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## Triglycerides are Negatively Correlated with Cognitive Function in Non-demented Aging Adults

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### Abstract

**Objective**—Vascular risk factors like hyperlipidemia may adversely affect brain function. We hypothesized that increased serum triglycerides are associated with decreased executive function and memory in non-demented elderly subjects. We also researched possible vascular mediators and white matter microstructure as assessed with diffusion tensor imaging (DTI).

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**Design/Methods**—Participants were 251 non-demented elderly adults (54% male) with a mean age of 78 (SD=6.4; range: 62–94) years and a mean education of 15.6 (SD=2.9; range: 8–23) years. Fasting blood samples were used to detect serum triglyceride and LDL levels along with ApoE4 status. DTI was used to determine whole brain fractional anisotropy (FA). Composite executive (EXEC) and memory (MEM) scores were derived from item response theory. Clinical Dementia Rating (CDR) scores provided informant-based measures of daily functioning.

**Results**—Triglyceride levels were inversely correlated with executive function, but there was no relationship with memory. Controlling for age, gender, and education did not affect this correlation. This relationship persisted after controlling for vascular risk factors like LDL, total cholesterol, CDR and ApoE4 status. Lastly, adding whole brain FA to the model did not affect the correlation between triglycerides and executive function.

**Conclusions**—Triglyceride levels are inversely correlated with executive function in non-demented elderly adults after controlling for age, education, gender, total cholesterol, LDL, ApoE4 status, CDR, and white matter microstructure. The fact that the effect of triglycerides on cognition was not clearly mediated by vascular risks or cerebrovascular injury raises questions about widely held assumptions of how triglycerides might impact cognition function.

### Search Terms

All Cerebrovascular disease/stroke; Metabolic disease (inherited); All Cognitive Disorders/ Dementia; Cognitive aging; fMRI

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### Introduction

In the United States, over 10% of those aged over 65 are cognitively impaired (Dimopoulos et al., 2007) with vascular risk factors widely considered to be one of several potential contributing factors (Hokanson & Austin, 1996; Luchsinger JA., 2004; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). While the effect of risk factors like hypertension and type II diabetes on cognitive function are well established in literature, the relationship between triglycerides and cognition remains controversial (Luchsinger JA., 2004; Whitmer et al., 2005). Some studies suggest that increased serum triglycerides are correlated with poor cognitive performance (Dong, Zhang, Lu, & Flaherty, 2009; Rogers RL., Meyer JS., McClintic K., 1989), while others either find no relationship (Dong et al., 2009; Van Exel et al., 2002) or suggest that low serum triglyceride levels lead to poorer memory (Dimopoulos et al., 2007; Lepara, Valjevac, Alajbegovi, Zairagi, & Nakas-Indi, 2009). In addition, whereas most studies have focused on the relationship between triglycerides and memory (Dimopoulos et al., 2007; Dong et al., 2009; Lepara et al., 2009; Luchsinger JA., 2004; Whitmer et al., 2005), few have explored the effects of triglycerides on other measures of cognitive function, particularly executive function.

With the advent of clinical biomarkers has come an impetus for the detection of preclinical neurodegenerative disease. This has been a mainstay in the ongoing development of disease-modifying therapies and preventive treatments. Utilizing cerebrospinal fluid, high-field structural and functional magnetic resonance imaging, and inflammatory laboratory panels has proven to be time-consuming and costly. Blood-based phospholipid panels are currently

being investigated as a viable alternative for predicting phenotypic neurodegenerative conversion, and findings have been thus far encouraging (Mapstone et al., 2014). Understanding how other potential blood-based biomarkers may be used in the detection of early neurodegenerative disease and disease progression will be crucial in further advancing the field of neurological treatment for these conditions.

Triglycerides have been well implicated in the pathogenesis of cardiovascular disease, and have been shown to mediate the uptake of a number of gastrointestinal hormones such as leptin, ghrelin and insulin across the blood brain barrier (Banks, 2012; Urayama & Banks, 2008). These findings have received a growing body of interest, especially as it relates to the role of maintaining healthy cognition in older adults. It is well established that chronic elevation of circulating triglycerides is closely associated with metabolic dysregulation and inflammation, risk factors of cognitive impairment (Ford, N. A., DiGiovanni, J., & Hursting, 2013; Jung & Choi, 2014; Welty, 2013).

Biomarkers of metabolic dysregulation, including central obesity, hypertriglyceridemia and insulin-resistance have consistently shown to have inverse relationships with memory (Farr et al., 2008) and executive function systems (Frazier et al., 2015). Given the significant associations between triglycerides and pro-inflammatory markers, it is not surprising that declines in memory (Gunstad, Paul, Cohen, Tate, & Gordon, 2006), executive function and processing speed performance (Marioni et al., 2009; Marsland et al., 2006) have often been observed in the setting of systemic inflammation. This relationship may be further modified by factors such as ApoE4 status (Schram et al., 2007), as well as cerebral white matter microstructure integrity (Bettcher et al., 2013). It is therefore reasonable to propose that circulating serum triglycerides may be related to memory (and executive function), and this relationship may be influenced by the ApoE4 allele, as well as microstructural white matter health in non-demented older adults. The current investigation aims to address two specific questions: (1) Do serum triglycerides correlate with memory and executive functions in non-demented aging adults? (2) What might be the underlying mechanisms driving the relationship between triglycerides and cognition?

## Methods

### Participants

Participants included 251, non-demented community dwelling older adults recruited to participate in a multi-site study “Aging Brain: Vasculature, Ischemia and Behavior” designed to investigate changes in brain structure and function associated with markers of atherosclerosis. Eligible subjects were over 60 years old, spoke fluent English and either had normal cognition or mild cognitive impairment which were denoted by a Clinical Dementia Rating (CDR) of either 0 or 0.5, respectively. Exclusion criteria included a current diagnosis of dementia, Major Depressive Disorder, history of schizophrenia, bipolar disorder, seizures, Parkinson’s disease, multiple sclerosis, head injury with loss of consciousness over 15 minutes, current drug or alcohol abuse, significant hematologic or metabolic illness, and the use of medications that affect cognition (e.g., prescription-level pain medications). Our final sample consisted of 251 participants (49.7% male) with a mean age of 78 (SD=6.4; Range: 66–95) years, and a mean education of 15.7 (SD=2.9, Range: 8–23) years. Participants

underwent neuropsychological assessment in addition to fasting blood-draws and an MRI scan. Initial analyses were based on a sample of 251, only a subset of 163 had whole brain fractional anisotropy (FA) data. Participant demographics are displayed in Table 1. Written informed consent was obtained from all participants at each participating institution following the protocols approved by the institutional review boards.

### **Cognitive Assessment**

Standardized neuropsychological tests were administered to all participants. Psychometrically-matched measures of executive function and verbal memory were created using item response theory, described in detail in a previous publication by Mungas et al (Mungas, Reed, & Kramer, 2003). The executive functioning measure (EXEC) is a composite derived from the Dementia Rating Scale Initiation–Perseveration subscale (Yamada, Mitsuno, Kato, & Hirano, 1997), the Wechsler Memory Scale—Revised digit span backward and visual span backward (Wechsler, 1987), and a controlled oral word fluency task (F-A-S) (Benton & Hamsher, 1989). The memory measure (MEM) was derived using total recall on Trials 2–6 on the Word List Learning Test of the Memory Assessment Scales (MAS) (Williams, 1991), as well as the short and long delayed free recall from the same test.

Scale construction methods for composite scores derived from a larger sample of 400 subjects and were guided by item response theory (IRT), a commonly used approach to large-scale psychometric test development. In short, IRT analyses produce scale level functions that characterize the inherent psychometric properties of the measure, including a scale that captures the reliability at each point along the ability continuum, which is derived from the testing information curve (TIC), as well as a scale that reflects the expected test score at each ability point, which is based on the testing characteristic curve (TCC). The two composite measures had TICs demonstrating high reliability ( $r = .90$ ) from approximately 2.0 standard deviations (SD) below the mean of the overall development sample to 2.0 SD above the mean. Consequently, EXEC and MEM measures have a broad range of measurement, unencumbered by floor or ceiling effects for participants, as well as linear measurement properties across the broad ability range. In addition, the measures allow for parametric testing, as they were near-normally distributed (Mungas, 2005).

### **Blood Draws**

Blood-draws were performed on fasting participants at baseline. Fasting blood samples were used to detect serum levels of triglycerides and low-density lipoprotein (LDL) using standard laboratory protocols. Blood samples were also used for genetic testing to determine ApoE4 status. Interval times between blood draws, neuropsychology testing and neuroimaging did not exceed 30 days.

### **MRI Acquisition and Processing**

Participants were scanned using a 3T or 4T MRI system at four different scanning sites - University of Southern California, University of California, Davis research center, San Francisco Veterans Administration Medical Center, and University of California, San Francisco Neuroscience Imaging Center. The University of Southern California used a 3T

General Electric Signal HDx system with an 8-channel head coil. Acquired images included a T1-weighted volumetric SPGR scan (TR = 7 ms, TE = 2.9 ms, TI = 650 ms, with 1 mm<sup>3</sup> isotropic resolution). The University of California, Davis (UC Davis) research center used a 3T Siemens Magnetom Trio Syngo system with an 8-channel head coil as well as a 3T Siemens Magnetom TrioTim system with an 8-channel head coil. Acquired images for all UC Davis participants included a T1-weighted volumetric MP-RAGE scan (TR = 2500, TE = 2.98, TI = 1100, with 1 mm<sup>3</sup> isotropic resolution). Participants were scanned at the San Francisco Veterans Administration Medical Center using a 4T Siemens MedSpec Syngo System with an 8-channel head coil. A T1-weighted volumetric MP-RAGE scan (TR = 2300, TE = 2.84, TI = 950, with 1 mm<sup>3</sup> isotropic resolution) was acquired. The University of California, San Francisco Neuroscience Imaging Center used a 3T Siemens Magnetom TrioTim system with a 12-channel head coil. Acquired images included a T1-weighted volumetric MP-RAGE scan (TR = 2500, TE = 2.98, TI = 1100, with 1 mm<sup>3</sup> isotropic resolution). Inter- and intra-reliability tests were run with preliminary experimental subjects on all scanners involved. A protocol comparable to that used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study was executed by Michael Weiner, MD for MRI harmonization and calibration between and within sites.

### **Diffusion Tensor Imaging (DTI) Acquisition and Processing**

DTI data were derived from skull-stripping, motion and eddy-current correction with FSL package and geometric distortion correction (Tao, Fletcher, Gerber, & Whitaker, 2009). FA images for each subject were generated and all FA images were re-sliced to the SPM8 white matter template using a rigid-body transformation (dimensions: 121 > 145 > 121 voxels, resolution: 1.5 mm<sup>3</sup>).

A probabilistic FA atlas including anatomical labels of 50 deep WM region of interests (ROIs) from the DTI of 200 subjects was taken from the 'JHU ICBM-DTI-81 atlas package (Oishi et al., 2008) and subsequently imported into SPM8 WM template. The re-sliced FA images were normalized to an intensity-averaged FA template using a diffeomorphic registration algorithm (DARTEL) (Ashburner, 2007). The template was generated from 182 Aging Brain research subjects (mean age 78 ± 6 years) who had no infarcts and whose white matter hyperintensity (WMH) burden volume was less than 0.5% of intracranial volume (ICV), indicating lack of significant WMH pathology (DeCarli et al., 1995). Individual FA images and the 'JHU ICBM-DTI-81' FA atlas were warped to the common space of the normalized FA template generated from 23 VBI-participants whose DTI data, other than being used in creation of the intensity-averaged FA template, were not part of the current analyses. DTI values were taken from voxels where FA was greater than 0.20, in efforts to avoid including surrounding gray matter or cerebral spinal fluid. We selected global brain FA as our primary predictor, which was generated by calculating the geometric mean of the following; projection, association, limbic, and commissural fiber tracts: corona radiata, internal and external capsule, corpus callosum, fornix, cingulum bundle, parahippocampal white matter, posterior thalamic radiation, inferior and superior frontal-occipital fasciculus, superior longitudinal fasciculus, sagittal striatum and uncinate fasciculus.

## Statistical Analysis

A linear regression model was used to study the cross-sectional correlation between serum triglycerides and cognitive function. Triglyceride values were logarithmically transformed to achieve normality and constant variance for our regression model. Dependent variables included composite scores for executive function (EXEC) and memory (MEM). Age, sex and years of education were used to control for demographic factors in our sample. Clinical dementia rating (CDR) scores were also added to control for severity of functional impairment. To address our question of whether other vascular risk factors could be responsible for the correlation between triglycerides and executive function, we added LDL, total serum cholesterol, mean arterial pressure (MAP), and the participant's Framingham Cardiovascular score (which includes diabetes) to our demographic and CDR covariates. APOE4 status, a measure of Alzheimer's disease risk was also included in the model. To determine if the relationship between triglycerides and cognition could be mediated by white matter microstructure, we repeated the linear regression model, adjusting for diffusion tensor imaging fractional anisotropy values. Analyses were performed using Statistical Package for the Social Sciences (SPSS® V.20, IBM, Chicago, Illinois) and Statistical Analysis System (SAS® V9.2, SAS Institute Inc., Cary, N.C., USA).

## Results

### Cross-sectional Analysis of Triglycerides and Cognitive Performance with Demographic Factors, Vascular Risk Factors and Additional Measures of Severity and Genetic risk

In our first model, cross-sectional analysis of triglycerides and executive function showed an inverse correlation between triglycerides and executive scores ( $p < 0.01$ ), but no significant relationship with memory ( $p = 0.29$ ). In the second model, (controlling for age, education, and sex) higher triglycerides remained correlated with worse executive functions ( $p = 0.004$ ). In addition to demographic factors, we also tested a third model in which we controlled for vascular and Alzheimer's disease risk factors that could also be contributing to the variance of our model. Even after adding LDL, cholesterol, FCRS Score, and ApoE4 status, in addition to age, education, and sex, and CDR score, higher triglycerides remained significantly correlated with poorer executive function ( $p = 0.03$ ).

In our fourth model, we controlled for DTI fractional anisotropy values using a smaller subset of patients to determine whether the relationship between triglycerides and executive function was due in part to microstructural white matter abnormalities. We chose to use DTI because it is a sensitive measure of white matter health and can provide inferences about cerebrovascular mechanisms as well as the microstructure within the neural network (Charlton, Schiavone, Barrick, Morris, & Markus, 2010). The effect of triglycerides on EXEC remained significant, suggesting that triglycerides do not affect executive function through white matter alterations ( $p = 0.02$ ; see Table 2 for fourth model).

In our final model, we controlled for specific cardiovascular risk factors including the individual components of the FCRS score to screen for potential confounders that could potentially explain the relationship between triglycerides and executive function. Variables in this model included age, education, gender, CDR score, systolic and diastolic blood



pressures, history of stroke, diabetes, MI, CABG, and the use of anti-hypertensive medication. Within this model, the effect of triglycerides on executive function remained significant, thereby suggesting the presence of an alternate pathway, independent of the above cardiovascular mediators, by which triglycerides may exert its influence.

## Discussion

The two major findings of this study are: 1) Higher levels of serum triglycerides are significantly related to worse executive functions, but not memory in non-demented community dwelling older adults; and 2) This relationship is independent of other vascular and Alzheimer's disease risk factors, as well as cerebral white matter microstructure.

Executive functions enable us to organize simple ideas and thought processes into complex goal directed activities, and facilitate execution of activities of daily living (ADLs). The observed association between triglycerides and executive function supports recent studies showing an inverse correlation between other cardiovascular risk factors and executive function in younger adult populations (Yaffe et al., 2014),(Nishtala et al., 2014), and Perlmutter et al. (Perlmutter et al., 1988) have previously reported a link between triglyceride levels in older diabetics.

Our second key finding was that the relationship between triglycerides and executive functioning was not mitigated by other vascular risk factors or even a marker of white matter microstructure. This finding raises questions about the widely held assumption that the impact of vascular risks on cognition is mediated by cerebrovascular changes. This lack of association is consistent with recent studies that have shown that higher body mass index correlates with deficits in cognition independent of its relationship to cardiovascular and cerebrovascular disease (Cournot et al., n.d.; M F Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Merrill F. Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005; Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009) Perhaps the association we see between triglycerides and cognition are mediated by an alternate pathway. Serum triglyceride levels have been shown to regulate blood-brain-barrier (BBB) transport of insulin and other gastrointestinal hormones, which may have downstream effects on cognition (Banks, 2012; Urayama & Banks, 2008). Recent studies have suggested systemic inflammation, known to be elevated in obese individuals (Gregor & Hotamisligil, 2011), as a potential mediator of obesity-associated cognitive decline (Trollor et al., 2012). We acknowledge, however, that our fractional anisotropy data involved a smaller subset of patients, and our analysis may have succumbed to low statistical power. In addition, we used whole brain FA as our predictor; but it is plausible that looking at more specific regions of interest like subcortical-frontal or fronto-parietal tracts may have yielded different results. Further studies will be required to confirm or refute this relationship.

For this project, we were interested in studying heterogeneous non-demented adults with a range of vascular risk factors and cognitive capacities. Our cohort, therefore, included individuals who, while not considered demented, nonetheless report a change in cognition from baseline. Given this, our results may reflect a snapshot of preclinical dementia, highlighted primarily by a triglyceride-associated decline in executive function. This theory

is consistent with recently published cross-sectional data by Harrington et al. that showed that executive function changes preceded memory in patients with preclinical Alzheimer's pathology (Harrington et al., 2013). Additionally, our data also adds validity to previous findings of a relationship between triglycerides and decreased global cognitive ability and is consistent with Rogers et al.'s finding which showed that treating patients with lipid-lowering drug Gemfibrozil improved cognitive performance as measure by Cognitive Capacity Screening Exam (CCSE) (Susan AF., Kelvin AY., Butterfield AD., Mohammad AH, Lin X., 2008). The authors report that lowering lipid levels improved cerebral blood flow, suggesting a relationship between cerebral perfusion, triglycerides, and cognitive function. While we controlled for vascular risk factors and fiber tract integrity in our models, we did not control for cerebral perfusion in our study.

The results of this study specifically stress the importance of triglycerides as a cognitive risk factor in aging adults. Monitoring and maintaining triglyceride values within normal ranges may prove instrumental in preventing cognitive decline and maintaining healthy cognitive function in our elderly population. We acknowledge that our study is cross-sectional, giving us only a single snapshot in time. Therefore, a longitudinal study of the relationship between triglycerides and cognitive function in aging adults will be the next important step in capturing the interplay between lipid status and the cognitive aging process.

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- Darvis T. Frazier: Design, Statistics and Manuscript preparation
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- Linda Chao: Imaging Data Preparation and Analysis
- Bruce Reed: Manuscript Preparation
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- Michael Weiner: Imaging, Data Preparation and Analysis
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- Helena Chui: Design
- Joel H. Kramer: Design and Manuscript Preparation

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**Table 1**

Participants (Valid n = 163)

	<b>Mean (SD)</b>	<b>Range</b>
<b>Age (years)</b>	78.2 (6.5)	66 – 92
<b>Education (years)</b>	15.7 (2.9)	9 – 24
<b>Global FA</b>	0.4 (0.02)	0.32 – 0.44
<b>Triglycerides (mg/dl)</b>	2.0 (0.2)	1.6 – 2.9
<b>LDL (mg/dl)</b>	94.6 (30.4)	25 – 202
<b>Cholesterol</b>	173.8 (37.3)	80 – 295
<b>MAP</b>	94.4 (10.9)	61 – 128
<b>FCRS</b>	13.36 (8.3)	2 – 56
<b>SBP</b>	139.0 (19.4)	96 – 206
<b>DBP</b>	72.4 (9.7)	42 – 100
<b>Memory Score</b>	98.6 (19.5)	52 – 141
<b>Executive Score</b>	94.1 (16.7)	48 – 129
	<b>Percentage of Total</b>	
<b>Sex (Male)</b>	57.9%	
<b>CDR of 0.5</b>	39.6%	
<b>ApoE4 Allele Carriers</b>	22.6%	
<b>MI</b>	14%	
<b>Stroke</b>	27.1%	
<b>Diabetes</b>	29.2%	
<b>Smoking</b>	94.3%	
<b>Anti-HTN</b>	76.3%	
<b>CABG</b>	19.5%	

Abbreviations: Global FA = Global Functional Anisotropy; LDL = low density lipoprotein; SD = standard deviation; MAP = Mean Arterial Pressure; FCRS = Framingham Cardiovascular Score; CDR = Clinical Dementia Rating; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MI = Myocardial Infarction; Anti-HTN = Anti-Hypertensives; CABG = Coronary Artery Bypass Graft

**Table 2**

Cross-sectional analysis of the effect of Triglycerides on dependent variable executive function while controlling for demographic factors and vascular risk factors, and microstructural white matter abnormalities

	$\beta$	SE	t	P-value
Age	-.46	.20	-2.27	.03
Education	1.40	.43	3.34	.01
Gender	4.77	2.87	1.66	.10
LDL	.10	.09	1.09	.28
CHOL	-.11	.08	-1.46	.14
MAP	-.61	.12	-.52	.61
FCRS	-.01	.20	-.03	.98
ApoE4 Status	-1.43	2.89	-.49	.62
CDR	-20.60	4.91	-4.19	.00
Global FA	-17.70	50.90	-.35	.73
Triglycerides	-13.20	6.03	-2.19	.03

Abbreviations: LDL= low density lipoprotein; CHOL = Cholesterol; MAP = Mean Arterial Pressure; FCRS = Framingham Cardiovascular Score; CDR = Clinical Dementia Rating; Global FA = Global Functional Anisotropy;  $\beta$  = Unstandardized Beta; SE = Standard Error



**Table 3**

Cross-sectional analysis of the effect of Triglycerides on dependent variable executive function while controlling for specific cardiovascular risk factors.

	$\beta$	SE	t	P-value
Age	-.31	.17	-1.83	.07
Education	1.28	.357	3.58	.00
CDR	-10.17	4.47	-2.27	.02
Stroke	8.20	2.53	3.25	.00
MI	.96	3.41	.28	.78
CABG	.98	2.97	.33	.74
Gender	2.65	2.11	1.25	.211
Diabetes	1.16	2.31	.50	.62
SBP	.06	.06	.91	.37
DBP	-.37	.13	-3.00	.00
Anti-HTN	4.4	2.6	1.73	.09
Smoking	-1.14	4.22	-.27	.79
Triglycerides	-10.47	4.82	-2.17	.03

Abbreviations: CDR = Clinical Dementia Rating; MI = Myocardial Infarction; CABG = Coronary Artery Bypass Graft; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure Anti-HTN = Anti-Hypertensives;  $\beta$  = Unstandardized Beta; SE = Standard Error