Original Article

Dietary saturated fats and apolipoprotein B48 levels are similarly associated with cognitive decline in healthy older aged Australians

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Background and Objectives: As the incidence and prevalence of Alzheimer's disease increases, so does the body of epidemiological and clinical research that suggests a relationship between dietary fatty acids, in particular saturates, and cognitive decline. In this study, we investigated the association between serum apolipoprotein B48 (apoB48), saturated fatty acid intake and consumption behaviour, and cognitive performance, in healthy, older aged Australians. **Methods and Study Design:** We retrospectively analysed fasted serum apoB48 concentrations, food frequency questionnaire, and cognitive performance data collected from 147 participants (98F|49M) over the age of 50. We used Spearman's correlations and a nested domain model to evaluate the relationship between serum apoB48, dietary behaviour and measures of cognitive performance. **Results:** Overall, we found that higher fasted apoB48 concentrations, and/or dietary behaviours which led to increased dietary consumption of diets high in saturated fatty acids, were inversely associated with cognition. Interestingly however, dietary behaviour patterns of saturated fatty acid consumption and serum apoB48 were linked with better secondary memory and perceptual speed, respectively. **Conclusions:** This is the first time that fasted apoB48 has been implicated as a biomarker for cognitive decline and Alzheimer's disease risk.

Key Words: Alzheimer's disease, apolipoprotein B, cognitive performance, dementia, saturated fatty acids

INTRODUCTION

In 2015-2017, between 40-50 million people were reported to be living with dementia worldwide[1] and these numbers are predicted to triple by 2050.[2] A large body of literature has implicated cardiovascular disease as a risk factor for dementia and indeed, hypercholesterolaemia during midlife is associated with increased risk of dementia and cognitive decline later in life.[3,4] Furthermore, increasing evidence from epidemiological and clinical studies suggests that diets high in saturated fatty acids (SFA), relative to mono- and poly-unsaturated fatty acids (MUFA/PUFA), also impair cognitive function and increase the risk of Alzheimer's disease (AD).[5-9] Epidemiological studies in study participants aged greater than 60 report that diets enriched in SFA and cholesterol are associated with the prevalence of late-onset AD, lower Mini Mental State Examination score, mild cognitive impairment and global cognitive decline.[6,10-13] Similarly, cross-sectional and longitudinal follow-up studies identified that higher intake of SFA in all stages of adulthood are associated with AD and impaired cognitive performance, including memory speed and flexibility, prospective memory, and global cognitive function[5,8] However, the complete mechanisms by which dietary consumption of SFA influences neurocognitive function and risk of developing AD, are currently unknown.

Apolipoprotein (apo) B48, a major structural protein of chylomicrons, is synthesised upon the combination of lipids and proteins in enterocytes[14] and thus considered a specific biomarker of postprandial chylomicron synthesis.[15] A previous study reported a four-fold increase in plasma apoB48 concentrations in subjects with AD compared to age-matched controls,[16] implicating the potential use of plasma apoB48 as a biomarker for cognitive decline and AD risk. However, the interplay between apoB48, dietary SFA and AD, has never been previously explored. Therefore, in the present study, we investigated the associations between fasting serum apoB48 and cog-

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Manuscript received 17 April 2020. Initial review completed 26 May 2020. Revision accepted 20 July 2020.
doi: 10.6133/apjcn.202009_29(3).0012

nitive performance relative to SFA intake and SFA consumption behaviour (SFA-cb), in generally healthy, middle-to-older aged Australians.

METHODS

Clinical cohort

The Curtin University Human Research Ethics Committee approved the procedures described in this study (HR97/2011). 250 participants (96 males, 154 females) over the age of 50 (range=51-91 years) were recruited in Western Australia, Australia. Following written consent, participants were subjected to a comprehensive medical history and medications questionnaire. Exclusion criteria for the study were: major surgery or other significant clinical event within the previous 6 months; current diagnosis with a psychiatric disorder and/or currently taking psychotropic medications; head injury within the past 5 years; haemophilia, cancer or HIV at any stage of life; renal impairment; liver dysfunction; endocrine disorders (type I or II diabetes, hyper/hypo-thyroidism or hyper/hypo-parathyroidism); Mini Mental State Examination (MMSE) score <24, as previously described.[17-19] 103 participants were excluded from the study due to incomplete cognitive and dietary assessments, and the final number of participants included in the analyses was 147. With a statistical power of 0.8 based on previous studies,[17-19] the sample size of 147 was sufficient to detect significance at r=0.23.

Assessment of cognitive performance

Cognitive performance was assessed by a series of established neuropsychological tests utilised to assess the domains of cognitive performance most likely to be affected by age-related cognitive decline, as described previously.[17,18] The tests consisted of Rey Auditory Verbal Learning Test (RAVLT),[20] Mini Mental State Examination (MMSE),[21] 60-item Boston Naming Test (BNT),[22] Delis–Kaplan Executive Function System (DKEFS) verbal fluency subtests,[23] digit span and digit-symbol coding subtests from the Wechsler Adult Intelligence Scale - 3rd edition (WAIS-III),[24] National Adult Reading Test (NART),[25] and the Stroop test (Victoria version).[26] Trained staff administered all cognitive performance tests under supervision of a registered clinical neuropsychologist. The result scores were converted into Z scores and standardised for correlation analyses.[17]

Food frequency questionnaire

The Food Frequency Questionnaire (FFQ) was designed specifically to capture data on fat intake and consumption behaviour based previous studies.[27] The questionnaire answers were coded and analysed by a single researcher. FoodWorks (version 9) was used to calculate nutrient values for each of the foods listed. The SFA content of 250 mL of each of the milk products consumed were entered into a spreadsheet (Microsoft Excel) and multiplied by 0 for not applicable; 1.25 for less than 250 mL (less than 1 cup); 3.75 for between 250 and 500 mL (1-2 cups); and 7.5 for 500 mL or more (2 cups or more). The resulting number was multiplied by the frequency of consumption (per day; per week; per month) and the mean score between each day, week, and month, were taken to calculate the average consumption pattern. Where the serving size for a particular food was available, the SFA content of the food item was entered into an Excel spreadsheet and multiplied by the frequency of consumption for the relevant month. If the serving size for basic meats was not available, the SFA content of fully-trimmed, semi-trimmed, and untrimmed (or normal fat, low fat, and no fat, where appropriate) piece of meat, was multiplied by the frequency of consumption per month. For combination dishes included in the FFQ, for example 'mixed dishes with lamb', the SFA content of a standardised serve of casserole, stir-fry, and curry was used (FoodWorks (version 9)), and the mean was taken and multiplied by the monthly frequency. When multiplied by the frequency of consumption, either weekly or monthly, all scores were divided and calculated into a total amount of SFA consumed per day.

Dietary behaviour patterns of SFA consumption (SFA-cb) was determined from a 12-part questionnaire within the FFQ aiming to determine the likeliness or unlikeliness to consume additional SFA (e.g. How often do you trim the fat when you cook/eat meat?). Answers were scored from zero to five; zero was assigned to an answer that indicates an individual least likely to consume additional SFA (e.g. 'never') and five given to behaviour most likely to consume additional SFA (e.g. 'always' or '4 or more days a week').

Measurement of serum apolipoprotein B48

Following an overnight fast for a minimum of least 8 h, blood was collected via venipuncture, processed for serum and stored at -80 °C. ApoB48 concentration was measured by using a commercial sandwich ELISA kit using a monoclonal antibody raised against the C-terminal region of apo B48 (Shibayagi Human apo B48 ELISA Kit, Ishihara, Shibukawa, Japan) according to the manufacturer's instructions.[28]

Measurement of plasma lipids

Plasma concentrations of triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol, were analysed by a commercial pathology laboratory, PathWest, using an Architect ci8200/ c16000 Analyser and diagnostic analysis reagent kits (Abbott Laboratories, Abbott Park, IL, USA).

Statistical analyses

We utilised probability sampling method in this study. The relationship between SFA intake, SFA-cb, and fasting apoB48 and cognitive performance, was considered using Spearman's correlations and a nested domain Bayesian mixed-model.29 Spearman's correlations were analysed for SFA intake, SFA-cb, and fasting apoB48, against all cognitive performance measures. The nested domain model increases power by pooling outcome estimates from within a cognitive domain toward each other, reducing Type S (sign) and Type M (magnitude) errors through shrinkage toward common estimates.30 The principal domains assessed were D1 - verbal ability [BNT and D–KEFS fluency (letter fluency and category fluency)]; D2 - Stroop [Colors response time and interference (Colors/Dots) ratio]; D3-secondary memory [total items recalled across learning trial, items recalled from interfer-

ence list, short delay free recall, long delay free recall, recognition "hits," short delay forgetting score (learning trial 5 - short delay), and long delay forgetting score (learning trial 5 - long delay)]; D4 - primary memory (digits forward and digits backwards); and D5 - perceptual speed (digit-symbol coding). The outcome measurements to be nested within each domain were chosen a priori. An objective Bayesian approach to setting the priors was used, that is all priors could be described as being weakly informative, or uninformative for the scale of the data. Priors for the overarching coefficients were described by a normal distribution with a mean = 0 and SD = 100. The remaining coefficients for the outcomes and domains were described as being derived from a normal distribution centered on 0 and a SD estimated from a half-Cauchy distribution centered on 0, and scale set to 25.[31] Outcome level errors were modeled as being derived from a t-distribution to render the analysis robust.[32] The prior for the SD for each outcome was described by a uniform distribution between 0 and 100 and the degrees of freedom parameter was estimated from the inverse of a uniform distribution with lower and upper limits of 0.001 and 0.5. A large estimate for the degrees of freedom parameter indicates that the residuals can be described by a normal distribution, while a smaller degrees of freedom parameter indicates that the data have fatter tails and data points in this region are appropriately downweighted. Each variable was scaled to a mean of 0 and a SD of 1. If a smaller score on any neuropsychological measure indicated "better" performance, the score was inverted. After 5000 adaptation steps and 50,000 burn-in steps, a total of 50,000 Markov Chain Monte Carlo (MCMC) samples (thinned every tenth step) were saved across three chains for the final parameter estimates. Convergence was confirmed by examining plots of the posterior and using the Gelman–Rubin diagnostic. All posterior distributions used for inference had a minimal effective sample size of at least 1000 (usually ~10,000). The means ±95% highest density intervals (HDI) of the posterior distribution were used to describe the credibility interval for each of the parameter estimates.[32] All statistical analyses were conducted in R version 3.0.0 using the "rjags" package. All data presented were adjusted for age and sex.

RESULTS

The demographic profile of the participants are presented in Table 1. Of the 147 participants included in this analysis, 98 were female and 49 were male. The mean age of the participants was 64.5±7.13 and fasted blood glucose levels ranged between 4.2 and 9.1 mmol/L, with a mean of 5.29±0.71 mmol/L. The mean triglyceride and total cholesterol concentrations were 1.14±0.53 and 5.2±1.01 mmol/L, respectively, whilst the mean LDL-cholesterol and HDL cholesterol were 3.14±0.86 and 1.58±0.43 mmol/L, respectively. MMSE scores of the participants ranged from 24 to 30. These data indicate that the participants were generally healthy.

Table 1. Measures of age, SFA intake, SFA-cb, fasting apoB48, and MMSE scores and cognitive performance measures.

		Mean	Standard deviation	Range
Sex (F|M)	98|49			
Age		64.5	7.13	50-83
Glucose (mmol/L)		5.29	0.71	4.2-9.1
SFA intake (g)		19.4	10.80	1.54-99.01
SFA-cb		1.18	0.47	0-2.67
Fasting apoB48 (μg/mL)		5.67	4.05	0.47-23.40
Triglyceride (mmol/L)		1.14	0.53	0.4-3.3
Cholesterol (mmol/L)		5.2	1.01	2.8-7.6
LDL Cholesterol (mmol/L)		3.14	0.86	0.9-5.0
HDL Cholesterol (mmol/L)		1.58	0.43	0.8-3.3
MMSE		28.70	1.32	24-30
Cognitive performance measures				
Perceptual speed				
Digit-symbol coding		65.10	13.21	25-95
Primary memory				
Digits forward		10.57	2.16	6-16
Digits backward		7.01	2.37	3-18
Secondary memory -RAVLT				
Interference list		5.06	1.74	1-10
Short-delay recall		9.13	2.92	1-15
Long-delay recall		9.15	3.15	0-15
Recognition 'hits'		13.48	1.67	8-15
Stroop				
Colours time		28.71	10.53	14-18
Interference (C/D)		2.17	0.71	1.04-7.06
Verbal ability - DKEFS				
Letter fluency		41.28	11.11	7-71
Category fluency		44.29	8.51	27-67
Switching total		13.76	2.83	4-21

SFA: saturated fatty acid; SFA-cb: SFA consumption behaviour; apoB48: apolipoprotein B48; MMSE: mini mental state examination; C/D: Colors/Dots ratio; DKEFS: Delis–Kaplan executive function system; RAVLT: Rey auditory verbal learning test.

The mean fasting serum apoB48 levels was 5.67±4.05 µg/mL. The mean SFA intake was 19.4±10.80 g/day whilst the mean SFA-cb score was 1.18±0.47. Fasting serum apoB48 levels showed a weak correlation with SFA intake (0.155, p=0.061), whilst no association with SFA-cb was observed (0.012, p=0.885) (Figure 1). The association between SFA intake and SFA-cb was moderate and statistically significant (0.239, p=0.004). Plasma triglycerides strongly correlated with apoB48 (0.536, p<0.0001), whilst weak associations were found with both SFA intake (0.069, p=0.404) and SFA-cb (0.063, p=0.451). Similarly, fasting apoB48 were significantly associated with total cholesterol (0.292, p=0.0003) and LDL-cholesterol (0.312, p=0.0001), whilst a weak correlation was indicated between SFA intake and SFA-cb. In contrast, HDL cholesterol was inversely correlated with fasting apoB48 (–0.229, p=0.005), whilst weaker associations were observed with SFA intake (–0.050, p=0.547) and SFA-cb (–0.092, p=0.267). Interestingly, fasting apoB48 was inversely associated with age (–0.153, p=0.063) and SFA intake (–0.051, p=0.542).

Figure 2 presents the association between fasting serum apoB48, SFA intake, and SFA-cb, and cognitive performance measures, assessed by a nested domain model presented as a heat map. Serum apoB48 levels showed inverse associations across all measures of verbal episodic performance as indicated in RAVLT short- and long-delay, recognition, and sum of trials 1-5. Similarly, SFA-cb and SFA intake also showed modest correlations with RAVLT short/long delay and sum of trials 1-5. Additionally, Spearman's correlation coefficient analyses showed similar inverse associations between apoB48 levels and SFA-cb with RAVLT scores (Figure 3).

On the other hand, nested domain model assessment indicated that fasting serum apoB48 concentrations were positively associated with perceptual speed measure of digit symbol coding and primary memory domains (digits forward and backward; Figure 2). Similar positive correlations were also detected between SFA-cb and digits forward, backwards and symbol coding outcomes, whilst a modest inverse relationship between digits assessments and SFA intake were observed. Such positive associations between fasting apoB48 and digits forward, digits backwards and digit symbol coding, were also indicated with Spearman's correlation analysis (Figure 3).

A summary of findings is presented in Figure 4.

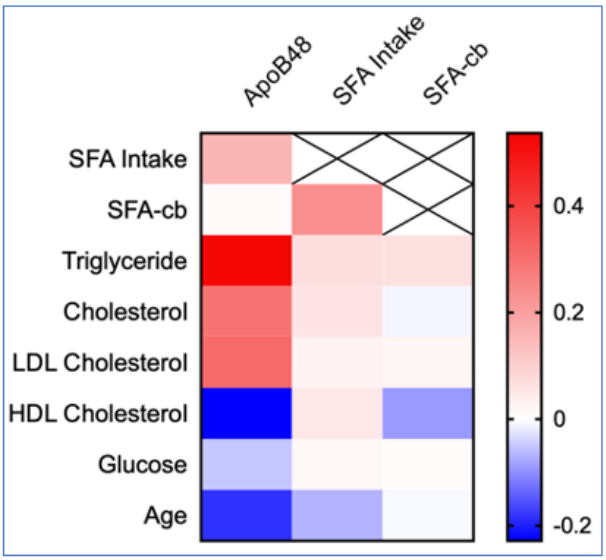

Figure 1. General correlation profile of apoB48, SFA intake and SFA-cb. Correlation coefficient was analysed between fasted serum apoB48, saturated fatty acid (SFA) intake, and SFA consumption behaviour (cb) and plasma lipid profile, glucose and age.

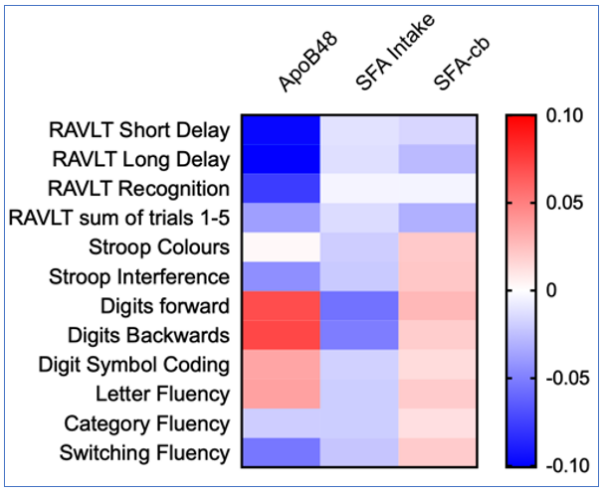

Figure 2. Nested domain model analyses between apoB48, SFA and cognition. Heat map shows the relationship between fasting apoB48, saturated fatty acid (SFA) intake, and SFA consumption behaviour (cb) and cognitive performance measures from the nested domain Bayesian model.

DISCUSSION

In this study, we examined the relationship between SFA dietary behaviour, serum apoB48 levels, and cognitive performance, in generally healthy Australian adults over the age of 50. We found that fasting apoB48 measures were inversely associated with secondary memory performance measures. To our knowledge, this is the first study to report the inverse association between fasting apoB48 and verbal episodic memory and attention, including measures of short-term memory, short-delay working memory, long-delay memory, recognition memory, and working memory. The current study also found that dietary SFA-cb that led to increased intake of SFA had an inverse impact on short- and long-term memory recall. This observation is consistent with previous studies where the dietary consumption of SFA was shown to be positively associated with dementia, Alzheimer's disease, mild cognitive impairment and cognitive decline.[33] Furthermore, our findings also support previous animal studies where the ingestion of an SFA-enriched diet increased the synthesis of intestinal apoB48 and Alzheimer's disease amyloid protein, neuronal dysfunction and cognitive decline.[34-36] Additionally, these findings may have implications for other metabolic disorders such as insulin resistance/diabetes where postprandial hypertriglyceridemia or lipoproteinemia are often observed.

Whilst the mechanisms underlying the inverse association between fasting apoB48, SFA-cb and SFA intake, and hippocampal-dependent memory recall were not directly investigated in this study, previous studies suggest

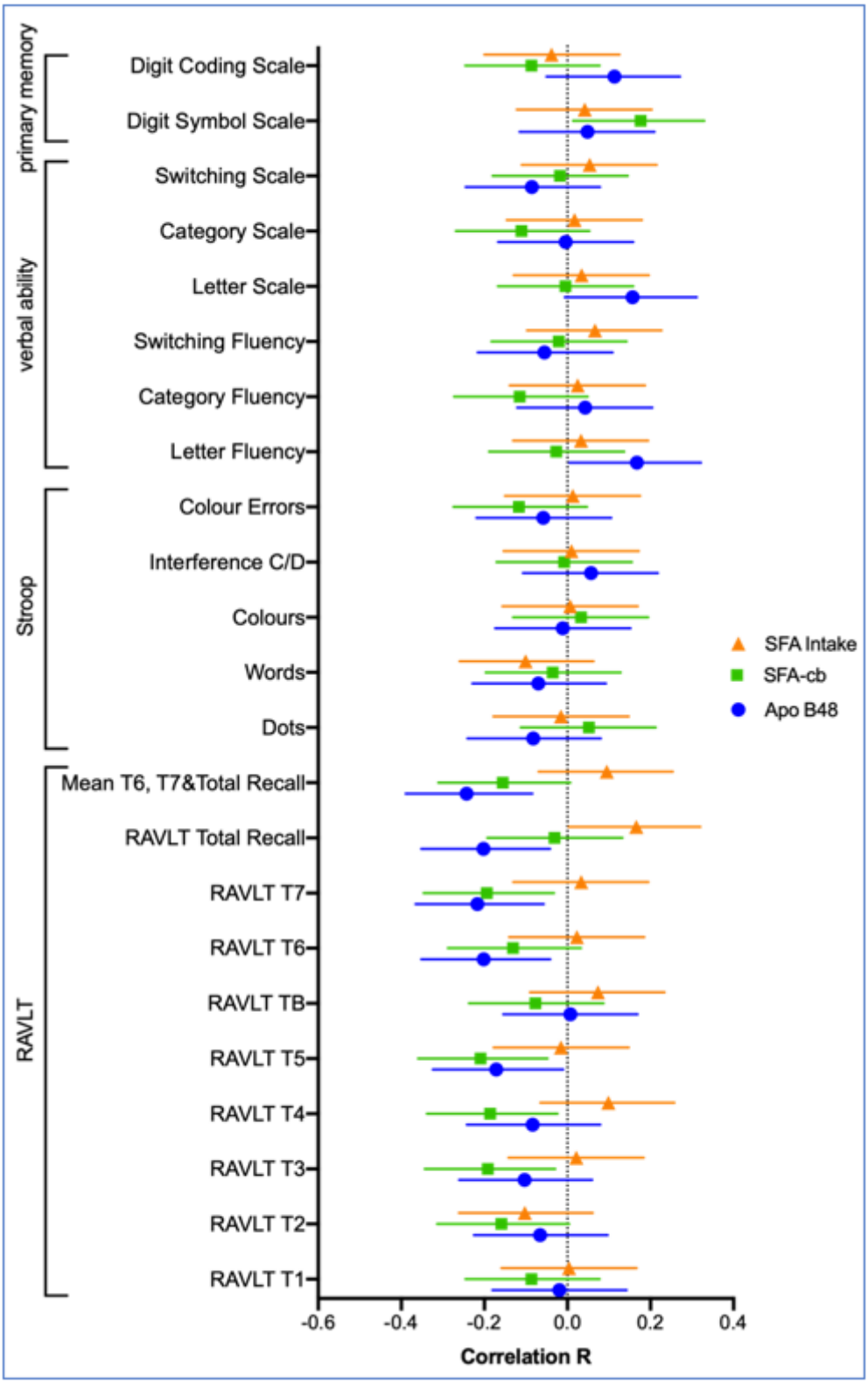

Figure 3. Spearman's correlation coefficients between apoB48, SFA, and cognitive performance. Standardized slope of Spearman's coefficients for the association between fasting serum apoB48, saturated fatty acid (SFA) intake, and SFA consumption behaviour (cb) and cognitive performance measures are shown.

that consuming a diet enriched in SFA compromises cerebrovascular integrity within the hippocampal formation, which decreases neural function and ultimately, memory performance.[5-8] This effect has been reported in rodent models fed a diet with modest increases in SFA content, resulting in a loss of cortical cholinergic neurons, a decline in spatial memory[37] and impaired hippocampal-dependent cognitive functions.[38,39] Our previous studies have also showed that chronic long-term feeding of SFA-enriched diets resulted in significant breakdown of the cerebrovascular blood-brain barrier, heightened neuroinflammation and neurodegeneration, and subsequently, a decline in neurocognitive function in wild-type mice.[36,40,41] Moreover, Kaplan and Greenwood found that greater dietary intake of SFA results in the use of protein as the preferred energy source over carbohydrates, re-

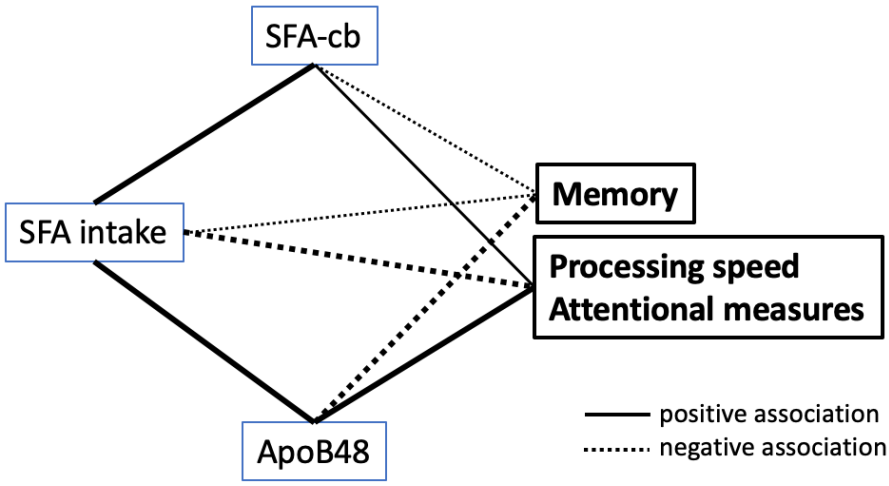

Figure 4. Summary of findings. The findings of this study is summarised showing the associations between saturated fatty acids (SFA) consumption behaviour (cb), SFA intake, fasting serum apolipoprotein B48 (apoB48) and cognitive performance. Red lines and blue lines show positive and negative associations, respectively, whilst the thickness of the line represents the strength of correlation.

sulting in decreased insulin sensitivity and thereby glucose uptake of the brain via the GLUT4 receptor, which led to memory impairment and delayed reaction times.[42]

Interestingly, in the present study, we found that serum apoB48 levels and SFA-cb were positively associated with processing speed, working memory and attentional measures. A recent paper reported that in males, apoB values predicted better perceptual speed performance up until the age of 65,[43] findings consistent with our study. However, the underlying mechanisms of how apoB48 and dietary SFA positively impact on perceptual speed are currently unknown.

A clear limitation of the data is the lack of congruity between SFA-cb and fasting apoB48 with SFA intake. Despite clear correlations made between the other variables and memory performance, the SFA intake data does not follow the same relationship observed. It indicates that in relation to establishing a clear link between diet and disease, evaluating dietary behaviours may be an advantageous alternative to measuring nutrient intake, as they may capture usual or habitual dietary intake and do not rely on frequency or portion sizes.[44] As well as substantive epidemiological research that has identified the debilitating effect of dietary SFAs on cognitive performance,[5-8] future FFQs could include questions that describes participant SFA-cb over their life course. Another potential confounding factor is that the data of SFA intake and SFA-cb were based on participants' memory recall. Thus, for the participants who exhibited lowered memory and cognitive performance, the dietary data collected may not be as accurate. In addition, the study was only done as preliminary screening for future studies and did not include other demographic and lifestyle factors such as education, smoking and physical activity, as covariates for statistical analyses. These points will need to be considered and addressed in the future studies. The FFQ tool we used in this study was not designed to capture the intake of industry processed foods, thus was unable to accurately estimate the intake of trans fatty acids. Additionally, the intake of plant-derived micronutrients were not considered in the present study. Because such nutrients are mainly water-soluble and are not metabolised through the chylomicron pathway, we considered that these factors less relevant to the primary focus of the present study, which is on the interplay between saturated fatty acid intake, chylomicrons and cognitive performance.

In conclusion, this study identified a potential biomarker, fasting apoB48, in assessing cognitive decline and AD risk, which indeed implicates a putative role of apoB48 in the underlying mechanisms of SFA-induced cognitive deficits. We also demonstrated that SFA-cb is linked with a decline in short- and long-term memory recall, which suggests public health messages should be tailored to dietary behaviour change rather than being nutrient-focused. Future studies with more accurate measures of nutrient intake are needed to further interrogate the relationship between SFA intake and cognitive performance. The analyses of other dietary lipids intake including trans-fatty acids, n-3/6/9, food sources, and their effects on cognitive performance in relation to plasma apoB48 levels, may also provide further important mechanistic insights and opportunities to mitigate risks for cognitive decline.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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