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ORIGINAL RESEARCH

Dietary Saturated Fat Intake Moderates the Effect of Plasma Triglycerides on Memory Performance in Middle-Aged Adults

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Purpose: With Alzheimer's disease and related dementias are projected to triple by 2050, addressing modifiable health and lifestyle factors is crucial to prevention and reducing the associated public health burden. This study investigates the interaction between triglyceride levels and dietary fat intake and diet quality on memory performance in middle-aged adults at heightened risk for metabolic health issues.

Patients and Methods: Community-dwelling adults aged 40–65 with cardiometabolic health risks participated in this cross-sectional study. Participants with a history of neurological or psychiatric conditions were excluded. Dietary intake was self-reported through a 3-day food record, and serum triglyceride levels were measured. Neuropsychological testing assessed memory performance. Cross-sectional regression analyses examined how dietary fat intake and quality interact with triglyceride levels to affect memory performance in 146 adults.

Results: The analysis revealed a significant interaction between triglyceride levels and the ratio of dietary saturated fat to total caloric intake on memory performance ($\beta = -0.087$, $p = 0.022$). The relationship between triglyceride levels and memory performance was modified by the ratio of saturated fat to total caloric intake. At higher levels of saturated fat intake, higher triglycerides were associated with worse memory performance. However, at lower levels of saturated fat intake, the association between triglycerides and memory performance was not statistically significant. Better adherence to USDA dietary guidelines, reflected by higher Healthy Eating Index 2020 scores, was associated with better memory performance ($\beta = 0.018$, $p < 0.002$), regardless of triglyceride levels.

Conclusion: Diet quality, as indicated by adherence to dietary guidelines, supports cognitive health. Elevated triglycerides combined with a high ratio of dietary saturated fat intake were associated with poorer memory performance. Precision nutrition strategies aimed at reducing saturated fat intake in midlife adults with elevated triglyceride levels may help mitigate memory-related cognitive decline and enhance brain health.

Plain Language Summary: This study explored how diet and triglyceride levels (a type of fat in the blood) might influence memory and the risk of Alzheimer's disease and other dementias in adults at higher risk. We focused on middle-aged adults (ages 40-65) who had cardiometabolic health issues, such as obesity, high blood pressure, high cholesterol, or diabetes. We worked with 146 adults from the community who reported their eating habits over three days and took tests to measure triglyceride levels and memory performance. The study found that higher triglyceride levels combined with a diet high in saturated fats (common in many Western diets) were linked to poorer memory performance. However, adults with high triglycerides who ate less saturated fat performed better on memory tests than those with higher saturated fat intake. Overall, following a healthier diet was associated with better memory, regardless of triglyceride levels. These findings suggest that improving diet quality—by adhering to dietary guidelines—could help protect brain health and reduce memory problems. For people with high triglycerides, cutting back on saturated fat may help improve memory and protect against cognitive decline. These results point to the importance of personalized nutrition strategies to support brain health and potentially reduce the risk of memory loss as we age.

Keywords: cardiometabolic, Western diet, cognition, midlife

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Introduction

With Alzheimer's disease and related dementias (ADRD) projected to triple by 2050, and existing drug treatments proving inadequate or inaccessible,[1] addressing modifiable health and lifestyle factors is essential for preventing ADRD and reducing the associated public health burden. Research has underscored the mechanisms linking metabolic health to dementia, highlighting the importance of managing metabolic risk factors in midlife as a promising strategy to mitigate the development and progression of ADRD.[2] Among the plethora of cardiometabolic risk factors, elevated triglyceride levels are of particular interest because they disrupt the blood-brain barrier,[3] promote vascular dysfunction,[4] and are independently associated with cerebral amyloidosis.[5] Furthermore, elevated triglycerides are often the only metabolic syndrome component that predicts the onset of all-cause dementia.[6]

Triglycerides, blood lipids stored in adipose tissue as an energy source, play a significant role in regulating metabolic functions.[7] Beyond their metabolic role, triglycerides also have broader implications for cognitive functioning. As they can cross the blood brain barrier, triglycerides accumulate in the brain over time, as evidenced by their detection in human cerebrospinal fluid.[3] In human adults, elevated serum triglycerides and the triglyceride to high-density lipoproteins (HDL) ratio are associated with disruptions in hippocampal neuronal connections and organization before any detectable hippocampal atrophy.[8] This suggests a deleterious effect of elevated triglyceride levels on hippocampal tissue integrity and function through mechanisms such as the release of pro-inflammatory cytokines, disrupting vascular endothelial function, reducing cerebral perfusion, and mimicking chronic neuroinflammation seen in older adults. Moreover, Sanjana et al demonstrated that the triglyceride to HDL ratio was independently associated with memory performance, highlighting subtle memory-related cognitive deficits linked to heightened cardiometabolic risk profiles in adults without clinical signs of impairment. In animal models, an accumulation of serum triglycerides can block the activation of leptin and insulin receptors within the central nervous system, further impacting learning and memory processes.[3] This potentially critical effect of triglycerides on memory-related brain structures and cognitive performance has significant implications for daily functioning, personal independence, and quality of life in midlife.[9]

Considering the risk of high triglycerides for memory-related cognitive impairment, Dimache et al provide a review supporting the negative association between triglyceride levels and cognitive functioning. This is evidenced by large longitudinal studies linking elevated triglycerides in midlife to the incidence of Alzheimer's disease, vascular cognitive impairment, and increased amyloid-beta deposition.[10] Notably, 20-year cohort studies in adults reveal that elevated triglyceride levels in midlife serve as predictive markers for memory and global cognitive decline[11] and Alzheimer's disease pathology.[12] These findings further support the involvement of triglycerides in preceding cognitive impairment and the development of ADRD, underscoring the potential for interventions targeting triglyceride levels to mitigate cognitive decline and improve brain health. Yet, not everyone who suffers from hypertriglyceridemia experiences early cognitive impairments. The precise biological mechanisms linking high triglyceride levels to cognitive decline remain elusive as they are likely complex and may be influenced by individual differences in health behaviors.

Dietary fat intake and diet quality may serve as significant health behaviors influencing cognitive vulnerability in those with elevated triglycerides, highlighting a potential interaction that could exacerbate cognitive decline. Research consistently supports that adhering to the Mediterranean diet has been linked to reduced cognitive decline and a decreased risk of ADRDs.[13] Additionally, research on diet quality measured by the Healthy Eating Index (HEI) has shown that higher HEI scores are associated with better processing speed, executive functioning,[14] and a lower risk of incident dementia.[15] Moreover, over a 13-year period, better adherence to a long-term higher quality diets was associated with larger hippocampal volumes in middle-aged adults.[16] Conversely, Western dietary patterns have been associated with poorer cognitive performance in a cross-sectional study, although a 20-year follow-up study found no significant association.[17] Moreover, a systematic review found no clear association between the intake of various classes of dietary fats and the risk of the development of ADRD.[18] These contrasting findings highlight the complexity of the relationship between diet and cognitive function. It is possible that long-term studies or large-scale systematic reviews may overlook specific vulnerabilities, such as metabolic health or genetic predispositions, which could modulate the effect of diet on cognitive outcomes. This underscores the need for further investigation to better understand the contexts in which dietary interventions may be most effective in mitigating cognitive decline.

Research synthesizing diet-related cognitive and brain outcomes highlights how dietary fats influence brain health, emphasizing that the type of fat plays a crucial role in brain function.[19] Both saturated and unsaturated fats are digested into free fatty acids and monoglycerides, absorbed in the intestines, and transported by chylomicrons to tissues where they are broken down by lipoprotein lipase. Wang et al describe how the type of fat differentially affects triglyceride metabolism and clearance from the bloodstream. Saturated fats increase low-density lipoprotein (LDL) cholesterol and decrease HDL cholesterol, which raises cardiovascular disease risk and contributes to liver fat accumulation. In contrast, unsaturated fats, including monounsaturated and polyunsaturated fats, lower LDL cholesterol, increase HDL cholesterol, improve lipid profiles, reduce inflammation, and are readily oxidized for energy.[20] For individuals with elevated triglycerides, modifying specific dietary fat intake is recommended, as saturated fats promote triglyceride synthesis and impair clearance, whereas polyunsaturated and monounsaturated fats have the opposite effect.[21]

Elevated saturated fat intake, a key characteristic of the Western diet, has been associated with poorer global cognitive function, prospective memory decline, and an increased risk of mild cognitive impairment in midlife, even after adjusting for demographic factors, vascular health, and Apolipoprotein E (APOE) ε4 status.[22] In contrast, high intake of polyunsaturated fatty acids is linked to better semantic memory. Saturated fat intake has also been shown to promote neuroinflammation and accelerate hippocampus-dependent memory decline in both rodent models[23,24] and adult humans.[25] Furthermore, randomized controlled trials indicate that saturated fat increases serum endotoxin concentrations, while n-3 fatty acids reduce inflammatory serum markers.[26] However, these studies have not explored how dietary factors interact with memory-related cognitive impairment in middle-aged adults with existing metabolic health risks. Memory performance is particularly critical in this context, as adults with metabolic syndrome and cardiometabolic risk profiles often show memory deficits.[27] This highlights the need to investigate how memory-related cognitive vulnerabilities associated with elevated triglyceride levels may vary with different nutrient intakes or diet quality, to best inform whether precision nutrition interventions may effectively address these observed cognitive vulnerabilities. Our study aims to contribute to this ongoing dialogue by examining how dietary fat intake, particularly saturated fat, interacts with triglyceride levels to influence memory performance in midlife adults.

Given the significant impact of dietary fat intake on cognitive function and brain health, it is important to consider genetic risk influences, particularly the APOE ε4 allele, which is the most significant genetic risk factor for ADRD.[28] This allele influences lipid metabolism, brain cholesterol levels, and the development of amyloid-β and tau pathologies central to ADRD.[29] According to Raulin et al, individuals with the APOE ε4 allele exhibit different responses to dietary fats and metabolic functions compared to non-carriers. Our previous research demonstrates that greater dietary polyunsaturated fat intake is associated with better memory performance in healthy middle-aged adults who were APOE ε4 non-carriers, but not for ε4 carriers.[30] Additionally, in adults with metabolic syndrome who are APOE ε4 carriers, we examined the effects of large neutral amino acids on brain health through neuroimaging results. Specifically, we found a positive association between serum concentrations of tryptophan and phenylalanine and the amount of white matter hyperintensities in adults with metabolic syndrome who are APOE ε4 carriers, while no such relationship was observed in non-carriers.[31] Therefore, to build on these findings and further clarify the relationship between diet, metabolic health, and cognitive outcomes, it is essential to account for the APOE genotype.

This cross-sectional study aims to investigate how the relationship between serum triglyceride levels and memory performance is influenced by dietary saturated fat intake and overall diet quality in middle-aged adults with metabolic health and genetic risk factors for ADRD. We hypothesize that elevated triglycerides, when combined with a diet high in saturated fat, may synergistically worsen memory function in midlife. The study seeks to inform precision nutrition interventions aimed at mitigating memory-related cognitive decline in adults with elevated triglyceride levels, while also providing insights for developing individualized preventive strategies for those at risk of ADRDs.

Material and Methods

Study Participants and Design

This cross-sectional study included community-dwelling adults in midlife with heightened cardiometabolic health risks. Selection of the participants was based on the following inclusion criteria: (1) age 40–65 years old; (2) a score of >24 on

the Mini-Mental State Examination® (MMSE®), to ensure exclusion of people with severe cognitive impairment;[32] and (3) a score of >70 on the Wechsler Test of Adult Reading (WTAR), to ensure intellectual function within the average range.[33] Exclusion of participants was based on the following criteria: (1) presence or history of neurological or psychiatric disease (eg, Stroke, Parkinson's Disease, Epilepsy, Huntington's Disease, etc).; (2) smoking (including regular use of cigarettes, e-cigarettes, vaping devices, and any other form of tobacco or nicotine consumption); and (3) incomplete study visits. The Institutional Review Board at the University of Texas at Austin approved all study procedures (#2016-09-0135 and #2011-07-0025). This study was conducted in accordance with the Declaration of Helsinki. All participants provided written, informed consent before enrolling in the study.

Three-Day Food Record

Dietary intake was assessed using a self-reported, 3-day food record. The 3-day food record is a valid tool for dietary assessment and is more reliable than commonly used Food Frequency Questionnaires.[34] Participants were instructed to select 3 days (2 weekdays and 1 weekend day) that represent their typical eating habits, ensuring a balance of dietary intake across different days of the week. Participants were specifically asked to avoid reporting on days involving special occasions, holidays, or events that might not reflect their usual eating patterns. The food records consisted of sections for participants to write down the time, amount, description, and any relevant notes for all foods and beverages consumed. Each participant was encouraged to provide as much detail as possible, including portion sizes, preparation methods, and brand names when applicable. Additionally, participants were encouraged to estimate portion sizes using common household measures (eg, cups, teaspoons, or visual guides) and were provided with resources (eg, food portion images) to support accurate estimations. To ensure accurate and consistent reporting, participants were given identical instructions and a sample entry showing how to fill out the food record with appropriate detail. Participants were reminded to complete the food record as honestly and accurately as possible and were reassured that their responses would be kept confidential.

Any unclear or missing entries were clarified by a research assistant during subsequent study visits, allowing for verification and correction if necessary to minimize reporting errors or misunderstandings.

Dietary Analysis

All the dietary data obtained were analyzed by a registered dietician using the Nutritionist Pro® Software Version 4.0.[35] All analyzed data was reported as nutritional summaries, including total energy intake, macronutrients, micronutrients, vitamins, amino acids, and food exchanges for each participant.

The average amount of saturated fat consumed over 3 days was converted into a ratio of dietary saturated fat to total caloric intake by transforming grams of saturated fat into kilocalories (9 kcal/gram of fat) and adjusting for total energy intake using the average kilocalories consumed. This ratio of dietary saturated fat to total caloric intake was used for subsequent dietary fat intake analyses.

Diet quality was calculated based on each participant's adherence to USDA dietary guidelines. Nutritional summaries were transformed into HEI-2020 total scores by applying the scoring guidelines for the 13 food components outlined by Shams-White et al.[36] These components include adequacy components (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids) and moderation components (sodium, refined grains, saturated fats, and added sugars). Each food component's intake was scored proportionately, and the HEI-2020 total score was obtained by summing all individual component scores, yielding a possible score range of 0 to 100. Higher scores indicate better adherence to the USDA 2020–2025 Dietary Guidelines for Americans, representing better diet quality. By examining both the ratio of dietary saturated fat to total caloric intake and HEI-2020 total scores, we can determine if the association between of dietary saturated fat intake and memory performance are independent of overall diet quality.

Unusual or implausible caloric values were identified using a linear regression analysis of caloric intake and body mass index. Participants with standardized residuals of total energy intake greater than ±3 standard deviations from the mean were classified as implausible reporters and excluded from the analysis.

Health Assessment and Blood Collection

Participants provided self-reported medical history and medication details before the health assessment. They were instructed to fast for 12 hours prior to their appointment to ensure accurate measurement of fasting glucose and lipid levels. Health assessments were scheduled in the morning to standardize timing across participants. Participants visited a university research laboratory for the health assessment. Blood samples were collected by certified phlebotomist research assistants via venipuncture through the antecubital vein. Fasting glucose levels were measured using standard enzymatic techniques. Serum concentrations of triglycerides, HDL, LDL, and total cholesterol were measured immediately after the blood draw using a commercial device.[37] Triglyceride values below 45 mg/dL or above 650 mg/dL were excluded due to uncertain reliability, as described by the manufacturer. Additionally, outlier triglyceride concentrations were detected using the interquartile range method and removed from the analyses.[38] Blood pressure was measured using the cuff technique on the right brachial arm. Participants were seated for at least 5 minutes and a correctly sized cuff was applied to the right arm. Systolic and diastolic measurements were recorded. Anthropometric measurements, including height and weight, were taken using a balance beam scale. Measurements were recorded in the morning, after participants had fasted for 12 hours, to minimize any potential variations caused by daily fluctuations in weight. Participants were instructed to wear light weight clothing and remove their shoes before the measurements. All procedures were conducted by trained research assistants to ensure consistency and accuracy across participants.

Apolipoprotein E ε4 Genotyping

Saliva samples were collected during the health assessment using the Oragene Discover (OGR-500) kit, with participants produced 500 uL of saliva using the prepIT·L2P kit from DNAgenotek. Genomic DNA was extracted and purified according to the manufacturer's instructions. All purified samples were stored at −40 °C before the genotyping process. Using polymerase chain reaction amplification and Sanger sequencing, ApoE genotyping, originally described by Olesen et al,[30] was conducted with Variant Reporter Software[39] at the DNA Sequencing Facility at the University of Texas at Austin. The study participants were classified into two groups: participants carrying one or two copies of the ApoE ε4 allele (ApoE ε4 carriers) or participants not carrying any copy of the ApoE ε4 allele (ApoE ε4 non-carriers).

Neuropsychological Testing

Participants completed the MMSE® to assess global functioning, the WTAR to assess premorbid IQ, and the California Verbal Learning Test (CVLT-II) to assess verbal learning and memory.[40] A memory composite was computed as the average of the z-scores from the short delay recall, long delay recall, and recognition discriminability subscales from the CVLT-II.

Cross-Sectional Interaction Analyses

Cross-sectional regression analyses were conducted using R Statistical Software.[41] Four regression models were conducted to investigate the interactions and associations between dietary fat intake and diet quality with triglycerides on memory performance. First, multiple regression models were used to explore interaction effects: one examining the interaction between the ratio of saturated fat in total energy intake and triglyceride levels on memory performance, and the other between HEI-2020 total score and triglycerides on memory performance. Next, two linear regressions were conducted to test the main effect of triglycerides and dietary quality on memory with triglyceride serum levels and the HEI-2020 total score as predictor variables to memory performance, separately. Covariates, including age, sex, education, diabetes status/diagnosis (or medication for diabetes), cholesterol medication, hypertension status/diagnosis (or medication for hypertension), APOE-ε4 status, and BMI were integrated in all analyses.

Results

Sample Characteristics

A total of 146 participants were included in the cross-sectional analyses, with a summary of participant demographics and health measures described in Table 1. Three participants were excluded from analysis due to their total energy intake residuals exceeding 3 standard deviations from the mean. Dietary fat intake and diet quality measures were normally

Table 1 Selected Participant Characteristics (n = 146)

Characteristic	Value (Mean ± SD)	Count (n, %)
Age, in years	50.6 ± 6.7	–
Sex		
Female	–	82, 56.1
Male	–	64, 43.8
Race and ethnicity		
White, non-Hispanic	–	79, 54.1
Hispanic/Latino	–	29, 19.9
Black/African American	–	9, 6.2
Asian	–	2, 1.4
Other	–	8, 5.5
Multiple races/ethnicities	–	14, 9.6
Missing	–	5, 3.4
Education, in years	16.3 ± 2.4	–
MMSE® score	28.8 ± 1.3	–
APOE-ε4 carriers	–	40, 27.4
Taking diabetes medication	–	15, 10.3
Taking antihypertensive medication	–	33, 22.6
Taking cholesterol medication	–	23, 15.8
Fasting glucose, in mg/dL	96.2 ± 18.4	–
Systolic blood pressure, in mmHg	121.7 ± 14.7	–
Diastolic blood pressure, in mmHg	72.8 ± 10.2	–
Total cholesterol, in mg/dL	197.4 ± 48.2	–
Height, in m	1.69 ± 0.09	–
Body weight, in kg	94.1 ± 33.2	–
BMI, in kg/m^2	32.8 ± 11.3	–
BMI ≥ 35 kg/m^2	–	39, 26.7
HEI-2020	49.3 ± 11.0	–
Average energy intake, in kcal	1940 ± 581	–
Average intake saturated fat, in grams	25.4 ± 11.7	–
Saturated fat in energy intake, in %	11.7 ± 3.9	–

Abbreviations: SD, standard deviation; MMSE®, Mini-mental state examination; APOE-ε4, Apolipoprotein E ε4 allele; mg/dL, milligrams per deciliter; mmHg, millimeters of mercury; HEI-2020, Healthy Eating Index 2020; m, meter; kg, kilogram; kcal, kilocalories; %, percentage.

distributed (Figure 1). Our sample had a mean age of 50 years, with the majority holding a college education and all exhibiting intact global cognition. The sample is representative of the racial and ethnic diversity of Texas at the state level. Notably, the prevalence of APOE-ε4 carriers, individuals with diabetes, and those taking cholesterol and antihypertensive medications aligns with the risk profiles associated with ADRD.[42,43] This suggests that while our sample does not exhibit cognitive impairment, it is representative of individuals at increased risk for developing ADRD.

Ratio of Dietary Saturated Fat to Total Caloric Intake with Triglyceride Levels Interaction on Memory Performance

The interaction analysis revealed that the association between triglyceride levels and memory performance varied according to the ratio of dietary saturated fat to total caloric intake ($\beta = -0.087$, $p = 0.022$, 95% CI = [−0.161, −0.013]. Specifically, at higher triglyceride levels (one SD above the mean), a higher ratio of saturated fat intake was linked to poorer memory performance. In contrast, at lower saturated fat intake ratio levels (one SD below the mean), there was no significant association between triglycerides and memory performance (Figure 2). Notably, a Johnson-Newman simple slope analysis of triglycerides and memory performance reveals that at a ratio of saturated fat to total

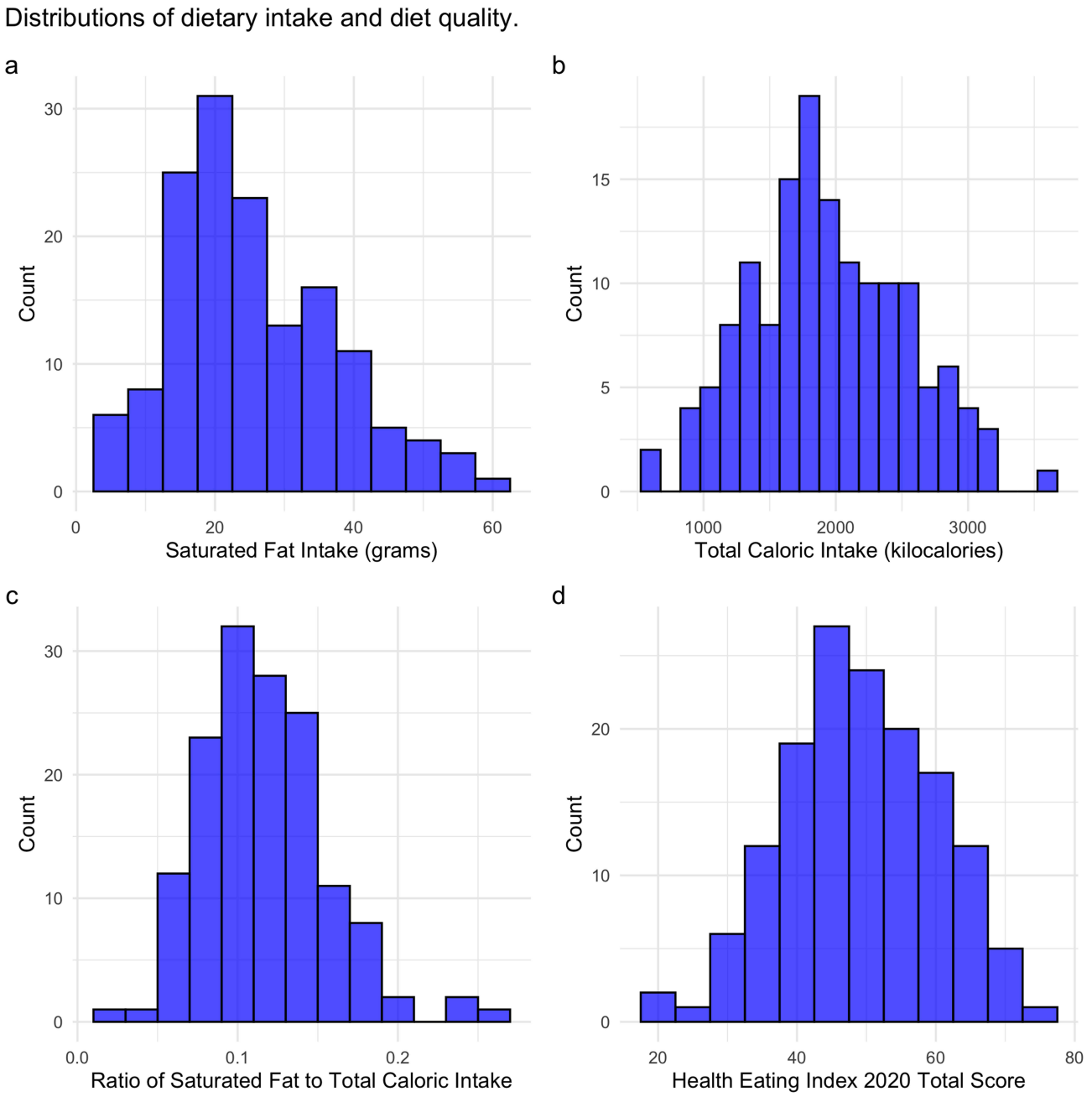

Figure 1 Histograms illustrating the distributions of dietary intake and diet quality variables extracted from 3-day food records are shown. Panel (**a**) displays the distribution of the three-day mean dietary saturated fat intake in grams. Panel (**b**) presents the distribution of the three-day mean total caloric intake in kilocalories. Panel (**c**) depicts the distribution of the three-day mean ratio of dietary saturated fat to total caloric intake, reflecting the ratio of dietary saturated fat intake. Panel (**d**) illustrates the distribution of the mean Healthy Eating Index 2020 Total Score.

caloric intake of 0.077 (one standard deviation below the mean), the t-value is 1.167 with a p-value of 0.243; at the mean ratio of saturated fat to total caloric intake of 0.117, the t-value is −0.665 with a p-value of 0.507; and at a ratio of saturated fat to total caloric intake of 0.156 (one standard deviation above the mean), the t-value is −2.540 with a p-value of 0.010. Further, the Johnson-Newman simple slope analysis reveals that when the ratio of saturated fat intake exceeds 14% of total caloric intake, elevated triglyceride levels are significantly associated with poorer memory performance. These results suggest that elevated triglycerides are not associated with memory deficits when the ratio of saturated fat intake is low. In a sensitivity analysis, we examined the effect of APOE-ε4 status by comparing the results from the

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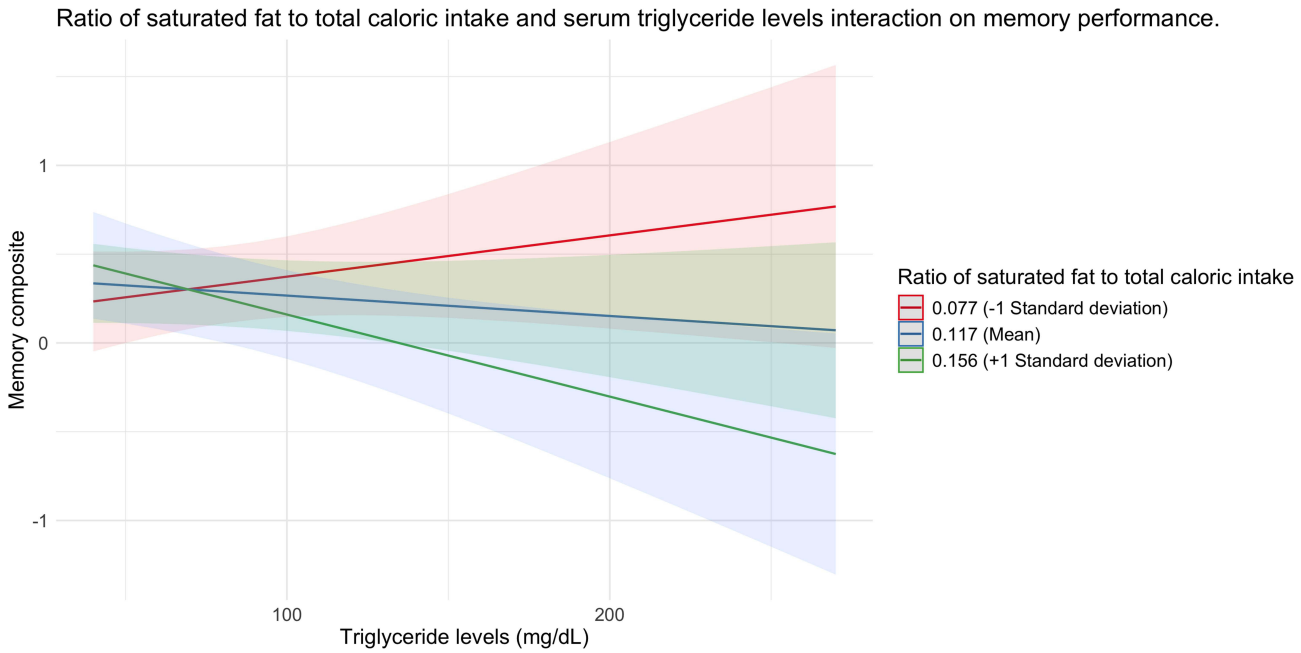

Figure 2 The interaction analysis reveals that dietary saturated fat intake moderates the relationship between plasma triglyceride levels and memory performance. Participants with elevated triglycerides who consume a high-saturated fat diet exhibit poorer memory performance. The interaction effect between triglyceride levels and dietary saturated fat intake on memory composite scores is significant ($\beta = -0.087$, $p = 0.022$), indicating that this interaction significantly contributes to variations in memory performance, while controlling for age, sex, education, genetic risk, and medications. The overall model was significant ($F(11, 134) = 2.376$, $p = 0.010$, $R^2 = 0.163$). **Abbreviation**: SD, standard deviation.

model with and without APOE-ε4. The exclusion of APOE-ε4 status did not alter the relationships between the interaction term (triglycerides and saturated fat intake) and memory performance.

Serum Triglycerides and Memory Performance

A separate regression analysis testing the association between memory performance and serum triglyceride levels revealed no significant association ($\beta = -0.002$, $p = 0.167$, 95% CI = [−0.004, 0.001]). The overall model was significant ($F(9, 136) = 2.132$, $p = 0.031$, $R^2 = 0.124$).

Diet Quality Interaction and Regression on Memory Performance

To evaluate the relationship between dietary quality and memory performance, we conducted two separate analyses: one examining the interaction effect between diet quality and triglyceride levels on memory performance, and the other assessing the main effect of diet quality on memory performance. First, a multiple linear regression analysis tested the interaction between HEI-2020 scores and triglyceride levels on memory performance. This interaction was not significant, although the overall model was significant ($F(11, 134) = 2.904$, $p = 0.002$, $R^2 = 0.192$). Second, a separate multiple linear regression analysis evaluated the main effect of HEI-2020 scores on memory performance. This analysis revealed a significant positive association between HEI-2020 scores and memory performance ($\beta = 0.018$, $p < 0.002$, 95% CI = [0.007, 0.030]), indicating that higher HEI-2020 scores are related to better memory performance, independent of other covariates (Figure 3). The overall model for this main effect was also significant ($F(9, 136) = 3.151$, $p < 0.002$, $R^2 = 0.173$).

Discussion

The results of this study provide deeper insights into the intricate relationship between triglyceride levels, memory performance, and dietary fat intake and quality. The study suggests that dietary fat intake and quality may serve as modifiable factors for managing cognitive risk in individuals with heightened cardiometabolic risks. While high triglyceride levels in midlife are a recognized risk factor for cognitive vulnerability, our findings suggest that dietary

Figure 3 Greater adherence to the United States Dietary Guidelines, as indicated by Health Eating Index 2020 Total Score, is associated with better performance on memory tests. The multiple linear regression analysis reveals a significant main effect between by Health Eating Index 2020 Total Score and memory performance ($\beta = 0.018$, $p < 0.002$), while controlling for age, sex, education, genetic risk, and medications. The overall model was significant ($F(9, 136) = 3.151$, $p < 0.002$, $R^2 = 0.173$).

fat intake may significantly influence this risk. Our findings suggest that dietary saturated fat intake moderates the relationship between triglycerides and memory performance, with individuals with high triglycerides and low saturated fat intake showing fewer memory deficits compared to those with a higher ratio of saturated fat. Specifically, when the ratio of saturated fat to total caloric intake exceeds 14%, there is a significant association between high triglycerides and poorer memory performance, even after controlling for age, sex, education, genetic risk, and medication use.

Furthermore, better adherence to USDA dietary guidelines, as indicated by higher HEI-2020 scores, is associated with 1.8% improvement in memory performance across all adults, regardless of triglyceride levels. While our study cannot definitively establish causality, the positive relationship between adherence to these guidelines and memory performance underscores the potential benefits of diet in protecting cognitive function. These findings align with existing literature on the detrimental effects of Western dietary patterns on cognitive function, likely mediated through inflammatory pathways[44] and accelerated brain aging.[45]

Importantly, we did not observe a significant interaction effect between HEI-2020 scores and triglyceride levels on memory performance. This suggests that, while following USDA guidelines is broadly beneficial, individuals with elevated triglycerides specifically benefit from diets low in saturated fats. For instance, the USDA Dietary Guidelines for 2020–2025 recommend limiting saturated fat intake to less than 10% of daily calories. However, only about one-third of US adults meet this recommendation, with adherence even lower among non-Hispanic White Americans—less than one-fourth—compared to higher rates observed in Asian, Black, and Hispanic Americans.[46] Our study sample, predominantly non-Hispanic White Americans, reflects these adherence patterns, with 34.2% (n=50) meeting the USDA guideline of less than 10% of calories from saturated fat. This observed gap in adherence aligns with general population trends and underscores the broader goal for Americans to improve their diet quality, particularly among groups with lower adherence rates, such as non-Hispanic White Americans.

Recent research has shown that APOE-ε4 affects various brain cell types, including neurons, astrocytes, microglia, and oligodendrocytes, which can alter cholesterol metabolism and contribute to ADRD pathology.[47] To assess the potential modifying role of APOE-ε4 on the relationship between dietary factors and memory performance, we

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conducted a sensitivity analysis by comparing models with and without the APOE-ε4 status variable. Our results indicated that the inclusion or exclusion of APOE-ε4 did not significantly alter the associations between triglycerides, saturated fat intake, and memory performance. This suggests that, in our sample, dietary saturated fat intake may independently moderate the association between triglycerides and memory performance, regardless of genetic risk associated with APOE-ε4. However, it is important to note that our study may have been underpowered to detect small to moderate genetic effects, which could explain the lack of significant findings. The complexity of the APOE-ε4 genotype should not be overlooked, as it not only affects cholesterol metabolism but also interacts with factors like neuroinflammation and amyloid pathology in shaping cognitive outcomes.[48] Future research, with larger and more diverse samples and adequate statistical power, is needed to better understand the intricate interactions between genetic predisposition, environmental exposures, and lifestyle behaviors on ADRD pathology. Such studies could help disentangle these complex relationships and inform more targeted interventions for cognitive health.

Future studies should investigate the potential cognitive benefits of replacing saturated fat with healthier fat alternatives, such as polyunsaturated fats, particularly for individuals with elevated triglycerides. Given the metabolic implications of high triglyceride levels, exploring the effects of such dietary substitutions could offer valuable insights into how specific fats and carbohydrates influence cognitive function. Precision nutrition approaches, which tailor dietary recommendations to individual metabolic profiles, may help identify the most beneficial dietary strategies for mitigating cognitive decline. These strategies may involve targeted adjustments to dietary saturated fat intake, advocating for the adoption of brain-healthy dietary patterns such as the Mediterranean diet, and promoting the substitution of saturated fatty acids with foods rich in mono- and polyunsaturated fatty acids. Such research could provide critical evidence for developing targeted dietary interventions aimed at improving brain health in high-risk populations. Moreover, our findings underscore the broader policy implications of dietary fat intake, particularly the role of saturated fats, in preventing cognitive decline. Public health policies should prioritize reducing saturated fat intake across all population groups, with a specific focus on curbing the overreliance on highly processed foods that are rich in unhealthy fats. The rise in agricultural production of inexpensive inputs, such as corn and palm, has contributed to the proliferation of processed, convenient, and affordable foods, characteristic of Western dietary patterns.[49] These foods often contain excessive levels of salt, sugar, fat, and additives, which negatively impact health. To address this, a shift in food systems is essential, one that supports public health initiatives and encourages adherence to dietary guidelines. By advocating for evidence-based policies that promote healthier, more accessible food choices and regulate the production of saturated fat-rich foods, we can foster a food environment that not only improves metabolic health but also protects cognitive function and aging.

A major strength of this study is the inclusion of a diverse sample of midlife adults with various metabolic and genetic risk factors for ADRDs. While we focused on elevated triglycerides as a key metabolic risk factor, the broader variability in metabolic health status in our sample enhances the ecological validity of our findings, as it better represents the population at higher risk for ADRDs. Rather than excluding individuals with comorbidities, we aimed to assess how dietary factors, particularly saturated fat intake, may influence cognitive vulnerabilities in this high-risk group. This approach is valuable for identifying potential dietary interventions for improving cognitive health in midlife individuals already dealing with metabolic challenges. Moreover, the variability in adherence to USDA Dietary Guidelines within our sample, including many following Western diet patterns, strengthens the study's capacity to explore the complex interactions between diet, metabolic health, and cognitive function. Overall, the focus on a sample with metabolic risk factors allows for a more nuanced understanding of how dietary interventions might be targeted to individuals at greater risk for cognitive decline. Elevated triglycerides, for example, may serve as a marker for insulin resistance or other underlying metabolic conditions, which could influence both triglycerides and cognitive outcomes. Future research could further explore this relationship by incorporating additional metabolic markers alongside triglycerides to better isolate the effects of dietary fat intake on cognitive health.

A limitation of this study is its cross-sectional design, which suggests potential associations but cannot establish causality. This design does not provide temporal insights into the trajectory of the relationship between triglyceride levels, memory performance, and dietary fat intake over time. To establish causal links, future research should include longitudinal studies and randomized controlled trials to determine whether dietary interventions targeting saturated fat can mitigate the risk of cognitive decline, particularly in individuals with metabolic risk factors like elevated

triglycerides. Longitudinal studies to expand upon this research are essential for identifying temporal patterns and providing a more comprehensive understanding of how dietary fat impacts cognitive outcomes across the lifespan. Such research will be crucial for informing early intervention strategies and guiding long-term dietary recommendations to reduce dementia risk and promote healthy aging. Moreover, this study is specifically aimed at detecting modifiable lifestyle factors that could delay the onset or prolong cognitive health. Accordingly, our inclusion and exclusion criteria were designed to include only participants without significant cognitive impairment, thereby reducing the risk of confounding due to pre-existing neurological or psychiatric conditions. However, it is important to note that participants with an MMSE® score greater than 24 may still exhibit early-stage cognitive impairment,[50] which could reflect underlying neurodegenerative pathology. To improve diagnostic accuracy, future studies could integrate advanced neuroimaging and additional diagnostic cognitive assessments. Additionally, as diet data were collected via self-report, dietary intake and quality scores may be biased and reflect broader factors that influence both diet and cognitive outcomes. For instance, individuals with healthier diets may also engage in other positive health behaviors not captured in this study. Future research should include additional measures of health behaviors to more accurately isolate the effects of dietary fat on cognitive function.

Conclusion

Our study provides evidence that dietary saturated fat intake and poor adherence to dietary guidelines may exacerbate memory vulnerabilities in individuals with metabolic health risks. Our findings underscore the importance of precision nutrition strategies tailored to an individual's metabolic profile, as these could optimize cognitive outcomes and help prevent cognitive decline in at-risk populations. Specifically, individuals with elevated triglycerides may benefit from reducing saturated fat intake. While the adhering to the US dietary guidelines may offer general benefits for cognitive health, our results emphasize the importance of limiting saturated fat intake for those with high triglycerides. Overall, these findings suggest that dietary interventions targeting saturated fat could improve cognitive health in midlife individuals at risk for cognitive decline. Although we did not directly examine the replacement of saturated fat with other macronutrients, future research should explore how such substitutions may protect cognitive function in those with and without metabolic risk. Future studies should also examine the interactions between diet and cognitive function, particularly in populations with comorbid metabolic risk factors.

Data Sharing Statement

The data used to support the findings of this study are available from authors upon special request.

Ethical Approval and Consent to Participate

The Institutional Review Board at the University of Texas at Austin approved all study procedures (#2016-09-0135 and #2011-07-0025). This study was conducted in accordance with the Declaration of Helsinki. All participants provided written, informed consent before enrolling in the study.

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Disclosure

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References

1. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. *Alzheimers Res Ther*. 2017;9(1):71. doi:10.1186/s13195-017-0297-z
2. Craft S. The Role of Metabolic Disorders in Alzheimer Disease and Vascular Dementia: two Roads Converged. *Arch Neurol*. 2009;66(3):300–305. doi:10.1001/archneurol.2009.27
3. Banks WA, Farr SA, Salameh TS, et al. Triglycerides cross the blood–brain barrier and induce central leptin and insulin receptor resistance. *Int J Obes 2005*. 2018;42(3):391–397. doi:10.1038/ijo.2017.231
4. Zhang BH, Yin F, Qiao YN, Guo SD. Triglyceride and Triglyceride-Rich Lipoproteins in Atherosclerosis. *Front Mol Biosci*. 2022;9:9151. doi:10.3389/fmolb.2022.909151
5. Choi HJ, Byun MS, Yi D, et al. Association Between Serum Triglycerides and Cerebral Amyloidosis in Cognitively Normal Elderly. *Am J Geriatr Psychiatry*. 2016;24(8):604–612. doi:10.1016/j.jagp.2016.03.001
6. Raffaitin C, Gin H, Empana JP, et al. Metabolic Syndrome and Risk for Incident Alzheimer's Disease or Vascular Dementia: the Three-City Study. *Diabetes Care*. 2009;32(1):169–174. doi:10.2337/dc08-0272
7. Luo L, Liu M. Adipose tissue in control of metabolism. *J Endocrinol*. 2016;231(3):R77–R99. doi:10.1530/JOE-16-0211
8. Sanjana F, Delgorio PL, Hiscox LV, et al. Blood lipid markers are associated with hippocampal viscoelastic properties and memory in humans. *J Cereb Blood Flow Metab*. 2021;41(6):1417–1427. doi:10.1177/0271678X20968032
9. Hill NL, McDermott C, Mogle J, et al. Subjective cognitive impairment and quality of life: a systematic review. *Int Psychogeriatr*. 2017;29 (12):1965–1977. doi:10.1017/S1041610217001636
10. Dimache AM, Şalaru DL, Sascău R, Stătescu C. The Role of High Triglycerides Level in Predicting Cognitive Impairment: a Review of Current Evidence. *Nutrients*. 2021;13(6):2118. doi:10.3390/nu13062118
11. Power MC, Rawlings A, Sharrett AR, et al. Association of midlife lipids with 20-year cognitive change: a cohort study. *Alzheimers Dement J Alzheimers Assoc*. 2018;14(2):167–177. doi:10.1016/j.jalz.2017.07.757
12. Nägga K, Gustavsson AM, Stomrud E, et al. Increased midlife triglycerides predict brain β-amyloid and tau pathology 20 years later. *Neurology*. 2018;90(1):e73–e81. doi:10.1212/WNL.0000000000004749
13. van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, van de Rest O. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diets Are Associated with Less Cognitive Decline and a Lower Risk of Alzheimer's Disease-A Review. *Adv Nutr Bethesda Md*. 2019;10(6):1040–1065. doi:10.1093/advances/nmz054
14. Fan Y, Zhang Y, Li J, et al. Association between healthy eating index-2015 and various cognitive domains in US adults aged 60 years or older: the National Health and Nutrition Examination Survey (NHANES) 2011–2014. *BMC Public Health*. 2021;21(1):1862. doi:10.1186/s12889-021-11914-2
15. Hu E, Wu A, Dearborn J, et al. Adherence to the Healthy Eating Index-2015 (HEI-2015), Cognitive Function, and Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Study (OR32-01-19). *Curr Dev Nutr*. 2019;3:nzz052. doi:10.1093/cdn/nzz052.OR32-01-19
16. Akbaraly T, Sexton C, Zsoldos E, et al. Association of Long-Term Diet Quality with Hippocampal Volume: longitudinal Cohort Study. *Am J Med*. 2018;131(11):1372–1381.e4. doi:10.1016/j.amjmed.2018.07.001
17. Dearborn-Tomazos JL, Wu A, Steffen LM, et al. Association of Dietary Patterns in Midlife and Cognitive Function in Later Life in US Adults Without Dementia. *JAMA Network Open*. 2019;2(12):e1916641. doi:10.1001/jamanetworkopen.2019.16641
18. Nwaru BI, Dierkes J, Ramel A, et al. Quality of dietary fat and risk of Alzheimer's disease and dementia in adults aged ≥50 years: a systematic review. *Food Nutr Res*. 2022;66:8629. doi:10.29219/fnr.v66.8629
19. Chianese R, Coccurello R, Viggiano A, et al. Impact of Dietary Fats on Brain Functions. *Curr Neuropharmacol*. 2018;16(7):1059–1085. doi:10.2174/1570159X15666171017102547
20. Wang TY, Liu M, Portincasa P, Wang DQH. New insights into the molecular mechanism of intestinal fatty acid absorption. *Eur J Clin Invest*. 2013;43(11):1203–1223. doi:10.1111/eci.12161
21. Luna-Castillo KP, Olivares-Ochoa XC, Hernández-Ruiz RG, et al. The Effect of Dietary Interventions on Hypertriglyceridemia: from Public Health to Molecular Nutrition Evidence. *Nutrients*. 2022;14(5):1104. doi:10.3390/nu14051104
22. Eskelinen MH, Ngandu T, Helkala EL, et al. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. *Int J Geriatr Psychiatry*. 2008;23(7):741–747. doi:10.1002/gps.1969
23. Duffy CM, Hofmeister JJ, Nixon JP, Butterick TA. High fat diet increases cognitive decline and neuroinflammation in a model of orexin loss. *Neurobiol Learn Mem*. 2019;157:41–47. doi:10.1016/j.nlm.2018.11.008
24. Granholm AC, Bimonte-Nelson HA, Moore AB, Nelson ME, Freeman LR, Sambamurti K. Effects of a Saturated Fat and High Cholesterol Diet on Memory and Hippocampal Morphology in the Middle-Aged Rat. *J Alzheimers Dis JAD*. 2008;14(2):133–145. doi:10.3233/JAD-2008-14202
25. Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Dietary fat intake and 6-year cognitive change in an older biracial community population. *Neurology*. 2004;62(9):1573–1579. doi:10.1212/01.wnl.0000123250.82849.b6
26. Lyte JM, Gabler NK, Hollis JH. Postprandial serum endotoxin in healthy humans is modulated by dietary fat in a randomized, controlled, cross-over study. *Lipids Health Dis*. 2016;15(1):186. doi:10.1186/s12944-016-0357-6
27. Foret JT, Oleson S, Hickson B, Valek S, Tanaka H, Haley AP. Metabolic Syndrome and Cognitive Function in Midlife. *Arch Clin Neuropsychol*. 2020;36(6):897–907. doi:10.1093/arclin/acaa112
28. Farrer LA, Cupples LA, Haines JL, et al. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: a Meta-analysis. *JAMA*. 1997;278(16):1349–1356. doi:10.1001/jama.1997.03550160069041
29. Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. *Mol Neurodegener*. 2022;17(1):72. doi:10.1186/s13024-022-00574-4
30. Oleson S, Eagan D, Kaur S, et al. Apolipoprotein E genotype moderates the association between dietary polyunsaturated fat and brain function: an exploration of cerebral glutamate and cognitive performance. *Nutr Neurosci*. 2018;23(1):1–10. doi:10.1080/1028415X.2018.1547857
31. Youn C, Caillaud ML, Li Y, et al. Interplay of Large Neutral Amino Acids, Metabolic Syndrome, and Apolipoprotein E ε4 on Brain Integrity at Midlife. *Lifestyle Genomics*. 2024;17(1):113–121. doi:10.1159/000540336
32. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198. doi:10.1016/0022-3956(75)90026-6

33. Holdnack HA. *Wechsler Test of Adult Reading: WTAR*. The Psychological Corporation; 2001.
34. Yang YJ, Kim MK, Hwang SH, Ahn Y, Shim JE, Kim DH. Relative validities of 3-day food records and the food frequency questionnaire. *Nutr Res Pract*. 2010;4(2):142–148. doi:10.4162/nrp.2010.4.2.142
35. Axxya Systems. Nutritionist Pro® Software (Version 4.0) [Software] 2006.
36. Shams-White MM, Pannucci TE, Lerman JL, et al. Healthy Eating Index-2020: review and Update Process to Reflect the Dietary Guidelines for Americans,2020-2025. *J Acad Nutr Diet*. 2023;123(9):1280–1288. doi:10.1016/j.jand.2023.05.015
37. Alere. *Alere Cholestech LDX® System [Medical device]* 2013.
38. Kwak SK, Kim JH. Statistical data preparation: management of missing values and outliers. *Korean J Anesthesiol*. 2017;70(4):407–411. doi:10.4097/kjae.2017.70.4.407
39. Thermo Fisher Scientific. Variant Reporter.
40. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test. 2nd Edition* ed. Pearson; 2000.
41. R Core Team. *R Statistical Software*. 2022.
42. Roberts RO, Geda YE, Knopman DS, et al. Association of Duration and Severity of Diabetes Mellitus With Mild Cognitive Impairment. *Arch Neurol*. 2008;65(8):1066–1073. doi:10.1001/archneur.65.8.1066
43. Kivipelto M, Helkala EL, Laakso MP, et al. Apolipoprotein E ε4 Allele, Elevated Midlife Total Cholesterol Level, and High Midlife Systolic Blood Pressure Are Independent Risk Factors for Late-Life Alzheimer Disease. *Ann Intern Med*. 2002;137(3):149–155. doi:10.7326/0003-4819-137-3-200208060-00006
44. Beilharz JE, Maniam J, Morris MJ. Diet-Induced Cognitive Deficits: the Role of Fat and Sugar, Potential Mechanisms and Nutritional Interventions. *Nutrients*. 2015;7(8):6719–6738. doi:10.3390/nu7085307
45. Zwilling CE, Wu J, Barbey AK. Investigating nutrient biomarkers of healthy brain aging: a multimodal brain imaging study. *Npj Aging*. 2024;10(1):1–12. doi:10.1038/s41514-024-00150-8
46. Bowman SA, Clemens JC. Saturated fat and food intakes of adults: what We Eat in America, NHANES 2017–2018. In *FSRG Dietary Data Briefs*. United States Department of Agriculture (USDA); 2022. Accessed June 26, 2024. http://www.ncbi.nlm.nih.gov/books/NBK588575/.
47. Jeong W, Lee H, Cho S, Seo J. ApoE4-induced cholesterol dysregulation and its brain cell type-specific implications in the pathogenesis of Alzheimer's disease. *Mol Cells*. 2019;42(11):739–746. doi:10.14348/molcells.2019.0200
48. DiBattista AM, Heinsinger NM, Rebeck GW. Alzheimer's disease genetic risk factor apoe-ε4 also affects normal brain function. *Curr Alzheimer Res*. 2016;13(11):1200–1207. doi:10.2174/1567205013666160401115127
49. Hall KD. Did the food environment cause the obesity epidemic? *Obesity*. 2018;26(1):11–13. doi:10.1002/oby.22073
50. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res*. 2009;43(4):411–431. doi:10.1016/j.jpsychires.2008.04.014