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Current Serum Lipoprotein Levels and fMRI Response to Working Memory in Midlife

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Key Words
Brain imaging · Cholesterol · Cognition · Cognitive impairment · Vascular causes · Working memory

Abstract
Aims: Given that high cholesterol levels at midlife are a risk factor for future cognitive decline, the goal of the current study was to determine if cholesterol-related alterations in the cerebrovascular response to cognition could be detected at midlife. ***Methods:*** Forty adults, aged 40–60 years, performed a 2-Back working memory task during fMRI. The associations between serum total cholesterol, HDL-cholesterol, and total cholesterol/HDL-cholesterol concentrations to task-related activation intensity were modeled using multivariate multiple regression (two-tailed $p < 0.02$). ***Results:*** Higher levels of total cholesterol/HDL-cholesterol related to reduced working memory-related activation intensity in the left inferior parietal lobe, right superior frontal gyrus, and right middle frontal gyrus. ***Conclusion:*** These data provide preliminary support for a deleterious effect of elevated total cholesterol/HDL-cholesterol ratio on cerebrovascular support for cognition in midlife.

Introduction

High cholesterol, one of the most prevalent medical conditions among developed nations, plays a primary pathogenic role in the development of atherosclerosis and coronary heart disease [1]. These conditions have a well-established impact on cardiac-related mortality [2], and more recent evidence indicates that they may increase vulnerability to cognitive impairment and dementia [3]. In elderly adults, atherosclerosis is associated with poorer attention-executive function [4] and altered brain response to a cognitive challenge [5]. In addition, the degree of atherosclerosis has been shown to correlate with dementia severity [6], implicating sclerotic processes in the onset or progression of dementia. Thus, as a predictor of atherosclerosis, high cholesterol levels may be a modifiable risk factor for future cognitive decline and dementia.

Interestingly, epidemiological studies investigating the association between serum cholesterol levels and risk of dementia appear inconclusive, with high serum cholesterol levels relating to dementia risk in some studies [7–9] and the opposite relationship [10–12] or null findings reported in other studies [13, 14]. A careful analysis of the literature, however, reveals that elevated cholesterol levels in midlife are consistently associated with a high risk of cognitive impairment later in life [7, 9], while low cholesterol levels correlate with dementia onset in the el-

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Table 1. Participant characteristics (n = 40)

Age, years	50.7 ± 6.3
Sex, male/female	23/17
Race	
Caucasian	19 (47.5)
Hispanic	15 (37.5)
Asian	1 (2.5)
African-American	2 (5.0)
Other	3 (7.5)
Education, years	15.1 ± 2.4
BMI	29.5 ± 5.8
Systolic blood pressure, mm Hg	123.6 ± 12.7
Diastolic blood pressure, mm Hg	77.0 ± 9.8
Total cholesterol, mg/dl	216.9 ± 48.3
HDL-cholesterol, mg/dl	48.6 ± 14.5
Total/HDL cholesterol, mg/dl	4.8 ± 1.6
Triglycerides, mg/dl	155.3 ± 85.6
Glucose, mg/dl	96.7 ± 9.3

Figures in parentheses are percentages.

derly [10–12]. A possible explanation for this finding is that co-morbidities that lower cholesterol, such as respiratory disease, malnutrition, and cancer, are increasingly common in older age [15], and may obscure the relationship between high serum cholesterol and dementia risk.

In order to obtain a clear understanding of how cholesterol levels impact cognition, it is necessary to conduct examinations in midlife when co-morbidities are relatively uncommon. Real-time assessments have been limited, however, because behavioral indicators of cognitive decline do not typically emerge until late in life [16]. The decades separating cholesterol measurement and assessment of cognitive outcomes make it difficult to assess the pathophysiological processes underlying the impact of cholesterol on cognition and limit the opportunities to intervene before irreversible cognitive loss has ensued. The advent of neuroimaging techniques has created new opportunities to examine neuropathological changes very early in the disease process [17]. In particular, functional magnetic resonance imaging (fMRI) is especially useful for detecting cognitive vulnerability because it examines cerebral hemodynamic response to cognitive challenges and has the ability to detect altered response in individuals at risk of cognitive decline before behavioral performance is impaired [18–20].

The aim of the current study was to determine the association between serum lipid concentrations and the blood oxygen level-dependent (BOLD) response to cognition in middle-aged adults. Fasting levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and total cholesterol/HDL-cholesterol were examined in relation to the BOLD response during a 2-Back verbal working memory task. Based on previous fMRI studies on cardiovascular risk [5, 20, 21], we hypothesized that higher total cholesterol, higher total cholesterol/HDL-cholesterol, and lower HDL cholesterol levels would be related to reduced activation intensity during the 2-Back working memory task.

Material and Methods

Participants

Right-handed adults between the ages of 40 and 60 years were recruited through flyers and newspaper advertisements. Individuals with a history of coronary artery disease, angina pectoris, myocardial infarctions, heart failure, and cardiac surgery were excluded. Participants were required to be to be free of lipid-lowering medications to remove variability due to length of medication exposure. Additional exclusion criteria included history of neurological disease (e.g. stroke, Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g. schizophrenia, bipolar disorder), substance abuse (i.e. diagnosed abuse and/or previous hospitalization for substance abuse), metabolic disorder (i.e. diabetes, thyroid disorder), smoking (within the last 2 years), and MRI contraindications. Forty-three participants completed the initial screening, and were enrolled in the study after providing written consent. Three participants were excluded from analyses because their fasting blood glucose concentrations classified them as diabetic based upon the American Diabetes Association classification criteria (fasting blood glucose >126 mg/dl) [22]. Participant characteristics are presented in table 1.

Procedures

The study was approved by the Institutional Review Board of The University of Texas at Austin, and all volunteers provided written informed consent before enrollment. Participants were required to complete a medical history interview in which medical conditions and treatments were coded as either present or absent based on participants' self-reports. Participants then underwent a full neuropsychological evaluation, brain imaging, and a general health assessment, including a fasting blood draw for lipid and glucose assay. Visits were conducted on separate days and participants completed the study within 1 month.

Neuropsychological Assessment

All participants completed a 2-hour assessment battery including standard clinical neuropsychological instruments with established reliability and validity [23]. The battery included measures of global cognitive functioning (Mini Mental Status Exam [24]; Wechsler Abbreviated Scale of Intelligence, WASI, full-scale IQ [25]), language (WASI Vocabulary Subtest [25]; Category Fluency for Animals [26]), visual-spatial ability (Rey Complex Figure Test-Copy, RCF-Copy [27]; WASI Matrix Reasoning Subtest [25]), memory (California Verbal Learning Test II [28]; Rey Complex Figure Test, RCF [27]), attention-executive-psychomotor functioning (Wechsler Adult Intelligence Scale-III, WAIS-III, Digit

Span Subtest [29]; Controlled Oral Word Association Test [30]; Grooved Peg Board, Dominant Hand [31] Trail Making Test A and B [32]), and emotional functioning (Beck Depression Inventory II [33]; Spielberger Trait Anxiety Inventory [34]). All tests were administered and scored by a trained research assistant using standard administration and scoring criteria.

General Health Assessment

Participants abstained from caffeine and fasted for at least 4 h prior to the assessment. Body weight in kilograms and height in centimeters were measured on a beam-balance scale for the subsequent calculations of BMI. BMI was calculated by dividing weight in kilograms by height in meters squared. Following 15 min of rest, participants sat upright while brachial blood pressure was measured using a semi-automated device. Approximately 3 ml of fasting blood was collected from the antecubital vein by venipucture. The concentrations of glucose, triglycerides, total cholesterol, and HDL-cholesterol were measured using standard enzymatic technique.

Working Memory Task Paradigm

Working memory was assessed using a verbal n-Back task, consisting of alternating blocks of 0-Back, 2-Back, and rest conditions [35, 36]. During each 0- and 2-Back block, a series of 12 individual consonants were visually presented in random order for 500 ms each with a 2,500-ms inter-stimulus interval. Participants responded to target letters (33% in each block) using a 2-button MR-compatible response box. In the 0-Back condition, the target was a pre-specified letter (H) and in the 2-Back condition, the target was any letter that was identical to the one presented 2 stimuli earlier. Task performance was assessed by measuring mean accuracy rates and reaction time for all correct trials. During each rest block, a fixation cross appeared in the middle of the screen for 30 s. The task was programmed and presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, Pa., USA). During neuroimaging, 2 consecutive 6-min runs consisting of 3 blocks of alternating 0-Back, 2-Back, and rest conditions were presented. Before neuroimaging, participants were given an opportunity to practice the task on a laptop computer to ensure adequate performance.

Neuroimaging Data Acquisition

MRI data for each participant were acquired in a single session on a 3-T GE Signa Excite MRI scanner equipped with a standard head coil. T_1-weighted anatomical scans of the entire brain in the sagittal plane were collected using a high-resolution spoiled gradient echo sequence (256 × 256 matrix, FOV = 24 × 24 cm^2, 1-mm slice thickness, 0 gap). Functional imaging was performed while participants completed the 2-Back task. The task was back-projected from a laptop onto a screen positioned at the participant's head, and viewed through a double-mirror attached to the head coil. Functional imaging was performed using a whole-brain echo-planar imaging sequence (TR = 3,000 ms, TE = 30 ms, FOV = 24 × 24 cm^2, 64 × 64 matrix, 42 axial slices, 3-mm slice thickness, 0.3-mm gap).

Neuroimaging Data Processing

All echo planar images were processed using Analysis of Functional NeuroImages (AFNI) software [37]. Each time series was spatially registered to the sixth volume of the session to reduce the effects of head movement. This AFNI 3-dimensional registration program also yields information on displacement and rotation for each volume, which was used later to further correct motion. All participants moved less than 1.5 mm per imaging run, and no participants were excluded from the analyses due to excessive head motion. Data preprocessing also included adjustment for differences in adjacent slice timing due to interleaved slice acquisition, temporal smoothing, and spatial filtering. Task-related brain activation was determined using within-subject voxel-wise multiple regression analyses with the following parameters: a 0-Back/2-Back reference waveform convolved with a γ-function and covariates accounting for instruction screens and head movement.

Table 2. A priori regions of interest

Region	X	Y	Z
Left middle frontal gyrus	–33	4	56
Left medial frontal gyrus	–5	19	44
Right superior parietal lobule	37	–63	53
Left inferior parietal lobule	–49	–52	44
Left middle frontal gyrus	–44	45	13
Right superior frontal gyrus	33	48	15
Right middle frontal gyrus	32	5	55
Right inferior frontal gyrus	47	14	3

In order to elaborate upon prior research examining cerebral hemodynamics and cardiovascular function, a priori regions of interest (ROIs) were defined. A separate data set was used to create empirically defined task-related ROIs for hypothesis testing in order to avoid circularity. The task used to create the ROIs was identical to the one used in the current study. The sample and the creation of the ROIs are described in detail in Haley et al. [5]. Briefly, the ROIs were created by transforming the results from individual multiple regression analyses to standard stereotaxic space [38] and converting them to z-scores. The z-scores were then thresholded at $p < 0.05$, corrected for multiple comparisons using the false discovery rate (FDR) supplied by AFNI. Voxels were included in the final mask if they were significantly active in over 90% of all participants. Finally, active voxels were defined as a cluster if they were contiguous and formed a volume of at least 200 μl. Eight cortical ROIs were identified using this process (table 2). Anatomical designations were assigned to the ROIs according to the ROI center in Talairach coordinates. This empirically defined mask was then applied to the results from the individual multiple regression analyses in the current study sample transformed to standard stereotaxic space, using the fully automated 3dmaskave plug-in in AFNI. This program allows one to compute the average over an ROI of all voxel values from an input dataset. Average unthresholded t values within each ROI for each person were used as measures of task-related activation intensity in subsequent analyses for hypothesis testing. These 8 a priori ROIs were used because they represented the most stable activation pattern in response to the task used in this study from a similar yet separate sample of participants.

Statistical Analyses

Neuropsychological measures were grouped into 1 of 5 cognitive domains: (1) global cognitive functioning, (2) language func-

Table 3. Neuropsychological test results

Global cognition	
Mini Mental Status Exam	28.4 ± 1.3
WASI Full-Scale IQ	115.9 ± 11.2
Language	
WASI Vocabulary Subtest	65.4 ± 10.2
Category Fluency for Animals	25.2 ± 5.7
Visual-spatial	
WASI Matrix Reasoning Subtest	26.6 ± 3.8
RCF-Copy	30.9 ± 3.1
Memory	
California Verbal Learning Test II	
Immediate recall	10.9 ± 3.0
Delayed recall	11.3 ± 3.3
Recognition (yes/no)	3.1 ± 0.7
RCF	
Immediate recall	16.7 ± 4.8
Delayed recall	16.4 ± 4.9
Recognition discrimination	19.8 ± 2.4
Attention-executive-psychomotor function	
Controlled Oral Word Association Test	39.3 ± 10.1
Trail Making Test A, s	30.1 ± 9.0
Trail Making Test B, s	73.8 ± 27.8
WAIS-III Digit Span Subtest, total	17.1 ± 3.7
Grooved Pegboard-Dominant Hand, s	77.0 ± 15.9
Emotional function	
Beck Depression Inventory II	6.6 ± 6.2
Spielberger Trait Anxiety Inventory	33.2 ± 8.2

Table 4. Serum cholesterol levels and cognitive test performance

	p values		
	total	HDL	total/HDL
Global cognition	0.96	0.24	0.50
Language	0.54	0.48	0.55
Visual-spatial	0.96	0.86	0.97
Memory	0.16	0.60	0.74
Attention-executive-psychomotor	0.96	0.25	0.14

tions, (3) visual-spatial abilities, (4) memory functions, and (5) attention-executive-psychomotor functions. The following test scores were included in each domain and raw total scores were utilized unless otherwise stated:

(1) *Global*. Mini Mental Status Exam [24] and WASI Full Scale IQ [25].

(2) *Language*. WASI Vocabulary Subtest [25] and Category Fluency for Animals [26].

(3) *Visual-Spatial*. RCF-Copy [27] and WASI Matrix Reasoning Subtest [25].

(4) *Memory*. California Verbal Learning Test II immediate recall, delayed recall, and recognition discrimination [28]; RCF immediate recall, delayed recall, and recognition discrimination [27].

(5) *Attention-Executive-Psychomotor Functions*. Trail Making A and B time to completion [32], Controlled Oral Word Association Test [30], WAIS-III Digit Span Subtest [29], and Grooved Pegboard-Dominant Hand time to completion [31].

Participants' raw test scores were converted to z-scores using the study sample mean and SD. Timed test scores were multiplied by –1 so that higher scores indicate better performance. Five composite cognitive domain z-scores were calculated for each participant by averaging the z-scores of all tests within that domain.

Descriptive statistics were calculated for demographics, medical variables, and raw cognitive test scores. Serum cholesterol levels (total cholesterol, HDL-cholesterol, and total cholesterol/HDL-cholesterol) were assessed in relation to cognitive test performance using multivariate multiple regression with all cognitive domain scores entered at once.

The impact of each cholesterol measure on mean 2-Back-related activation intensity was analyzed using a single multivariate multiple regression that simultaneously included all a priori ROIs. Age, sex, and overall cardiovascular risk score were selected a priori as covariates because of their established association with serum cholesterol levels. An overall cardiovascular risk score was created by coding the presence or absence of risk factors other than hypercholesterolemia defined by the American Heart Disease Association [BMI $\geq$30 kg/m^2, hypertension (SBP $\geq$140 mm Hg or DBP $\geq$90 mm Hg or usage of anti-hypertensive medications), hyperglycemia (fasting glucose $\geq$110 mg/dl), smoking (self-report of prior history)] [39] and summing their total to create a composite score (range 0–4). A Sidak-corrected α level of 0.02 was used as the criterion of statistical significance to account for multiple comparisons and preserve the 5% type I error rate.

In exploratory follow-up analyses, a correlation was conducted to explore the association between mean 2-Back accuracy and reaction time and 2-Back activation intensity within the three ROIs significant in the fully-adjusted regression model. A two-tailed α level of 0.05 was used as the criterion for significance for this analysis. Data were analyzed using SPSS 16.0 computer software (SPSS Inc., Chicago, Ill., USA).

Results

Descriptive Statistics

Demographic and medical variables of the sample (means ± SD) are reported in table 1. Table 3 displays the mean raw cognitive test scores and their SD. Descriptive statistical analyses revealed a cognitively normal, ethnically diverse, middle-aged sample, well representative of the population of the state of Texas based on the year 2000 US census data for the state.

Serum Cholesterol Levels in Relation to Cognitive Test Performance

As presented in table 4, no association was found between total cholesterol, HDL-cholesterol, or total cholesterol/HDL-cholesterol and measures of global cognitive function, language, visual-spatial ability, memory, or at-

Table 5. Serum cholesterol and mean 2-Back-related activation intensity controlling for sex, age, and cardiovascular risk

Region	Total			HDL			Total/HDL		
	F	p (overall model)	p (cholesterol β)	F	p (overall model)	p (cholesterol β)	F	p (overall model)	p (cholesterol β)
Left middle frontal gyrus	0.67	0.616	0.797	1.10	0.370	0.203	1.60	0.197	0.069
Left medial frontal gyrus	1.51	0.220	0.963	1.55	0.210	0.722	2.06	0.108	0.182
Right superior parietal lobule	2.21	0.880	0.131	1.63	0.189	0.528	2.94	0.034	0.034
Left inferior parietal lobule	3.12	0.032	0.020	1.42	0.248	0.803	3.58	0.015*	0.010*
Left middle frontal gyrus	0.42	0.796	0.286	0.23	0.917	0.504	0.62	0.650	0.168
Right superior frontal gyrus	2.17	0.092	0.029	0.73	0.577	0.319	3.43	0.018*	0.002*
Right middle frontal gyrus	1.31	0.285	0.211	2.36	0.072	0.144	4.24	0.007*	0.006*
Right inferior frontal gyrus	0.67	0.616	0.032	0.11	0.980	0.641	0.43	0.786	0.227

All F values have degrees of freedom of 4, 35. * $p < 0.02$.

tention-executive-psychomotor functioning. These findings were not surprising considering the relatively young age of our sample and their overall level of cognitive ability (mean full-scale IQ = 116).

Serum Cholesterol Levels in Relation to 2-Back-Related Activation Intensities

In the fully adjusted multivariate multiple regression analyses, neither total cholesterol nor HDL-cholesterol were significantly related to mean 2-Back-related activation intensity (table 5). However, there was a trend towards total cholesterol relating to lower 2-Back-related activation intensity in the left inferior parietal lobe ($F_{4, 35} = 3.121$, $p = 0.027$, total cholesterol $\beta = -0.375$, $p = 0.020$).

For total cholesterol/HDL-cholesterol, the fully adjusted multivariate regression model successfully predicted mean 2-Back-related activation intensity in the left inferior parietal lobe ($F_{4, 35} = 3.583$, $p = 0.015$), right superior frontal gyrus ($F_{4, 35} = 3.433$, $p = 0.018$), and right middle frontal gyrus ($F_{4,35} = 4.244$, $p = 0.007$) (table 5). The independent effects of age, sex, and cardiovascular risk score did not account for any unique variance in 2-Back-related activation intensity. However, higher total cholesterol/HDL-cholesterol levels were predictive of lower 2-Back-related activation in all three ROIs; the left inferior parietal lobe ($\beta = -0.438$, $p = 0.010$), right superior frontal gyrus ($\beta = -0.539$, $p = 0.002$), and right middle frontal gyrus ($\beta = -0.455$, $p = 0.006$). This relationship remained unchanged after further adjustment for level of education [left inferior parietal lobe ($F_{5, 34} = 3.176$, $p = 0.019$, total cholesterol/HDL-cholesterol $\beta = -0.401$, $p = 0.018$), right superior frontal gyrus ($F_{5, 34} = 2.674$, $p = 0.038$, total cholesterol/HDL-cholesterol $\beta = -0.535$, $p = 0.003$), and right middle frontal gyrus ($F_{5, 34} = 3.572$, $p = 0.011$, total cholesterol/HDL-cholesterol $\beta = -0.426$, $p = 0.011$)]. Lower activation intensity in the left inferior parietal lobe was significantly related to lower 2-Back accuracy ($r = 0.324$, $p = 0.047$) and slower reaction time ($r = -0.338$, $p = 0.038$).

Discussion

The goal of the current study was to determine if serum cholesterol levels at midlife relate to an altered pattern of cerebrovascular response to a challenging cognitive task. We found that higher total cholesterol/HDL-cholesterol levels were associated with lower 2-Back-related activation intensity in a network of regions implicated in working memory performance [35, 36]. Our pattern of results is supported by several longitudinal studies, which have reported that higher total cholesterol levels at midlife predict an increased risk of cognitive decline and dementia in old age [7, 9]. Additionally, a study examining identical twins determined that lower levels of HDL-cholesterol at midlife related to a greater volume of cerebral white matter hyperintensities approximately 30 years later [40]. Together these prior studies provide strong evidence that serum cholesterol levels at midlife are harmful to cognitive and cerebral health. However, in prior research, the clinical manifestations of decline have not been detected until much later in the life span. The current study extends the literature by demonstrating that high total cholesterol/HDL-cholesterol levels predict alterations in the cerebrovascular response to a cognitive challenge as early as midlife. These results bear important considerations for interven-

tions. Taking steps to reduce total cholesterol and raise HDL-cholesterol levels at midlife may attenuate cerebrovascular changes, potentially reducing risk of cognitive decline in the future.

The main finding in the current study was that total cholesterol/HDL-cholesterol related to lower activation intensity in the right superior frontal gyrus, the right middle frontal gyrus, and the left inferior parietal lobe during the working memory task. These regions have been consistently shown to be activated across working memory studies and are implicated in maintaining, monitoring, and manipulating information [35, 36]. Similar impairments in these cognitive processes have been observed in older adults with atherosclerosis [4]. Additionally, a prior fMRI study on elderly adults with cardiovascular disease found a negative association between the degree of atherosclerosis and working memory-related activation intensity in the right middle frontal gyrus [5], mirroring the results with high total cholesterol/HDL-cholesterol in the current study. Given that high total cholesterol/HDL-cholesterol levels predict the risk of atherosclerosis [41], the participants in our sample may be showing early evidence of vascular-related alterations in the executive function system. While the current analyses do not enable us to determine if cholesterol directly mediates task performance, preliminary evidence for this interpretation is the fact that lower activation in the left inferior parietal lobe was related to poorer task performance and slower reaction time. The inferior parietal lobe has diffuse connections with the frontal lobe, which enable it to play a role in attention regulation and task preparation processes critical to executive function [42].

It is of note that total cholesterol/HDL-cholesterol was the only serum lipid to relate to 2-Back-related cerebrovascular response. The majority of studies on midlife cholesterol levels and cognitive outcomes have focused on single parameter lipids as opposed to ratios [7, 9, 11, 43]. Most consistently high total cholesterol levels have been reported to have negative implications for future cognitive performance [7, 9] with some support existing for the harmful impact of low HDL-cholesterol levels [43, 44]. In the current study, neither total cholesterol nor HDL-cholesterol levels alone significantly related to the cerebrovascular response to cognition. The discrepancy between our findings and previous studies may be attributed to our sample of cognitively-intact middle-aged adults free from cardiovascular disease. Within this relatively healthy sample, total cholesterol/HDL-cholesterol may have been the only lipid marker sensitive enough to relate to cerebrovascular response to a cognitive challenge due to the fact that the ratio is sensitive to the cumulative effect of small increases in total cholesterol in conjunction with small decreases in HDL-cholesterol. Numerous studies have indicated that total cholesterol/HDL-cholesterol is the single best serum lipid predictor of atherosclerosis and coronary heart disease [45–47]. In fact, the Framingham equation for 10-year coronary heart disease risk assessment includes both total cholesterol and HDL-cholesterol, essentially incorporating the ratio in the calculation [48]. In addition to predicting atherosclerosis and coronary heart disease, total cholesterol/HDL-cholesterol levels also strongly relate to metabolic syndrome, a disorder composed of a clustering of cardiovascular risk factors (i.e. hypertension, hyperglycemia, dyslipidemia, and obesity) [49]. Metabolic syndrome is an established risk factor for cardiac-related mortality [49] and accumulating evidence indicates that metabolic syndrome may impair cognition. Older adults with metabolic syndrome perform more poorly on cognitive tasks [50, 51], particularly on measures of processing speed and executive functioning [52]. Moreover, the presence of metabolic syndrome has been associated with accelerated cognitive decline and increased risk of dementia [53–57]. Thus, as a robust predictor of both atherosclerosis and metabolic syndrome, total cholesterol/HDL-cholesterol may be particularly sensitive to early alterations in cognitive and cerebral health.

Cholesterol's impact on cognition and cerebral health may be mediated by alterations in vascular structure and function. Under normal conditions, endothelial cells in the arterial wall maintain vascular tone through the release of vasoactive substances, particularly the potent vasodilator nitric oxide [58]. However, coronary risk factors damage the endothelium and limit its ability to govern vascular tone [59]. High levels of LDL-cholesterol, the primary component of total cholesterol, are particularly detrimental to endothelial function. LDL particles preferentially bind to the intimal sub-layers of arteries, recruiting macrophages, activating a local inflammatory response, and stimulating a cascade of events that contribute to atherosclerosis [60]. The corresponding damage to the endothelium results in downregulation of nitric oxide and impaired vasoreactivity. HDL-cholesterol can at least partially mitigate this damage through reverse cholesterol transport [61]. In reverse cholesterol transport, HDL-cholesterol removes cholesterol from bodily tissues, including the vascular wall, and delivers it to the liver for excretion. Moreover, HDL-cholesterol activates endothelial nitric oxide synthase, upregulating the release of nitric oxide and increasing vasomotor function [62].

Nitric oxide availability affects vasomotor regulation in both the peripheral and cerebral arteries. In the brain, inhibition of nitric oxide release has been associated with reduced basal cerebral blood flow [63]. Chronic reductions in cerebral blood flow may negatively impact cognition because cognitive effort increases the demand for oxygen in engaged brain regions [64]. In the current study, higher levels of total cholesterol/HDL-cholesterol were related to lower cerebrovascular response to a cognitive challenge in the absence of global cognitive impairment, potentially indicating lower yet sufficient blood flow delivery in response to cognitive demands. If impairments in vascular tone worsen over time, blood flow may be further restricted, increasing vulnerability to cerebral white matter hyperintensities, a risk factor for stroke and dementia [65]. It is worth noting that in many fMRI studies, lower cerebrovascular response to a cognitive task has been interpreted as evidence of greater processing efficiency [18, 19]. However, reduced cerebrovascular response to a cognitive challenge has consistently been found in patients at increased risk for vascular cognitive impairment [5, 20, 21]. Furthermore, in the current study, reduced cerebrovascular response to a working memory task was related to poorer task performance and reaction time, defying an interpretation of greater processing efficiency in this case.

The strengths and limitations of the current study must be considered. The primary strength of the current study was its detailed characterization of the study participants in terms of medical history and cognitive function. Objective assessment of physiological indices such as fasting glucose levels allowed for exclusion of those with undiagnosed medical co-morbidities. The detailed cognitive assessment provided a thorough assessment of participants' cognitive functioning across multiple domains, including global cognitive functioning, language functions, visual-spatial abilities, memory, and attention-executive-psychomotor functions. However, the overall sample size was relatively small, so the present findings must be considered preliminary. The cross-sectional nature of our study is also a limitation. The current study found that cerebrovascular alterations associated with high total cholesterol/HDL-cholesterol levels could be detected as early as midlife. Longitudinal studies will be critical in determining whether these alterations are predictive of individual cognitive trajectories. Future studies would also benefit by expanding neuroimaging methods to include detection of white matter hypertensities, and quantification of baseline cerebral blood flow and BOLD response to non-cognitive challenges. Given the paucity of data on midlife cardiovascular risk and cerebral health, these assessments would be advantageous for characterizing this population and in determining if the changes detected in this study are specific to cognition or related to global changes in cerebrovascular reactivity or cerebrovascular coupling.

In conclusion, we found that higher total cholesterol/HDL-cholesterol levels at midlife related to lower cerebrovascular response to a working memory task in the right superior frontal gyrus, right middle frontal gyrus, and left inferior parietal lobe. These findings are supported by longitudinal studies, which have demonstrated that higher total cholesterol levels at midlife increase the risk of cognitive decline and dementia in old age [7, 9]. The novel component of the current study was that it provided a real-time assessment of the impact of serum cholesterol on the brain at midlife by implementing fMRI. The findings suggest that high total/HDL-cholesterol levels may affect cerebrovascular response to cognition as early as midlife when behavioral performance is still intact. Considering the modifiable nature of serum lipids and the necessity for find preventive strategies for dementia, longitudinal investigations on the predictive validity of these findings for future cognitive outcomes are warranted.

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