	0.21
Alcohol (g/week)	48.2	95.1	29.5***	50.2	0.37
Cognitive outcomes ^d					
Global Composite	−0.15	0.06	0.09***	0.04	0.24
Visual Spatial Memory and Organization	−0.16	0.06	0.10***	0.04	0.25
Verbal Memory	−0.11	0.05	0.06*	0.04	0.17
Working Memory	−0.08	0.05	0.05	0.04	0.13
Scanning and Tracking	−0.11	0.06	0.06*	0.04	0.17
Similarities	−0.14	0.06	0.08**	0.04	0.22
Mini-Mental State Examination	−0.08	0.06	0.05*	0.04	0.14

CES-D Center for Epidemiological Studies Depression Scale, HDL high-density lipoprotein, LDL low-density lipoprotein.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for differences between groups.

^a Obesity defined as body mass index ≥ 30 kg/m².

^b Hypertension defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or taking antihypertensive medications.

^c Diabetes defined as fasting plasma glucose ≥ 126 mg/dL, or taking antidiabetic medications.

^d Mean z-scores and SE.

^e Effect sizes reported where $p < 0.05$.

MMSE (covariate set 3, all $p < 0.05$). There were no associations observed between chocolate intake and Verbal Memory.

5. Secondary analyses

In a secondary analysis, we asked whether cognitive performance predicted chocolate consumption rather than the other way round. This analysis was conducted on a sample of participants ($n = 333$) who had completed a cognitive assessment in waves 1–4 of the MSLS, but also completed the dietary questionnaire at wave 6, a mean of 18.0 years later (Crichton, Elias, Davey, Alkerwi, & Dore, 2014). Cognition was assessed using the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955), consisting of a total WAIS score, Verbal subscale score and Performance subscale score. There were no significant associations between chocolate intake and the total WAIS ($p = 0.90$), Verbal subscale ($p = 0.70$) or Performance subscale ($p = 0.80$) (all adjusted for age, sex and education).

Although income did not fit our criteria for inclusion as a covariate (did not correlate significantly with chocolate intake), it may influence food choices and dietary patterns. We therefore

added income to the basic model, and the results remain unchanged.

6. Discussion

Chocolate intake was positively associated with cognitive performance, across a range of cognitive domains in this dementia-free, community-dwelling population. The associations between more frequent weekly chocolate consumption and cognitive performance remained significant after adjustment for a number of cardiovascular risk factors, including total and LDL-cholesterol, glucose levels, and hypertension. Associations were not attenuated with the addition of dietary variables (alcohol, meats, vegetables, and dairy foods), indicating that chocolate may be associated with cognition irrespective of other dietary habits.

A number of studies provide support for the role of cocoa flavanols in cognition (Field et al., 2011; Mastroiacovo et al., 2015; Scholey et al., 2010). In a placebo-controlled, double blind study, (Scholey et al. 2010) compared cognitive effects following the consumption of drinks containing either 520 mg of cocoa flavanols,

Table 2
Multivariate adjusted mean (z-scores) (and SE) for each cognitive outcome across increment levels of chocolate intake, N = 968.

Cognitive outcome	Covariate set ^a	Chocolate intake category						R ^{2b}	p linear
		<once/week n = 337 (34.8%)		Once/week n = 265 (27.4%)		>once/week n = 366 (37.8%)			
		Mean	SE	Mean	SE	Mean	SE		
Global Composite	1	-0.155	0.047	0.038 ^{c*}	0.053	0.129 ^{****}	0.045	0.262	<0.001
	2	-0.154	0.048	0.024 ^{c*}	0.052	0.142 ^{****}	0.046	0.302	<0.001
	3	-0.141	0.046	0.032 ^{c*}	0.051	0.124 ^{****}	0.044	0.353	<0.001
Visual-Spatial Memory and Organization	1	-0.170	0.048	0.035 ^{c*}	0.053	0.150 ^{****}	0.046	0.239	<0.001
	2	-0.153	0.046	0.046 ^{c*}	0.051	0.126 ^{****}	0.045	0.345	<0.001
	3	-0.140	0.046	0.048 ^{c*}	0.050	0.113 ^{****}	0.044	0.368	<0.001
Verbal Memory	1	-0.101	0.050	0.114 ^{c*}	0.057	0.025	0.048	0.144	0.07
	2	-0.093	0.051	0.133 ^{c**}	0.055	0.006	0.049	0.210	0.17
	3	-0.097	0.051	0.140 ^{c**}	0.055	0.004	0.049	0.229	0.16
Working Memory	1	-0.082	0.053	0.029	0.060	0.121	0.051	0.049	0.048
	2	-0.059	0.054	0.053	0.059	0.042	0.052	0.133	0.18
	3	-0.059	0.054	0.063	0.058	0.034	0.051	0.151	0.22
Scanning Tracking	1	-0.110	0.045	-0.029	0.050	0.121 ^{***}	0.043	0.331	<0.001
	2	-0.109	0.044	-0.020	0.048	0.104 ^{***}	0.042	0.427	0.001
	3	-0.099	0.044	-0.019	0.047	0.093 ^{***}	0.042	0.440	0.002
Similarities	1	-0.143	0.053	0	0.060	0.144 ^{****}	0.051	0.040	<0.001
	2	-0.087	0.050	0.041	0.055	0.086 ^{c*}	0.048	0.222	0.015
	3	-0.076	0.050	0.047	0.054	0.072	0.048	0.256	0.037
Mini-Mental State Examination	1	-0.090	0.053	0.024	0.060	0.079	0.051	0.042	0.023
	2	-0.066	0.052	0.059	0.057	0.076	0.050	0.156	0.053
	3	-0.069	0.052	0.061	0.056	0.077	0.050	0.174	0.048

Multivariate tests: covariate set 1: F (Wilks' lambda) = 2.93, $p < 0.001$; covariate set 2: $F = 2.43$, $p = 0.004$; covariate set 3: $F = 2.21$, $p = 0.009$.

^a Covariate set 1 – adjustment for age and sex; Covariate set 2 – adjustment for age, sex, education, total cholesterol, glucose, LDL-cholesterol, hypertension, and total serves from all foods; Covariate set 3 – adjustment for variables in set 2 + dietary intake of alcohol, meats, vegetables, and dairy foods.

^b Adjusted R² for multiple comparisons (Bonferroni).

^c significantly different from <once/week group, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

994 mg of cocoa flavanols, or a matched control drink in 30 healthy young adults. Mood and cognitive performance were assessed over 60 min post-drink. Performance on a serial subtraction task significantly improved following consumption of both flavanol-containing drinks, compared to the control. The 994 mg cocoa flavanol beverage significantly increased the speed on visual information processing responses, while increases in self-reported 'mental fatigue' were significantly attenuated by the consumption of the 520 mg beverage.

(Field et al. 2011) similarly examined the acute effects of cocoa flavanols on cognitive function (reaction time, visual spatial working memory), visual contrast sensitivity, and motion sensitivity, in a cross-over study in 30 healthy young adults. Participants consumed dark chocolate containing 720 mg cocoa flavanols, and a matched quantity of white chocolate. The dark chocolate improved visual spatial working memory, reaction time on some aspects of the test, contrast sensitivity, and reduced the time to detect motion direction. The authors attributed these findings to increased cerebral blood flow caused by the cocoa flavanols. Findings from these two studies demonstrated that improved cognitive effects may be observed at 90–120 min post-flavanol intake (Field et al., 2011; Scholey et al., 2010).

Findings from the recent CoCoA Study support this research (Mastroiaco et al., 2015). In this trial, the effects of daily consumption (for 8 weeks) of a drink containing low (48 mg), intermediate (520 mg), or high (993 mg) levels of cocoa flavanols on cognitive performance in 90 elderly, cognitively intact participants were examined. The intermediate and high flavanol groups both showed improvements in processing speed and attentional tasks (measured by the Trail Making Test), whilst improvements in verbal fluency (Verbal Fluency Test) were greatest for the high flavanol group. General cognition scores, as measured by the MMSE, were not significantly different between groups post-treatment. Further, improvements in insulin resistance, blood pressure, and lipid profile were detected in the high and intermediate flavanol groups,

compared with the low flavanol group. Importantly, benefits were noted at multiple intake amounts. Some improvement was observed in the low flavanol group for verbal fluency, however to a lesser degree than in the other two treatment groups. The authors attributed this to the methylxanthines (50 mg caffeine, 400 mg theobromine) in the low flavanol drink (Mastroiaco et al., 2015).

Other research has supported the action of the methylxanthines in chocolate, caffeine and theobromine, in relation to cognitive function. Coffee is consumed by millions of individuals from all over the world, possibly in part, due to its caffeine content. It is the best known psychoactive stimulant acting to improve short-term alertness and arousal (Mitchell et al., 2011; Yoshimura, 2005). Longer-term, population based studies have provided evidence that long-term caffeine intake may offer some protection against cognitive decline (Panza et al., 2015).

Studies by (Smit et al. 2004) have provided evidence for the beneficial effects of the methylxanthines contained in chocolate. They measured the effects on cognitive performance and mood from the consumption of the equivalent amount of cocoa powder and methylxanthines (caffeine and theobromine combination) found in a 50 g bar of dark chocolate. Identical improvements on energetic arousal and cognitive function were found for cocoa powder and the methylxanthines versus a placebo. In chocolate, both 'milk' and 'dark' chocolate methylxanthine doses improved cognitive function compared with 'white chocolate'. In subsequent work, Smit and Blackburn (2005) also demonstrated that the methylxanthines in amounts found in 50 g of chocolate may well contribute to our 'liking' of chocolate.

Other studies have supported the findings of (Smit et al. 2004), (Mitchell et al. 2011) compared the effects of caffeine (120 mg), theobromine (700 mg), the combination of both, or a placebo, on mood and cognitive performance (psychomotor speed). Theobromine alone decreased calmness, caffeine alone increased alertness and contentedness, while the combination of both had similar effects as caffeine alone on mood, although neither improved

psychomotor speed. However, the levels of caffeine and theobromine administered in this study were higher than what is present in chocolate products.

A number of recent reviews have explored the central actions of cocoa flavanols in relation to cognition (Sokolov et al., 2013) and mood (Smith, 2013). Excellent reviews by (Sokolov et al. 2013) and Williams and Spencer (2012) discuss how the actions of cocoa flavanols and flavonoids, respectively, impact upon neurocognition and behaviour. To summarize, flavanols have multiple effects on brain function, but their neuropsychological actions are likely to occur in two ways: 1) via direct interactions with cellular and molecular signalling cascades in brain regions involved with learning and memory, and 2) via increasing central and peripheral blood flow and promoting angiogenesis (Sokolov et al., 2013; Williams & Spencer, 2012).

Cardiovascular health is closely linked to cognitive health (Waldstein and Elias, 2014). Further, the relation between dietary habits and the human brain is complex and involves bi-directional communication. Intellectual status early in life may certainly effect good or poor food choices (Crichton et al., 2014). However, we were able to assess for any relation between cognitive performance measured at waves 1–4 of the MSLS, with chocolate intake at wave 6, and found no prospective associations. Performance on the WAIS, which combines both verbal and performance abilities, did not predict chocolate intake controlling for age, sex, and education.

Income may be another factor that potentially influences the relation between chocolate consumption and cognitive function. It may be speculated that higher income individuals may purchase and consume more chocolate, and in particular dark chocolate, which has a higher flavanol content. However, sensitivity analyses with income added to the basic model, did not change the findings. We also note that those who consumed chocolate more frequently drank significantly less alcohol. Another plausible explanation may be that alcohol actually has a deleterious effect on cognitive function, explaining the results observed. However, additional analyses revealed no association between alcohol intake and the Global Composite, Visual-Spatial Memory and Organization, Scanning and Tracking, or the Similarities test (all $p > 0.2$, all covariate set 3). Alcohol intake was, in fact, significantly, positively associated with Verbal Memory, Working Memory and the MMSE (unstandardized $B = 0.001$, $p < 0.05$ for all, covariate set 3) (data not shown).

7. Limitations

Some limitations of the present study should be acknowledged. Chocolate intake was self-reported, and therefore subject to inherent reporting error. The dietary questionnaire used did not require the respondent to differentiate between dark, milk or white chocolate. Most clinical trials have used dark chocolate as the source of cocoa flavanols. In 2012, the distribution share of chocolate in the United States by favourite chocolate type was 57% milk chocolate, 35% dark chocolate, and 8% white chocolate (Statista, 2015). We can therefore make the assumption that the majority of chocolate consumed in this sample was dark or milk, both containing cocoa flavanols to varying degrees. With the exception of the secondary analysis, the study was cross-sectional as longitudinal data following wave 6 were not available. This precludes any conclusions regarding a causal relationship between chocolate intake and cognition from being drawn. Future longitudinal studies in this area will be of value.

8. Strengths

Our study demonstrated positive associations between habitual chocolate consumption and cognitive performance. We were able

to statistically control for a number of cardiovascular, lifestyle and dietary variables that may impact upon a chocolate–cognition relationship. Despite the dietary intervention trials which have typically examined the effects from either a single dose or daily doses over periods up to several months, there have not been any large cross-sectional studies identified that have specifically examined chocolate intake in relation to cognitive performance. Further, we were able, with a prospective design, to examine the relation between early cognitive functioning (at waves 1 to 4) and chocolate consumption (at wave 6), and found no association.

9. Conclusion

It is evident that nutrients in foods exert differential effects on the brain. As has been repeatedly demonstrated, isolating these nutrients and foods enables the formation of dietary interventions to optimise neuropsychological health. Adopting dietary patterns to delay or slow the onset of cognitive decline is an appropriate avenue, given the limited treatments available for dementia. The present findings support recent clinical trials suggesting that regular intake of cocoa flavanols may have a beneficial effect on cognitive function, and possibly protect against normal age-related cognitive decline. Longer-term clinical trials will shed further insight into this association between chocolate, rich in cocoa flavanols, and neuropsychological health, and the mechanisms linking them. It will be important in future studies to investigate optimal quantities and duration of consumption to produce short or longer-term effects while taking into account overall dietary patterns, where foods high in flavonoids are consumed in combination. Enhancing chocolate and cocoa consumption whilst ensuring appropriate caloric intake will be an important consideration to optimise the benefits obtained from these foods.

Conflict of interest

The authors declare that they have no conflict of interests.

Acknowledgements

We thank the three primary investigators of the MSLS (Prof Merrill Elias, Prof Michael Robbins and David H. P. Streeten, MD). The research was supported in part by the National Heart, Lung, and Blood Institute (grants HL67358 and HL81290) and the National Institute on Aging (grant AG03055) of the National Institutes of Health to the University of Maine. GEC was supported by a Sidney Sax Research Fellowship (National Health and Medical Research Council, Australia, grant number APP1054567). AA was supported by a grant from the Fond National de Recherche for the project DIQUA-LUX (5870404), Luxembourg. The funding sources had no involvement in data collection, writing of the report or decision to submit the article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.appet.2016.02.010>.

References

- Bhagwat S., Haytowitz D. M., Holden J. M.. USDA Database for the Flavanoid content of Selected foods. Release 3.1. U.S. Department of agriculture, Agricultural research Service. Nutrient data Laboratory Home Page. Available from: <http://www.ars.usda.gov/nutrientdata/flav>.
- Bryan, J. (2004). Mechanisms and evidence for the role of nutrition in cognitive ageing. *Ageing International*, 29, 28–45.
- Camfield, D. A., Scholey, A., Pipingas, A., Silberstein, R., Kras, M., Nolidin, K., et al.

- (2012). Steady state visually evoked potential (SSVEP) topography changes associated with cocoa flavanol consumption. *Physiology & Behaviour* 2012, 105, 948–957.
- Crews, W. D., Jr., Harrison, D. W., & Wright, J. W. (2008). A double-blind, placebo-controlled, randomized trial of the effects of dark chocolate and cocoa on variables associated with neuropsychological functioning and cardiovascular health: clinical findings from a sample of healthy, cognitively intact older adults. *The American Journal of Clinical Nutrition*, 87, 872–880.
- Crichton, G. E., Bryan, J., Murphy, K. J., & Buckley, J. (2010). Review of dairy consumption and cognitive performance in adults: findings and methodological issues. *Dementia and Geriatric Cognitive Disorders*, 30, 352–361.
- Crichton, G. E., Elias, M. F., Buckley, J., Murphy, K. J., Bryan, J., & Frisardi, V. (2012). Metabolic syndrome, cognitive performance and dementia: a review. *Journal of Alzheimer's Disease*, 30, S77–S87.
- Crichton, G. E., Elias, M. F., Davey, A., Alkerwi, A., & Dore, G. (2014). Higher cognitive performance is prospectively associated with healthy dietary choices: the Maine Syracuse Longitudinal Study. *The Journal of Prevention of Alzheimer's Disease*, 2, 24–32.
- Dore, G. A., Elias, M. F., Robbins, M. A., Budge, M. M., & Elias, P. K. (2008). Relation between central adiposity and cognitive function in the Maine-Syracuse Study: attenuation by physical activity. *Annals of Behavioral Medicine*, 35, 341–350.
- Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F., & D'Agostino, R. B. (2000). The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort. *Archives of Neurology*, 57, 808–813.
- Elias, M. F., Elias, P. K., Seliger, S. L., Narsipur, S. S., Dore, G. A., & Robbins, M. A. (2009). Chronic kidney disease, creatinine and cognitive functioning. *Nephrology Dialysis Transplantation*, 24, 2446–2452.
- Elias, M. F., Robbins, M. A., Budge, M. M., Abhayaratna, W. P., Dore, G. A., & Elias, P. K. (2009). Arterial pulse wave velocity and cognition with advancing age. *Hypertension*, 53, 668–673.
- Elias, M. F., Robbins, M. A., Budge, M. M., Elias, P. K., Brennan, S. L., Johnston, C., et al. (2006). Homocysteine, folate, and vitamins B6 and B12 blood levels in relation to cognitive performance: the Maine-Syracuse study. *Psychosomatic Medicine*, 68, 547–554.
- Engler, M. B., Engler, M. M., Chen, C. Y., Malloy, M. J., Browne, A., Chiu, E. Y., et al. (2004). Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *The Journal of the American College of Nutrition*, 23, 197–204.
- Field, D. T., Williams, C. M., & Butler, L. T. (2011). Consumption of cocoa flavanols results in an acute improvement in visual and cognitive functions. *Physiology & Behavior*, 103, 255–260.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 129–138.
- Francis, S. T., Head, K., Morris, P. G., & Macdonald, I. A. (2006). The effect of flavanol-rich cocoa on the fMRI response to a cognitive task in healthy young people. *Journal of Cardiovascular Pharmacology*, 47(Suppl 2), S215–S220.
- Grassi, D., Lippi, C., Necozione, S., Desideri, G., & Ferri, C. (2005). Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. *The American Journal of Clinical Nutrition*, 81, 611–614.
- Gu, L., Kelm, M. A., Hammerstone, J. F., Beecher, G., Holden, J., Haytowitz, D., et al. (2004). Concentrations of proanthocyanidins in common foods and estimations of normal consumption. *Journal of Nutrition*, 134, 613–617.
- Haider, S., Batool, Z., Tabassum, S., Perveen, T., Saleem, S., Naqvi, F., et al. (2011). Effects of walnuts (*Juglans regia*) on learning and memory functions. *Plant Foods for Human Nutrition*, 66, 335–340.
- Heiss, C., Finis, D., Kleinbongard, P., Hoffmann, A., Rassaf, T., Kelm, M., et al. (2007). Sustained increase in flow-mediated dilation after daily intake of high-flavanol cocoa drink over 1 week. *Journal of Cardiovascular Pharmacology*, 49, 74–80.
- Heiss, C., Keen, C. L., & Kelm, M. (2010). Flavanols and cardiovascular disease prevention. *European Heart Journal*, 31, 2583–2592.
- Hooper, L., Kay, C., Abdelhamid, A., Kroon, P. A., Cohn, J. S., Rimm, E. B., et al. (2012). Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. *American Journal of Clinical Nutrition*, 95, 740–751.
- Jaccard, J., & Jacoby, J. (2010). *Theory construction and model-building skills: A practical guide for social scientists*. New York, NY: Guilford Press.
- Kaaks, R., & Riboli, E. (1997). Validation and calibration of dietary intake measurements in the EPIC project: methodological considerations. European Prospective Investigation into Cancer and Nutrition. *International Journal of Epidemiology*, 26(Suppl 1), S15–S25.
- van der Laan, M. J., Dudoit, S., & Pollard, K. S. (2004). Multiple testing. Part II. Step-down procedures for control of the family-wise error rate. *Statistical Applications in Genetics and Molecular Biology*, 3, Article14.
- Letenneur, L., Proust-Lima, C., Le Gouge, A., Dartigues, J. F., & Barberger-Gateau, P. (2007). Flavonoid intake and cognitive decline over a 10-year period. *American Journal of Epidemiology*, 165, 1364–1371.
- Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological assessment* (4th ed.). New York, NY, USA: Oxford University Press.
- Macht, M., & Dettmer, D. (2006). Everyday mood and emotions after eating a chocolate bar or an apple. *Appetite*, 46, 332–336.
- Macht, M., & Mueller, J. (2007). Immediate effects of chocolate on experimentally induced mood states. *Appetite*, 49, 667–674.
- Macready, A. L., Kennedy, O. B., Ellis, J. A., Williams, C. M., Spencer, J. P., & Butler, L. T. (2009). Flavonoids and cognitive function: a review of human randomized controlled trial studies and recommendations for future studies. *Genes & Nutrition*, 4, 227–242.
- Mastroiaco, D., Kwik-Urbe, C., Grassi, D., Necozione, S., Raffaele, A., Pistacchio, L., et al. (2015). Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study—a randomized controlled trial. *American Journal of Clinical Nutrition*, 101, 538–548.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology*, 34, 939–944.
- Mitchell, E. S., Slettenaar, M., van der Meer, N., Transler, C., Jans, L., Quad, F., et al. (2011). Differential contributions of theobromine and caffeine on mood, psychomotor performance and blood pressure. *Physiology & Behavior*, 104, 816–822.
- Nurk, E., Refsum, H., Drevon, C. A., Tell, G. S., Nygaard, H. A., Engedal, K., et al. (2009). Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. *Journal of Nutrition*, 139, 120–127.
- Panza, F., Solfrizzi, V., Barulli, M. R., Bonfiglio, C., Guerra, V., Osella, A., et al. (2015). Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. *Journal of Nutrition Health and Aging*, 19, 313–328.
- Parker, G., Parker, I., & Brotchie, H. (2006). Mood state effects of chocolate. *Journal of Affective Disorders*, 92, 149–159.
- Radloff, L. S. (1977). The CES-D Scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement*, 1, 385–401.
- Riboli, E., & Kaaks, R. (1997). The EPIC project: rationale and study design. European prospective investigation into cancer and nutrition. *International Journal of Epidemiology*, 26(Suppl 1), S6–S14.
- Robbins, M. A., Elias, M. F., Elias, P. K., & Budge, M. M. (2005). Blood pressure and cognitive function in an African-American and a Caucasian-American sample: the Maine-Syracuse Study. *Psychosomatic Medicine*, 67, 707–714.
- Scholey, A. B., French, S. J., Morris, P. J., Kennedy, D. O., Milne, A. L., & Haskell, C. F. (2010). Consumption of cocoa flavanols results in acute improvements in mood and cognitive performance during sustained mental effort. *Journal of Psychopharmacology*, 24, 1505–1514.
- Scholey, A., & Owen, L. (2013). Effects of chocolate on cognitive function and mood: a systematic review. *Nutrition Reviews*, 71, 665–681.
- Smit, H. J., & Blackburn, R. J. (2005). Reinforcing effects of caffeine and theobromine as found in chocolate. *Psychopharmacology (Berl)*, 181, 101–106.
- Smit, H. J., Gaffan, E. A., & Rogers, P. J. (2004). Methylxanthines are the psychopharmacologically active constituents of chocolate. *Psychopharmacology (Berl)*, 176, 412–419.
- Smith, D. F. (2013). Benefits of flavanol-rich cocoa-derived products for mental well-being: a review. *Journal of Functional Foods*, 5, 10–15.
- Sokolov, A. N., Pavlova, M. A., Klosterhalfen, S., & Enck, P. (2013). Chocolate and the brain: neurobiological impact of cocoa flavanols on cognition and behavior. *Neuroscience & Biobehavioral Reviews*, 37, 2445–2453.
- Solfrizzi, V., Panza, F., & Capurso, A. (2003). The role of diet in cognitive decline. *Journal of Neural Transmission*, 110, 95–110.
- Sorond, F. A., Lipsitz, L. A., Hollenberg, N. K., & Fisher, N. D. (2008). Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. *Neuropsychiatric Disease and Treatment*, 4, 433–440.
- Statista. Statistics and facts on the chocolate industry. Retrieved December 7, 2015; Available from: www.statista.com/statistics/238849/global-chocolate-consumption/.
- Tierney, M. C., Moineddin, R., & McDowell, I. (2010). Prediction of all-cause dementia using neuropsychological tests within 10 and 5 Years of diagnosis in a community-based sample. *Journal of Alzheimer's Disease*, 22, 1231–1240.
- Tierney, M. C., Yao, C., Kiss, A., & McDowell, I. (2005). Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. *Neurology*, 64, 1853–1859.
- United States Department of Agriculture. (2011). *MyPyramid.Gov*.
- Van Dyk, K., & Sano, M. (2007). The impact of nutrition on cognition in the elderly. *Neurochemical Research*, 32, 893–904.
- Waldstein, S. R., & Elias, M. F. (Eds.). (2014). *Neuropsychology of cardiovascular disease* (2nd ed.). New York: Taylor & Francis.
- Wechsler, D. (1955). *The measurement and appraisal of adult intelligence. Manual for the Wechsler Intelligence Scale*. New York: Psychological Corporation.
- Williams, R. J., & Spencer, J. P. (2012). Flavonoids, cognition, and dementia: actions, mechanisms, and potential therapeutic utility for Alzheimer disease. *Free Radical Biology & Medicine*, 52, 35–45.
- Wilson, P. K. (2010). Centuries of seeking chocolate's medicinal benefits. *Lancet*, 376, 158–159.
- Wolf, A. M., Hunter, D. J., Colditz, G. A., Manson, J. E., Stampfer, M. J., Corsano, K. A., et al. (1994). Reproducibility and validity of a self-administered physical-activity questionnaire. *International Journal of Epidemiology*, 23, 991–999.
- Yoshimura, H. (2005). The potential of caffeine for functional modification from cortical synapses to neuron networks in the brain. *Current Neuropharmacology*, 3, 309–316.