Title

Triglycerides Are Negatively Correlated With Cognitive Function in Nondemented Aging Adults

Journal

Neuropsychology, 31(6)

ISSN

0894-4105

Authors

Parthasarathy, Vishnu
Frazier, Darvis T
Bettcher, Brianne M
et al.

Publication Date

2017-09-01

DOI

10.1037/neu0000335

Peer reviewed

HHS Public Access

Author manuscript

Neuropsychology. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Neuropsychology. 2017 September ; 31(6): 682–688. doi:10.1037/neu0000335.

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

Vishnu Parthasarathy, MD, MS,
University of California, San Diego, Department of Emergency Medicine

Darvis T. Frazier, PhD,
University of California, San Francisco, Memory and Aging Center

Brianne M. Bettcher, PhD,
University of Colorado, Anschutz School of Medicine

Laura Jastrzab, BS,
University of California, San Francisco, Memory and Aging Center

Linda Chao, PhD,
University of California, San Francisco, Department of Radiology

Bruce Reed, PhD,
University of California, Davis, Alzheimer's Disease Research Center

Dan Mungas, PhD,
University of California, Davis, Alzheimer's Disease Research Center

Michael Weiner, MD,
University of California, San Francisco, Center for Imaging of Neurodegenerative Diseases

Charles DeCarli, MD,
University of California, Davis, Alzheimer's Disease Research Center

Helena Chui, MD, and
University of Southern California, Department of Neurology

Joel H. Kramer, PsyD
University of California, San Francisco, Memory and Aging Center

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).

Corresponding Author: Joel H. Kramer, University of California San Francisco, Memory and Aging Center, 1500 Owens St #320, San Francisco, CA 94158, Joel.kramer@ucsf.edu.

Statistical Analysis conducted by Vishnu Parthasarathy, MD, MS, University of California, San Diego and Darvis T. Frazier, PhD, University of California, San Francisco

Supplemental data: none.

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

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, Alajbegović, Zaćiragić, & Nakas-Ićindić, 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 ($r \geq .90$) 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^3 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^3 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^3 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^3 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^3).

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 Perlmuter et al. (Perlmuter 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.

Acknowledgments

Study funded by: National Institutes of Aging, Bethesda, MD (AG123435, AG10129) and by the California Department of Health Services Alzheimer's Disease Program (contract 94–20354, 94–20355, 98–14970, and 98–14971) Dr. Bettcher was supported by NIH-NIA K23AG042492. Dr. Weiner was supported by the following grants: following grants; 2U01AG024904, W81XWH-13-1-0259, W81XWH-12-2-0012, R01 AG10897, 1P41 EB015904, P01 AG19724, R01 AG032306, R01A G03879, ADNI 2-12-233036, 20110506, R01 MH098062-01 from the following sources; NIH/NIA/National Institute of Mental Health, DOD, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Merck, Avid, and the Veterans Administration (VA).

Citations

Ashburner J. A fast diffeomorphic image registration algorithm. NeuroImage. 2007; 38(1):95–113. http://doi.org/10.1016/j.neuroimage.2007.07.007. [PubMed: 17761438]

Banks, Wa. Role of the blood-brain barrier in the evolution of feeding and cognition. Annals of the New York Academy of Sciences. 2012; 1264(1):13–19. http://doi.org/10.1111/j.1749-6632.2012.06568.x. [PubMed: 22612379]

Benton, AL., Hamsher, KD. Controlled Oral Word Association Test, multilingual aphasia examination. AJA Associates; Iowa: 1989.

Bettcher BM, Walsh CM, Watson C, Miller JW, Green R, Patel N, … Kramer JH. Body Mass and White Matter Integrity: The Influence of Vascular and Inflammatory Markers. PLoS ONE. 2013; 8(10) http://doi.org/10.1371/journal.pone.0077741.

Charlton, Ra, Schiavone, F., Barrick, TR., Morris, RG., Markus, HS. Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline. Journal of Neurology, Neurosurgery, and Psychiatry. 2010; 81(1):13–19. http://doi.org/10.1136/jnnp.2008.167288.

Cournot, M., Marquie, J., Ansiau, D., Martinaud, C., Fonds, H., Ferrieres, J., Ruidavets, J. Relation between body mass index and cognitive function in healthy middle-aged men and women. n.d. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc5&AN=2006-13351-004\nhttp://brumario.usal.es:4550/resserv?sid=OVID:psyc5&id=pmid:&id=doi:10.1212/01.wnl.0000238082.13860.50&issn=0028-3878&isbn=&volume=67&issue=7&spage=1208&pages=12

DeCarli C, Murphy DG, Tranh M, Grady CL, Haxby JV, Gillette Ja, … Rapoport SI. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. Neurology. 1995; 45(11):2077–2084. http://doi.org/10.1212/WNL.45.11.2077. [PubMed: 7501162]

Dimopoulos N, Piperi C, Salonicioti A, Psarra V, Mitsonis C, Liappas I, … Kalofoutis A. Characterization of the lipid profile in dementia and depression in the elderly. Journal of Geriatric Psychiatry and Neurology. 2007; 20(3):138–144. http://doi.org/10.1177/0891988707301867. [PubMed: 17712096]

Dong CHB, Zhang HWY, Lu JWZ, Flaherty JH. Association of Cognitive Impairment with Serum Lipid/Lipoprotein among Chinese. Dementia and Geriatric Cognitive Disorders. 2009; 27:111–116. http://doi.org/10.1159/000194660. [PubMed: 19158441]

Elias MF, Elias PK, Sullivan LM, Wolf Pa, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity. 2003; 27(2):260–268. http://doi.org/10.1038/sj.ijo.802225.

Elias MF, Elias PK, Sullivan LM, Wolf Pa, D'Agostino RB. Obesity, diabetes and cognitive deficit: The Framingham Heart Study. Neurobiology of Aging. 2005; 26(SUPPL) http://doi.org/10.1016/j.neurobiolaging.2005.08.019.

Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE, … Morley JE. Obesity and hypertriglyceridemia produce cognitive impairment. Endocrinology. 2008; 149(5):2628–2636. http://doi.org/10.1210/en.2007-1722. [PubMed: 18276751]

Ford NA, DiGiovanni J, Hursting SD. Metabolic Perturbations Associated with Adipose Tissue Dysfunction and the Obesity–Cancer Link. Adipose Tissue and Cancer. 2013:1–14.

Frazier, DT., Bettcher, BM., Dutt, S., Patel, N., Mungas, D., Miller, J., … Kramer, JH. Relationship between Insulin-Resistance Processing Speed and Specific Executive Function Profiles in Neurologically Intact Older Adults; Journal of the International Neuropsychological Society. 2015. p. 1-7.http://doi.org/10.1017/S1355617715000624

Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annual Review of Immunology. 2011; 29:415–445. http://doi.org/10.1146/annurev-immunol-031210-101322.

Gunstad J, Paul R, Cohen R, Tate D, Gordon E. Obesity is associated with memory deficits in young and middle-aged adults. Eating Weight Disord. 2006; 11(March):e15–e19.

Harrington MG, Chiang J, Pogoda JM, Gomez M, Thomas K, Marion SD, … Fonteh AN. Executive function changes before memory in preclinical Alzheimer's pathology: A prospective, cross-sectional, case control study. PLoS ONE. 2013; 8(11) http://doi.org/10.1371/journal.pone.0079378.

Hokanson JE, Austin Ma. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. Journal of Cardiovascular Risk. 1996; 3(2):213–219. http://doi.org/10.1177/174182679600300214. [PubMed: 8836866]

Jung, UJ., Choi, M. Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease; International Journal of Molecular Sciences. 2014. p. 6184-6223.http://doi.org/10.3390/ijms15046184

Lepara O, Valjevac A, Alajbegović A, Začiragić A, Nakas-Ićindić E. Decreased serum lipids in patients with probable Alzheimer's disease. Bosnian Journal of Basic Medical Sciences/Udruzenje Basicnih Mediciniskih Znanosti = Association of Basic Medical Sciences. 2009; 9(3):215–220.

Luchsinger JAMR. Cardiovascular risk factors and Alzheimer's disease. Curr Atheroscler Rep. 2004; 6:261–266. [PubMed: 15191699]

Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, MacArthur LH, … Federoff HJ. Plasma phospholipids identify antecedent memory impairment in older adults. Nature Medicine. 2014; 20(4):415–8. http://doi.org/10.1038/nm.3466.

Marioni RE, Stewart MC, Murray GD, Deary IJ, Fowkes FGR, Lowe GDO, … Price JF. Peripheral levels of fibrinogen, c-reactive protein, and plasma viscosity predict future cognitive decline in

individuals without dementia. Psychosomatic Medicine. 2009; 71(8):901–906. http://doi.org/10.1097/PSY.0b013e3181b1e538. [PubMed: 19661193]

Marsland AL, Petersen KL, Sathanoori R, Muldoon MF, Neumann SA, Ryan C, … Manuck SB. Interleukin-6 covaries inversely with cognitive performance among middle-aged community volunteers. Psychosomatic Medicine. 2006; 68(6):895–903. http://doi.org/10.1097/01.psy.0000238451.22174.92. [PubMed: 17132839]

Mungas, D. Contributions of Subcortical Lacunar Infarcts to Cognitive Impairment in Older Persons. In: Paul, RH.Cohen, R.Ott, BR., Salloway, S., editors. Vascular Dementia. Totowa, NJ: Humana Press; 2005. p. 211-222.http://doi.org/10.1385/1-59259-824-2:211

Mungas D, Reed BR, Kramer JH. Psychometrically matched measures of global cognition, memory, and executive function for assessment of cognitive decline in older persons. Neuropsychology. 2003; 17(3):380–392. http://doi.org/10.1037/0894-4105.17.3.380. [PubMed: 12959504]

Nishtala A, Preis SR, Beiser A, Devine S, Hankee L, Seshadri S, … Au R. Midlife cardiovascular risk impacts executive function: Framingham offspring study. Alzheimer Disease and Associated Disorders. 2014; 28(1):16–22. http://doi.org/10.1097/WAD.0b013e3182a715bc. [PubMed: 23995818]

Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, … Mori S. NeuroImage Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial white matter. NeuroImage. 2008; 43(3):447–457. http://doi.org/10.1016/j.neuroimage.2008.07.009. [PubMed: 18692144]

Perlmuter LC, Nathan DM, Goldfinger SH, Russo Pa, Yates J, Larkin M. Triglyceride levels affect cognitive function in noninsulin-dependent diabetics. The Journal of Diabetic Complications. 1988; 2(4):210–213. http://doi.org/10.1016/S0891-6632(88)80011-4. [PubMed: 2976765]

Rogers RL, Meyer JS, McClintic KMK. Reducing Hypertriglyceridemia improves cog and cerebrovascular flow. Angiology. 1989; 40:260–269. [PubMed: 2705633]

Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: The Whitehall II Cohort Study. American Journal of Clinical Nutrition. 2009; 89(2):601–607. http://doi.org/10.3945/ajcn.2008.26482. [PubMed: 19073790]

Schram MT, Euser SM, De Craen AJM, Witteman JC, Frölich M, Hofman A, … Westendorp RGJ. Systemic markers of inflammation and cognitive decline in old age. Journal of the American Geriatrics Society. 2007; 55(5):708–716. http://doi.org/10.1111/j.1532-5415.2007.01159.x. [PubMed: 17493190]

Susan AF, Kelvin AY, Butterfield AD, Mohammad AH, Lin XNE. Obesity and Hypertriglyceridemia Produce Cognitive Impairment. Endocrinology. 2008; 149:2628–2636. [PubMed: 18276751]

Tao, R., Fletcher, PT., Gerber, S., Whitaker, RT. Lecture Notes in Computer Science (including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). Vol. 5636. LNCS; 2009. A variational image-based approach to the correction of susceptibility artifacts in the alignment of diffusion weighted and structural MRI; p. 664-675.http://doi.org/10.1007/978-3-642-02498-6_55

Trollor JN, Smith E, Agars E, Kuan Sa, Baune BT, Campbell L, … Sachdev P. The association between systemic inflammation and cognitive performance in the elderly: The Sydney Memory and Ageing Study. Age. 2012; 34(5):1295–1308. http://doi.org/10.1007/s11357-011-9301-x. [PubMed: 21853262]

Urayama A, Banks Wa. Starvation and triglycerides reverse the obesity-induced impairment of insulin transport at the blood-brain barrier. Endocrinology. 2008; 149(7):3592–3597. http://doi.org/10.1210/en.2008-0008. [PubMed: 18403490]

Van Exel E, De Craen aJM, Gussekloo J, Houx P, Bootsma-Van Der Wiel A, Macfarlane PW, … Westendorp RGJ. Association between high-density lipoprotein and cognitive impairment in the oldest old. Annals of Neurology. 2002; 51(6):716–721. http://doi.org/10.1002/ana.10220. [PubMed: 12112077]

Wechsler, D. Wechsler Memory Scale-Revised. New York: Psychological Corporation; 1987. http://doi.org/CRJ Alz lib Copy2 #617; CRJ Alz lib Copy2-Converted #617; CRJ Alz Library 2 shared lib-Converted #1309; MMM Master_Reference_List-Converted #168; JLW MCI-Converted #20; JLW VBMprediction-Converted #86; JLW PCA-Converted #56

Welty FK. How do elevated triglycerides and low HDL-cholesterol affect inflammation and atherothrombosis? Current Cardiology Reports. 2013; 15(9) http://doi.org/10.1007/s11886-013-0400-4.

Whitmer, Ra, Sidney, S., Selby, J., Johnston, SC., Yaffe, K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64(2):277–281. http://doi.org/10.1212/01.WNL.0000149519.47454.F2. [PubMed: 15668425]

Williams, J. Memory assessment scales. Odessa, FL: Psychological Assessment; 1991. …. Retrieved from http://www.learnpsychology.com/courses/neuroassmt/Unit5_Memory_Attention/MAS_Manual.pdf

Yaffe, K., Vittinghoff, E., Pletcher, MJ., Hoang, T., Launer, L., Whitmer, R., … Sidney, S. Early adult to mid-life cardiovascular risk factors and cognitive function. Circulation. 2014. http://doi.org/10.1161/CIRCULATIONAHA.113.004798

Yamada M, Mitsuno S, Kato S, Hirano H. Dementia rating scale. Nippon Rinsho Japanese Journal of Clinical Medicine. 1997; 55(Suppl 1):310–314.

Author Contributions

Vishnu Parthasarathy: Design, Statistics and Manuscript preparation

Darvis T. Frazier: Design, Statistics and Manuscript preparation

Brianne M. Bettcher: Statistics

Laura Jastrzab: Laboratory Analysis

Linda Chao: Imaging Data Preparation and Analysis

Bruce Reed: Manuscript Preparation

Dan Mungas: Statistics

Michael Weiner: Imaging, Data Preparation and Analysis

Charles DeCarli: Manuscript Preparation

Helena Chui: Design

Joel H. Kramer: Design and Manuscript Preparation

Author Dischlosures

Vishnu Parthasarathy: No disclosures

Darvis T. Frazier No disclosures

Brianne M. Bettcher: No disclosures

Laura Jastrzab: No disclosures

Linda Chao: No disclosures

Bruce Reed: No disclosures

Dan Mungas: No disclosures

Michael Weiner: served on the Scientific Advisory Boards for Pfizer, BOLT International, Neurotrope Bioscience, Eli Lilly, U. of Penn's Neuroscience of Behavior Initiative, National Brain Research Centre (NBRC), India, Dolby Family Ventures, LP, and ADNI. He served on the Editorial Boards for Alzheimer's & Dementia and MRI

Charles DeCarli: No disclosures

Helena Chui: No disclosures

Joel H. Kramer: No disclosures

Table 1

Participants (Valid n = 163)

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

	β	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; β = 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.

	β	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; β = Unstandardized Beta; SE = Standard Error