11-19-2015

Lipoproteins and Health Outcomes: Cognitive and Physical Function in Older Adults

Marianne Chanti-Ketterl
University of South Florida, mchantik@mail.usf.edu

Lipoproteins and Health Outcomes: Cognitive and Physical Function in Older Adults

by

Marianne Chanti-Ketterl

A dissertation submitted in partial fulfillment
of the requirements for the degrees of
Doctor of Philosophy
with a concentration in Aging Studies
School of Aging Studies
College of Behavioral and Community Sciences
University of South Florida

Co-Major Professor: Ross Andel, Ph.D.
Co-Major Professor: Alyssa Gamaldo, Ph.D.
Theresa M. Beckie, Ph.D.
William E. Haley, Ph.D.
Cathy L. McEvoy, Ph.D.

Date of Approval:
November 13, 2015

Keywords: cholesterol, lipids, cardiovascular, aging, elderly

DEDICATION

For Calvin.

ACKNOWLEDGEMENTS

First and foremost, I want to thank God for being my rock, guiding me throughout this process, and giving me the strength to seek my dreams. There are many people I want to acknowledge who guided and supported me throughout this process. First, I would like to thank my committee members, beginning with my adviser, Dr. Ross Andel for his guidance, perseverance and trust in me and for introducing me to the Czech data. I also want to thank him for keeping me focused and on my timeline. In addition I thank Dr. Alyssa Gamaldo for embracing me as her student and guiding me into the analysis and writing process, Dr. Cathy McEvoy for always welcoming me into her office and giving me advice despite her busy schedule, and Dr. William Haley for going the extra mile to support minority students as myself; I will forever be grateful to him for revising my writing and keeping me focused. Additionally, I would like to give a special thanks to Dr. Theresa Beckie because she supported and provided me with the opportunities to pursue this research career. I am also deeply thankful to my colleagues, Colleen Papas and Sarah Eisel for their help with the Czech data, to Lindsay Peterson for all the proof readings, and to Rosalyn Roker for being my sister in this process. I also want to thank the staff from the School of Aging Studies: Rosa, Pam, Lydia, Amy and Gail for their constant support and guidance. Additionally, I want to specially acknowledge the School of Aging Studies and the College of Behavioral and

Community Sciences for the fellowship provided throughout these three and a half years. Without that support this would not have been possible.

I want to acknowledge my parents Walter and my deceased mother Marielos, for their courage to pursue dreams in a new land and opening a world of opportunities for me. Without their love and support I wouldn't be here. I want to also acknowledge all my family and friends for their prayers and unconditional support, especially Eve, Fabeto, Grettel, Iris, and Jenssy. Last and certainly not least, I want to acknowledge my biggest supporter in this process, my husband Thomas Ketterl. Without his patience, love, commitment and support none of this would have ever happened. And to my son Calvin, for patiently traveling this rocky road with me and for showering me with the love, patience and understanding I needed to complete this journey.

TABLE OF CONTENTS

List of Tables

List of Figures

ABSTRACT

Cardiovascular health is a major determinant of quality of life and mortality, especially in older adulthood. With the world's oldest population increasing at expedited rates, challenges from cardiovascular conditions and its implications are spawning. Although it is well known that dyslipidemia may lead to cardiac events, less is known about the effects on cognitive and physical function in older adults. Epidemiological studies show that optimizing current preventive strategies even at older ages may reduce the incidence of cardiovascular comorbidity (e.g. hypertension, stroke) and increase quality of life. Determining the association between lipoproteins and cognitive and functional performance in older adults may help develop interdisciplinary interventions designed to maintain independence longer and improve the overall quality of life.

The current dissertation contains two studies examining serum lipoproteins, specifically total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) in older adults in relation to cognitive and functional outcomes. The first study examined the association between lipoproteins and cognitive performance in a cognitively normal older adult population. Results showed an association between low levels of TG and higher composite cognitive scores (CCS), but this association disappeared when apolipoprotein ε4 allele (APOE ε4 allele) was adjusted for in the model. High levels of

HDL-C were also associated with the CCS and this association remained significant even after adjusting for APOE ε4 allele. Furthermore, these associations were only significant among women. High HDL-C remained linked with visuospatial function and attention and working memory even after adjusting for APOE ε4 allele. Further moderation analysis indicated that the association between TGs, HDL-C and cognitive performance was moderated by the APOE ε4 allele. Stratification by carriers and non-carriers of the ε 4 allele indicated that the previous association was only significant for non-carriers.

The second study of this dissertation is a longitudinal analysis, which explored the association between TC, LDL-C, TG and HDL-C and physical function. Random effects analysis was used to assess whether lipoprotein levels affect subsequent change in physical function. All models were adjusted for baseline age, sex, education, and perceived current economic situation, cardiovascular risk factors and comorbidity inclusive of cognitive disability. Results showed that lower levels of TC and HDL-C had cross-sectional associations with more ADL disability but not longitudinally, and higher levels of TG were related to better grip function. Moderation analysis of the previous significant association indicated that only cognitive disability moderated the cross-sectional association between TC and for ADLs. Further stratification showed that the association was only pertinent for participants with cognitive disability. Independent of cardiovascular risk factors and an extensive list of comorbidities, older adults living in the community with higher levels of TC, TG and HDL-C were associated with better physical function outcomes. Lipid patterns in older adults may be indicative of physical

function and may serve clinicians as a tool to compress morbidity in older adults and help them maintain independence and a high quality of life for as long as possible.

In conclusion, lipid levels in older adults play an important role in maintaining cognitive and physical function into older ages, thus maintaining a good quality of life. Higher HDL-C seemed to be the lipid associated with maintaining cognitive function, while TC dominated the association with physical function.

CHAPTER 1: INTRODUCTION

Cardiovascular health is a major determinant of quality of life and mortality, especially in older adulthood. The American Heart Association estimates that 43.7 million Americans over the age of 60 currently have some form of cardiovascular disease (CVD) and these numbers are expected to increase[1]. Projections for the year 2030 indicate that about 72.8 million adults in the United States will be over the age of 65[2,3]. With the world's oldest population increasing at expedited rates, challenges from cardiovascular conditions and its implications are rising. Two important anticipated health challenges with the increasing older adult population is maintaining good cognitive and physical functioning. Today, 8% white, 11% African-American and 12% Hispanics Medicare beneficiaries have dementia[4]. With estimates of 5.1 million adults older than 65 with Alzheimer's dementia[4] and almost 16 million with some form of disability[5] occurrence of these conditions is worrisome especially since these seem to develop "silently" from subclinical vascular components. A study found that among older adults, 37% had subclinical cardiovascular disease[6]. The need to determine the contributing factors associated with these devastating diseases is imperative to prevent or delay these conditions and the socioeconomic implications for future generations.

The association between aging and the development of cardiovascular pathology is primarily due to arterial aging[7,8]. Research indicates that arterial aging gives rise to the development of a chronic inflammatory process that leads to atherosclerosis and

subsequent complications such as CVD[7,9-11], cognitive deterioration[12,13], and functional decline[13,14]. The combination of CVD, cognitive and/or physical limitations in older adults is of great public health importance as it can lead to faster rates of dependence, increases in healthcare costs, and overall decreases in the quality of life.

Research shows many influences involved in the process of vascular aging and the senescence of the endothelium[15,16]. One such factor is dyslipidemia, which has been repeatedly found to not only contribute for the progression of arterial aging but also CVD[8,17-19]. Dyslipidemia is defined as a disorder in lipoprotein metabolism in which there is either an overproduction or a deficiency of lipoproteins, usually presented as elevation of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) or a decrease in high-density lipoprotein cholesterol (HDL-C)[20]. Although some may argue that lipoprotein levels, versus aortic or carotid intima-media thickness, may reflect only a snapshot of vascular aging[16], properly assessing routine clinical biomarkers as proxies for vascular aging may prove to be a valuable and more economic easily accessible tool. Thus understanding the associations between lipids and health outcomes (e.g. cognitive and physical function) in older adults may provide the foundations to develop interdisciplinary interventions to maintain independence longer and improve the overall quality of life.

Studies with lipids have historically used conceptual models that have tended to be only bio-physiological and seldom inclusive of the wide range of variables needed to correctly determine the associations. A framework of biopsychosocial factors is needed to ultimately determine, if as a whole, they influence outcomes. Wilson and Cleary[21] proposed the Health-Related Quality of Life Conceptual Model, which incorporates

basic clinical science with social science measures to evaluate health outcomes according to underlying existing health conditions with the goal of describing health and critical concepts that are in the causal pathway.

Figure 1 shows the Health-Related Quality of Life Conceptual Model of patient outcomes by Wilson and Cleary (1995) as it is applied to the research performed in this dissertation. It provides basic understandings of the role of lipoproteins in cognitive and physical function among older adults. The model includes biological function measures (e.g., lipid levels), integrates symptoms and functional status measures as mid-factors, with measures of health perceptions and overall quality of life. This conceptual model considers biological and physiological factors, which are routinely used in clinical practice, as basic determinants of health and inter-relates them with psychosocial measures often used in behavioral research. The purpose of the model is to understand the overall associations of factors of interest, with the ultimate goal of finding methods to improve the quality of life. In figure 1 the original model has been modified by showing the category of functional status split in two boxes as (a) physical function and (b) cognitive function. The blue colored boxes with bold frames show the sections and variables included in this dissertation.

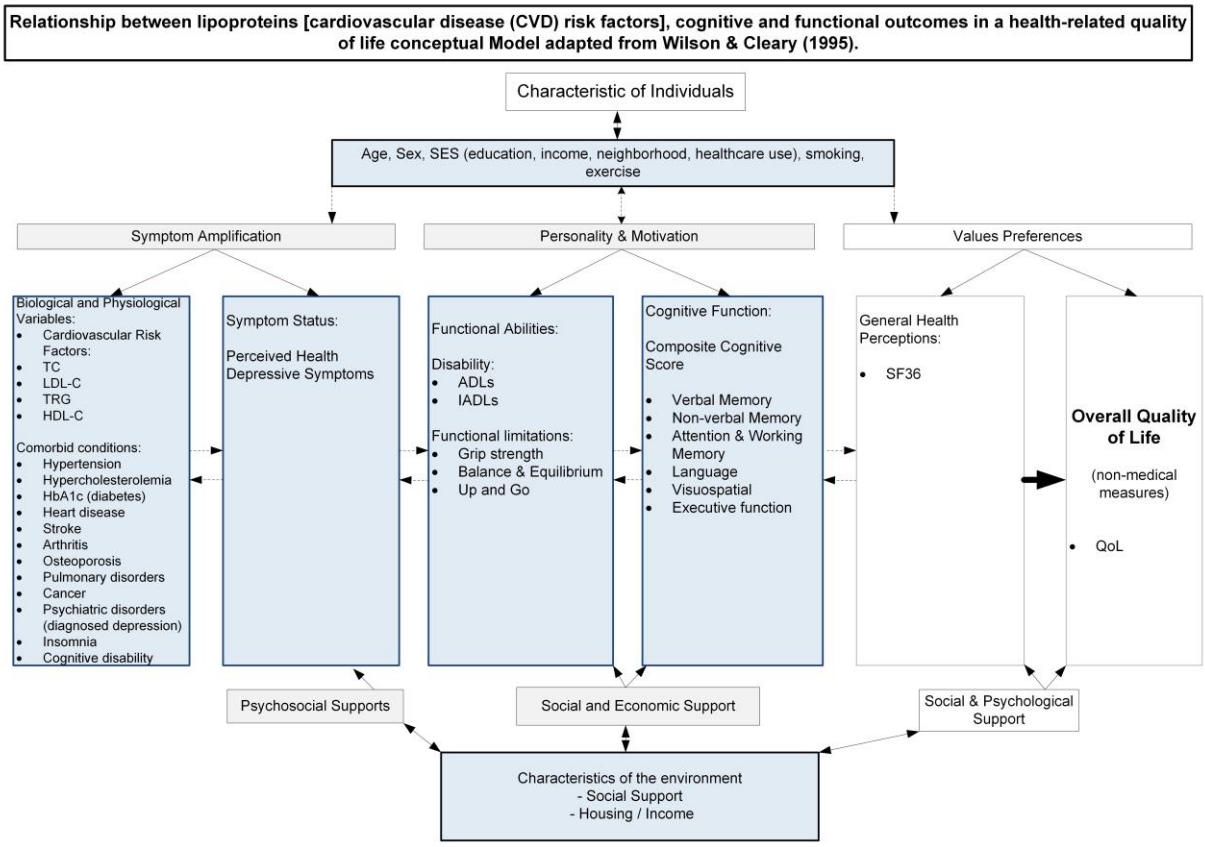

Figure 1. Modified health-related quality of life conceptual model of patient outcomes from Wilson & Cleary (1995).

To understand the association between lipoproteins and health outcomes in aging, it is important to first understand that lipoproteins are essential molecules the body needs to function properly. As defined, lipoproteins are molecules composed of a protein, or apoprotein, in contact with a lipid, cholesterol and/or triglyceride[22]. Proteins, also known as polypeptides, are made up of a linear chain of amino acids[23]. Lipids are non-polar organic solvents composed of fatty acids made up of a hydrocarbon chain that ends in a carboxylic acid group[23,24].

There are different types of circulating lipoproteins, categorized according to size and density; some are polar hydrophilic peripheral proteins and some are non-polar hydrophobic able to penetrate the lipid bilayer[25]. They can be divided in two major groups: cholesterol and triglyceride transporters. Cholesterol is essential in the aging process for cell division, brain and central nervous function as well as for numerous biological immune processes such as the production of hormones, vitamin D, and cell repair[26]. Cholesterol carrying lipoproteins are divided into LDL-C, or β-lipoproteins and HDL-C, or α-lipoproteins. LDL-C lipoproteins are commonly referred as "bad cholesterol" because they are the most involved in the formation of atherosclerosis, and HDL-C are often referred as the "good cholesterol" as they are known to be protective of CVD. Triglyceride (TG) lipoproteins can be intermediate density lipoproteins (IDL), very low density lipoproteins (VLDL), also known as pre-β-lipoproteins or chylomicrons, the largest and lowest in density among all plasma soluble lipoproteins[24,27]. TC is calculated by the sum of HDL-C plus LDL-C and twenty percent TG levels[28].

Normal clinical ranges for lipoproteins vary by age, sex, and ethnicity[29-31]. Table 1 provides lipid reference values for the general adult population as stipulated by the Adult Treatment Panel III report[32,33]. When these lipoproteins are outside the estimated ranges (above desired levels), there is an increased risk of cardiovascular disease[34,35]. Specific cardiovascular risk can be calculated based on established age, race, and sex specific risk equations[36,37]. In this dissertation, only TC, LDL-C, TG and HDL-C are explored as these are the routinely examined lipids in clinical practice.

Table 1. Normal Range of Lipoprotein Levels According to the ATP III Report*.

Lipoprotein	Normal/Desirable	Borderline High	High	Very High
TC	<200 mg/dL (<5.2mmol/l)	200-239 mg/dL (5.2- 6.2 mmol/l	≥240 mg/dL (6.2mmol/l)	n/a
LDL-C	<100 mg/dL optimal (<2.6 mmol/l) 100-129 mg/dL (2.6-3.4 mmol/l) Near or above optimal	130-159 mg/dL (3.4-4.1 mmol/l)	160-189 mg/dL (4.1-4.9 mmol/l)	≥190 mg/dL (>4.9 mmol/l)
TG	< 150 mg/dL (<1.7 mmol/l)	150-199 mg/dL (1.8-2.2 mmol/L)	200-499 mg/dL (2.3-5.6 mmol/L)	>500 mg/dL (>5.7 mmol/L)
HDL-C	<40 mg/dL is low and ≥60 mg/dL High/desirable (<1.0 mmol/l is low) and (≥1.5 mmol/l is High/desirable)			

*Note. TC=Total Cholesterol, LDL-C=Low Density Lipoprotein cholesterol, TG=triglycerides, HDL-C=High Density Lipoprotein cholesterol, mg=milligrams, dL=deciliter, mmol=millimol.*Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2001*

Lipoproteins, Cognitive and Functional Outcomes

Little is known about the association between lipoproteins, cognitive and physical function. Many of the same contributing factors for CVD continue to directly and actively influence cognitive function in older adults. It is not completely understood why there are inherent changes in cognition as people age. Changes in fluid intelligence such as decreased memory, less reasoning ability, more difficulty making new associations, lower ability to solve new problems, and perceptual speed and memory decline happen; yet, crystalized intelligence such as vocabulary and knowledge of general information increases[38]. Studies have related higher levels of TC and LDL-C among older adults with improved cognitive abilities and some suggest these may even protect cognition[39-

[42] and physical function[43,44]. Little research has been found associating TG to cognitive and/or functional outcomes among older adults. One study reported higher TG levels linked to worse cognitive performance in older adults[45]. A more recent study was able to detect a significant decline in vocabulary with higher TG levels over a 10-year period[46]. Higher levels of HDL-C are not only associated with CVD protection[1,47] but have also been associated with better cognitive performance[45,48,49].

Factors Affecting Lipoprotein Levels in Older Adults

Lipoprotein levels in older adults tend to be influenced by factors such as genetics[22,50]; ethnicity [51]; medications and/or treatment response[52-55]; lifestyle and environmental factors (e.g. sedentary lifestyle[10,56]); malnutrition[57,58]; frailty[59], and/or the existence of comorbid conditions (e.g. cancer, chronic diseases)[57,60].

Genetics play an important role in lipid metabolism. Although not extremely common in the general population, genetic variations such as homozygous familial hypercholesterolemia[22,50], a genetic mutation in the LDL-C receptor, apolipoprotein B or the protein convertase subtillisin kexin type 9 gene[61], or mutations in other genes or acquired defects can be responsible for lipid anomalies[62,63]. Most notably, the association between lipids and the apolipoprotein E (APOE) gene located on chromosome 19 has been reported. There are three common allele variants of this protein: ε2, ε3 and ε4 depending on the number of amino acids and their positions, and they vary by ethnicity[64]. APOE ε3 allele is the most common, but APOE ε4 allele is present in about a quarter of the general population and is associated with higher levels of TC and LDL-C[65,66]. Studies have shown that some isoforms of APOE (i.e., carriers of

the ε2 and/or ε3 allele show lower levels of TC and LDL-C and higher HDL-C) may inhibit the atherosclerotic process by its anti-oxidant and anti-inflammatory properties and can assist HDL-C in the cholesterol efflux thus lowering plasma cholesterol levels [47,64-68]. APOE carriers of at least one ε4 allele (ε2/ε4, ε3/ε4, or ε4/ε4) (APOE ε4) do not have these protective factors and have been associated with higher TC and LDL-C levels placing them at higher risk of myocardial infarctions and coronary heart disease than ε3 carriers[46,65]. Other genetic determinants identified through genome-wide association studies have identified several genes responsible for low and high levels of HDL-C[69].

Chronic conditions such as cardiovascular comorbidity (e.g., hypertension and stroke), diabetes, and depression are important intervening factors in the association between lipoproteins and aging[56]. These health conditions disrupt lipoprotein metabolism and are all significant determinants for quality of life having direct physical and social effects among elders. These factors are accounted for in the second study of this dissertation. While sex hormones also have an evident role in the lipid process[70,71], their influence may not be as significant among post-menopausal adults. Therefore, hormonal influence on lipids is not considered in this dissertation.

Response to cholesterol treatment (e.g. statins) diminishes with age[52], may aggravate comorbid conditions such as diabetes by increasing levels of hemoglobin A1c (HbA1c) and fasting glucose[72] and/or may cause important adverse side effects[73,74]. Secondary hyperlipidemia may also result from some commonly prescribed drugs such as steroids, progestin, hypoglycemics such as rosiglitazone, certain antipsychotic medications, commonly used antihypertensive medication and diuretics such as

hydrochlorothiazide and older generation beta-blockers[54,55]. The second study of this dissertation accounts for some of these medications.

In summary, many factors can increase or decrease lipoprotein levels; and all of them appear to be associated to abnormalities in synthesis, transport or degradation of the specific particles. Accounting for as many of these variables in studies looking at the association between lipoproteins and health outcomes is of great importance to properly interpret the results.

Lipoproteins, Cardiovascular Disease and Aging

As people age the risk of dyslipidemia increases; however, it is still unclear exactly why this occurs[20]. Middle aged adults and those in early older adulthood are known to have an increased risk of dyslipidemia, specifically hypercholesterolemia[75], which explains the strong relationship with increased risk of coronary heart disease and stroke after the age of 65[20,75,76]. Adults with cardiovascular risk factors in midlife, such as hyperlipidemia, and previous cardiovascular events are at increased risk of cognitive associated problems such as cognitive decline and dementia[77-83]. Analysis from the ONTARGET and TRANSCEND studies found an association between baseline mini-mental state exam scores <24/30 and 35% increased risk of having cardiovascular events; the authors suggest that perhaps cognitive impairment is just a marker of end-organ damage from vascular factors[80]. Others have found similar associations[82].

Contrary, among older adults, the literature indicates that lower levels of some lipids may be related to lower cognitive function[39,40,45,48,49,84,85] and difficulties in physical function and/or performing activities of daily living[86,87]. Despite important advancements,

the aging literature is far from reaching consensus in the exact relationship between lipoproteins, cognitive function and functional abilities. A summary of the latest research findings between TC, LDL-C, TG, and HDL-C and aging follows.

Lipoproteins and Aging

Total Cholesterol. Existing literature in cholesterol is complex and studies are filled with contradictory results when it comes to older adults. In the year 2000, decrease trends of TC were observed for both men and women over age 60; however, women maintained higher levels than men[88]. Research shows that in early and mid-life, adults able to sustain low TC levels have lower cardiovascular comorbidity and longer life expectancy[1]. However, in older adults, low TC levels have been associated with higher mortality[89-94], whereas increased levels are associated with reduced mortality[95]. But an association of lipids with mortality seems to have ethnic variations. Detrimental lipid levels do not appear to correlate with mortality among Hispanics[92]. Hispanics are known to have more cardiovascular risk factors than Whites[96] but have one of the lowest mortality from cardiovascular events[97]. Some have reported this overall mortality advantage in older Hispanics as the 'Hispanic Paradox'[98].

Low-density Lipoprotein Cholesterol. A limited number of studies have looked at LDL-C particles and longevity, but have found a positive association between low LDL-C and longer life[99-101]. LDL-C makes up 60-70% of TC in serum and is the main lipoprotein associated with risk of CVD and the most targeted lipoprotein in clinical practice[102-106]. Studies show an increase of LDL-C as people age[20,107]. Recent studies indicate that LDL-C increases progressively after the age of 20, in men it reaches a

plateau around 50-60 years and in women between 60-70[76]. In contrast, a recent study looking at 2,944 healthy Korean women to determine the effect of age on atherogenicity of LDL-C found mean levels of LDL-C increase by age groups up to age 59, but for groups in ages higher than 60 (ages of 60-79) LDL-C levels and particle size decreased[108]. However, in the United States, it is estimated that more than half (58.2%) of those over 65 years of age have high LDL-C levels[109], increasing the risk of CVD and mortality for this older cohort. In a study of dyslipidemia among Hispanics, the authors found significant differences in the levels LDL-C across background groups (e.g. Central American, Cuban, Dominican, Mexican and South Americans)[29]. Overall, high LDL-C was found in 36% of all Hispanics; Cubans and South Americans had the higher prevalence rates with 44.5 and 39.8 percent respectively, while Dominicans had the lowest prevalence at 31.6 percent[29]. Further studies of lipoproteins with different ethnic groups is needed to fully understand the lipid distribution in a population with various racial and ethnic groups.

High-density Lipoprotein Cholesterol. HDL-C measures the cholesterol content within alpha-HDL in plasma, but it does not differs the type of particle or size[47]. Research has shown that larger particle sizes of HDL-C have been associated with people without hypertension or CVD[100]. Larger particle size and lower particle concentrations have also been found among long-lived individuals[99,110], but in the Leiden Longevity Study this association on HDL particle phenotype was only found among women and was dependent on TG levels[99]. Studies have shown that HDL-C levels differ between men and women, with men usually presenting lower levels than women[45,85,88,111]. Among Hispanic individuals, women have been reported to have lower

levels of HDL-C than males[29]. HDL-C in general is well associated with cardiovascular events[47] even in patients taking statins[112]. Low levels of HDL-C have been known to be a major risk factor for cardiovascular disease[47,88,104,106,112-114], stroke[115] and mortality among older individuals[110,113]. However, resent research among the Framingham Offspring Study in adults older than 50 with more than 2 consecutive measures of HDL-C and no previous CVD found no association between HDL-C and cardiovascular events[116].

Triglycerides. As people age, TG levels seem to increase. This increase peaks in middle age for men and then decline, while in women the increase is maintained throughout life and manifests more in those taking estrogens[20,76]. Changes in hormones, dietary patterns, and metabolism have been associated with change in levels, but it is poorly understood why TG change with age. Over a quarter of adults older than 20 years have TG levels ≥ 150mg/dL but less than 3% actually take treatment[56]. Research from National Health and Nutrition Examination Survey (NHANES), shows that in adults 20-74 years of age, TG levels have increased by 6 mg/dL (0.07mmol/L) from 1988-1994 to 1999-2002[117]. Overall females have been found to have lower levels of TG than males[101,117]. A recent study found lower levels of TGs in the offspring of long-lived siblings than those of controls, and this again seemed significant for women only[101]. With the exception of Blacks, minorities in general, particularly Hispanics, have an increase prevalence of hypertriglyceridemia[51,97]. In NHANES, Mexican-Americans had higher levels of TG than non-Hispanic Blacks and non-Hispanic Whites[117].

Lipoproteins and Cognitive Function

Factors affecting cognitive function in older adults are still not well understood. While cognitive abilities (e.g., memory, speed, and attention) linked to fluid intelligence tend to decline with age, cognitive abilities (e.g., vocabulary and general information linked to crystallized intelligence) tend to increase and remain stable with age[38]. Recently, cardiovascular research has attempted to unfold the links between some well-known risk factors for CVD and these cognitive abilities (e.g. fluid and crystalized intelligence). Research looking at cardiovascular factors such as exercise, smoking, dyslipidemia, and hypertension has found associations with changes in cognitive functioning[78,118-121]. However, literature in the association between cognitive performance and lipoproteins is fairly recent, scarce and inconclusive for older adults. Most published studies have focused on risk of cognitive decline or dementia as outcomes and have not evaluated the actual cognitive performance as the primary result. In addition, most have measured cognition with brief, non-specific tests such as the Mini-Mental State Examination (MMSE); only few have used specific cognitive domains. Despite these limitations, several trends have been observed.

Total Cholesterol. The association between TC and cognitive performance seems driven as a function of age. Studies have found that overall high TC in midlife is detrimental to cognitive performance[42,122-124]. In contrast, several studies agree that higher levels of TC in older age correlate with improved cognitive function[39,40] and some have suggested that it may serve as a protective factor in old age[41,84,125,126]. A review study showed that overall, high midlife TC increased the risk of cognitive decline and dementia; but at older ages, high TC either had no association with cognitive function or

showed a protective relationship[122,123]. Van Vliet and colleagues suggest four possible explanations for why high midlife TC levels are a risk factor for late life cognitive decline and why high TC in older ages may be protective: high TC in midlife may be detrimental for cognition because: (1) cholesterol has a negative influence on deposition of beta-amyloid plaques in the brain and (2) has a direct effect on increasing CVD. In contrast, high TC may be protective of cognitive function in late life due to: (1) the direct effects of cholesterol on the maintenance of brain function (amongst which are synapse formation and maintenance) and (2) low TC levels in late life likely reflect general ill health, and may then be seen as an epiphenomenon[122,123]. A cross-sectional analysis of The Framingham Heart Study using adults 55-88 years old from the years 1974-1978 found lower TC levels (<180 mg/dL) associated with worse cognitive performance measured through a composite score as well as in individual cognitive domains[39]. Investigators from the Women's Health and Aging Study II also found that among older women, there was a dose-response association between TC levels and the Purdue Pegboard, higher levels of TC yielded better scores[127]. Yet others find no association at older ages[128-132]. This inconsistency of results is mostly due to different designs, populations studied (e.g. racial and/or ethnic differences), methods used in both the analysis of TC, and the battery of neuropsychological tests used.

Low-density Lipoprotein Cholesterol. Higher levels of LDL-C have been associated with some forms of fluid intelligence such as better memory performance in middle age, particularly for mental manipulation and rapid mental processing[85,132]. Higher LDL-C has also yield better immediate recall in some studies[48,132]. An analysis performed in The Longitudinal Aging Study Amsterdam (LASA) in the Netherlands,

conducted every three years on men and women between 55-85 years of age found a positive threshold effect at levels ≤ 4.2 and 3.8 mmol/L respectively for LDL-C on general cognition performance and information processing speed[48]. Lower levels of LDL-C have been associated with lower general cognitive performance[48] and have also been linked to lower fluid intelligence measured through processing speed in another study[133]. Yet others have been unable to find any association between LDL-C and cognition[49,129,134-136].

High-density Lipoprotein Cholesterol. Higher levels of HDL-C are not only associated with CVD protection[1,47] but have also been associated with better cognitive performance[45,48,49]. Interestingly, this protective effect of HDL-C seems to be sex driven predominating among women. High HDL-C levels yielded better maintenance of verbal ability (crystalized intelligence) in women over the age of 65, but not in men; better perceptual speed performance (fluid intelligence) was seen in women before age 65 only[85]. Among a sample of nonagenarians, (adults 90 years of age or older), low HDL-C was associated with poor scores in the Spanish version of the MMSE; but once covariates were adjusted in the model, the effect disappeared[137]. A similar association was seen by The Longitudinal Aging Study Amsterdam. However, when looking at specific cognitive domains, a positive association was observed between high HDL-C and better performance on immediate recall (Auditory Verbal Learning Test) and information processing speed in time-adjusted models but only immediate recall remained significant over time[48]. Despite the mentioned findings, many recent longitudinal studies have not been able to find any association between higher levels of HDL-C and any improvement in cognition[129,132,134,136]. It may be speculated that

differences in methodological approaches to these longitudinal studies such as diverse demographic characteristics of the samples (e.g. large age ranges, sex-specific samples, ethnic differences) may not capture significant lipid associations. The duration of the studies and the times lipids were collected may also have an impact on the lack of findings. If lipids in a longitudinal study were only measured once, this may underestimate the association of HDL-C or other lipids and cognitive function. Additionally, the types of cognitive measures included, the number of occasions participants tested, and the interval of time between the testing occasions may add to the limitations.

Triglycerides. Limited research has been found associating TG to cognitive function among older adults. A study among the oldest-old Chinese found that high TG in this group of older adults was associated with better cognitive function measured using the MMSE[138]. Contrariwise, an earlier study was able to detect a significant decline in vocabulary with higher TG levels over a 10-year period[46]. Atzmon and colleagues reported higher TG levels linked to worse cognitive performance in older adults[45]. The Swedish Adoption/Twin Study[85] found lower triglycerides related to better cognitive outcomes in women. Yet, others found no correlations between TG and the MMSE[139].

Apolipoprotein ε4 Allele and Cognition. Among older adults, research on the association between APOE ε4 allele and cognition has been centered on the increased risk of dementia and/or cognitive decline, less on cognitive function. Recent research has recognized that the APOE ε4 allele plays an important role in cognitive outcome differences[140-142]. Furthermore, within group differences have been observed on

different cognitive tests. A recent meta-analysis looking at 77 studies on cognitively healthy adults found that carriers of APOE ε4 allele performed worse on measures of episodic memory, executive functioning, and overall global cognitive ability than non-carriers of the APOE ε4 allele[143]. An earlier meta-analysis found that despite small group differences, compared to non-carriers of the ε4 allele, carriers had statistically significant worse performance on global cognitive function and episodic memory and executive function scores[140]. However, it is less clear the role APOE plays on cognitive performance among older adults. Research performed on adults older than 65 years of age free of dementia found that carriers of the APOE ε4 allele have more difficulty and decline more rapidly in semantic memory and perceptual speed but not in working memory or visuospatial skills[142].

APOE regulates lipid transport cholesterol and homeostasis in the brain[144] and the ε4 allele is known to increase the risk of CVD in part by being associated with pro-atherogenic TC, LDL-C levels and higher VLDL-cholesterol-to-HDL-C ratio[46,65,144]. The atherosclerotic process leads to cardiovascular pathology which is associated with cerebral hypoperfusion; microvascular hemorrhages, extracranial athero-embolisms and small vessel disease[77,145,146], all which increase the risk of cognitive dysfunction[40,79,121,147-153]. Thus, it is expected that APOEε4 will modify the association between lipoproteins and cognitive function in some extent.

Lipoproteins and Functional Outcomes

Cardiovascular disease is among the top 15 conditions that cause disability[1,86,154]. Disability is the inability or difficulty to carry out activities of daily living

(ADL) and problems performing instrumental activities of daily living (IADL)[155]. When ADL and/or IADLs become more effortful for older adults, health gradually declines, quickly leading to dependency, decreased quality of life, and increase health service utilization[156]. The prevalence of functional disabilities in those with CVD has been estimated around 23%; yet, independent of established CVD, some independent vascular risk factors have been associated with disability as well[86].

Some studies have associated low levels of TC[44] and low HDL-C[157] in older ages with mobility limitations and disability[43,44,157]. Recent studies from populations in Ireland and Italy, have found high levels of HDL-C associated with reduced risk of functional impairment even after accounting for other lifestyle-based CVD risk factors (e.g., smoking, exercise) and cardiovascular diseases such as stroke or coronary heart disease[86,158]. However, Welmer et al. (2014) observed an opposite trend in community dwelling older adults (60 years or older) enrolled in the Confucius Hometown Aging Project of China; among them, higher TC was related with functional limitations and dependence[87]. Much is still to be known about the relationship between lipids, functional limitations and disability, especially at advanced ages.

Aims

Research is just beginning to unravel the associations between lipids and cognitive and physical function. The literature is fairly recent, scarce and inconclusive. But this area of research is also crucial for understanding the effects of lipoproteins on cognitive and physical health, which can guide in developing effective interventions to maintain health in the aging population. Studies show that dyslipidemia may lead to

cardiac events and progressive deterioration of daily functional activities[86,154,159,160] and potentially contribute to cognitive deterioration[85,136,161-163]. However, most studies have not evaluated cognitive performance in the old as the primary outcome and have measured cognition mainly with brief, non-specific tests such as the MMSE. Additionally, functional limitations and disability, which are often collapsed as one, are rarely used as the primary outcome. Moreover, little is known about these topics in understudied populations. No previous study had looked at lipids and cognitive function in older adults who reside in the Czech Republic, nor had any study looked at the longitudinal association between lipids and physical function among Latinos.

As people are living longer, the concern for disease burden in older ages becomes increasingly important, especially when it comes to cardiovascular disease. Lipid disruption seems to be at the core of most cardiovascular pathology, thus the need to address their association with health outcomes in older adult populations. This dissertation anticipates contributing to the existing literature by improving the understanding of the association between serum lipoproteins and health outcomes by investigating the association between specific lipoproteins such as TC, LDL-C, TG, and HDL-C in relation to cognitive and physical function outcomes in adults over the age of 60. It is hypothesized that high levels of TC, LDL-C and HDL-C and low levels of TG in adults over the age of 60 will be associated with better cognitive and physical function.

The aim of this dissertation is addressed through two separate research studies, each with specific aims. Study one, looks specifically at the association between TC, LDL-C, TG and HDL-C and cognitive function in cognitively normal adults over the age of 60 residing in the Czech Republic. Study two, looks at the association between TC,

LDL-C, TG and HDL-C and physical function across three study waves between 2005 and 2010 in a population sample of adults over the age of 60 residing in Costa Rica. This population has not been previously examined in the literature in relation to the association of lipoproteins and physical function.

Study 1

Aim 1. The first aim was to examine the association between TC, LDL-C, TG and HDL-C and cognitive performance (measured as a composite cognitive score and separate cognitive domains: verbal and nonverbal memory; attention and working memory; language; visuospatial function; and executive function).

Hypothesis 1. Based on previous findings which suggest significant associations between lipoproteins and cognitive performance [39,41,42], it was hypothesized that high levels of TC, LDL-C and HDL-C and low levels of TG would be associated with better cognitive function (higher composite cognitive scores and higher scores in each individual cognitive domain: nonverbal and verbal memory; visuospatial function; executive function; attention and working memory; and language).

Aim 2. The second aim was to investigate whether age, sex and/or APOE ε4 allele status moderated any statistically significant association between each independent lipoprotein (TC, LDL-C, TG and HDL-C) and the composite cognitive scores in model 1.

Hypothesis 2. It was hypothesized that age, sex and/or APOE ε4 allele status would moderate any statistically significant association between each independent lipoprotein and the composite cognitive score. It was hypothesized that the association

between each independent lipoprotein and cognitive performance would be more pronounced in older participants. Specifically, it was also hypothesized that the association between lipoproteins and cognitive performance would differ between men and women with the expectation that the association would be more prevalent among women. It was also hypothesized that the association between lipoproteins and cognitive performance would be significant only among non-carriers of at least one APOE ε4 risk allele.

Study 2

Aim 1. The main purpose of this study was to determine if baseline measures of independent lipoproteins TC, LDL-C and HDL-C are associated with change in physical function taking into account demographics, cardiovascular risk factors and comorbidity in adults over the age of 60 participating in the Costa Rican Longevity and Healthy Aging Study (CRELES). Physical function measured as (a) disability (ADL and IADL disability) and (b) functional limitations (e.g. grip strength; equilibrium/balance; walking).

Hypothesis 1. It was hypothesized that those older adults with lower baseline levels of TC, LDL-C and HDL-C and high levels of TG would have worse physical function decline (more disability and functional limitations) over the study period even after adjusting for demographics and possible confounders.

Aim 2. The second aim was to investigate whether sex and/or cognitive disability moderated any statistically significant association between baseline lipoproteins (TC, LDL-C, TG and HDL-C) and change in physical function over time.

Hypothesis 2. It was hypothesized that sex and/or cognitive disability would moderate any statistically significant association between each independent lipoprotein and physical function. Specifically, it was also hypothesized that the association between lipoproteins and physical function would differ between men and women; with the expectation that physical function decline would be more prevalent among women. It was also hypothesized that the association between lipoproteins and physical function would be significant only among participants with cognitive disability.

This dissertation was approved and exempted by the Institutional Review Board of the University of South Florida on May15, 2015. Portions of the first study used in this dissertation have been published before in the Journal of International Psychogeriatrics[164] and are being used with permission of Cambridge Press.

CHAPTER 2: STUDY 1: CHOLESTEROL AND COGNITIVE PERFORMANCE AMONG COMMUNITY VOLUNTEERS FROM THE CZECH REPUBLIC

Abstract

Disruption of lipids, particularly high total cholesterol (TC), high low-density lipoprotein cholesterol (LDL-C), high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) correlates with cardiovascular disease and may also be associated with worse cognitive function in middle age adults, and particularly among women and apolipoprotein ε4 allele carriers (ε2/ε4, ε3/ε4, or ε4/ε4) (APOE ε4). This study looks at the association of six well-established cognitive domains and a composite cognitive score (CCS) and TC, LDL-C, TG, and HDL-C in older adults from the Czech Republic (n = 112) over the age of 60 with Mini-Mental State exam scores ≥24. Ordinary least squares regressions models were conducted. Model 1 adjusted for age, sex, education, and depressive symptoms and model 2 additionally adjusted for APOE ε4 allele. Furthermore, a moderation analysis by age, sex and the presence of at least one APOE ε4 allele was carried out. Results showed better CCS associated with lower levels of TG (p=.036) and higher levels of HDL-C (p=.008); the latter remained significant even after adjustment for APOE ε4 allele (p=.018). High HDL-C levels were associated with better visuospatial function (p=.043) and attention/working memory (p=.044) even after adjustment of the APOE ε4 allele. Moderation analysis indicated APOE ε4 allele as

theory significant moderator in the association between better CCS and low TG and high HDL-C among non-carriers only. Neither age nor sex moderated the effect of the association between any of the lipoproteins and CCS. Low TG and high HDL-C were the main lipoproteins associated with cognitive performance, with results somewhat more pronounced among women and non-carriers of the APOE ε4 allele. Further research is needed to first, test if maintaining lipoproteins at optimum recommended levels into older ages does maintain cognitive function. Second, future studies should strive to explore if boosting HDL-C levels positively changes cognitive function in aging populations.

Introduction

Dyslipidemia is a common medical problem that tends to occur with age. It increases the risk of adverse coronary events, especially after the age of 65[20,75,76] and has been found to be associated with poor cognitive function[78,118-121,124] as well as an increased risk of cognitive decline and dementia[77-83]. Previous research on the association between lipoproteins and cognitive function (e.g. measures of fluid and crystalized intelligence) has been limited, mostly performed among middle age adults and often from pharmacological intervention studies[78,79,121,132,165-170]. Few have evaluated cognitive performance only among older adults and the results have been inconsistent[39,40,45,48,49,84,85,127-129,171,172].

Recent investigations have observed correlations between high levels of total cholesterol (TC) and improved cognitive function in older adults[39,40,126]. Previous studies have even suggested that high TC levels may be associated with better

cognition in advanced old age[41,84,122,123,125,126]. Furthermore, a recent study suggested that the association between TC and cognition is U-shaped; indicating that both low and high levels of TC were associated with lower cognitive scores[173]. However, some studies have observed no association between lipoproteins and cognitive performance[128-132]. Given these inconsistent findings, further research with older adults is needed to understand the association between TC and cognitive function.

Lower levels of low-density lipoprotein cholesterol (LDL-C) have also been associated with lower general cognitive performance[48] and lower processing speed among older adults[133]. An earlier study conducted in postmenopausal women with established CVD found high levels of LDL-C related to worse cognitive performance[171]. Yet other investigators have not found any links between LDL-C and cognition[49,129,136], leaving room for additional research to support or refute the association between LDL-C and cognition.

Higher levels of high-density lipoprotein cholesterol (HDL-C) are not only cardio-protective; they also appear associated with better cognitive performance[45,48,49]; especially among women. High HDL-C levels have been specifically linked with better verbal ability in women only[85]. Additionally, baseline HDL-C have shown a positive association with immediate recall and speed of processing in both men and women[48]. However, many longitudinal studies have found no association between HDL-C and cognition[129,132,134,136,171].

Fewer studies have found significant associations between triglycerides (TG) and cognitive function. Earlier studies found that among older adults, those with low TG levels performed better on the Mini-Mental State Exam[45]. Particularly, within women,

lower TG were related to better cognitive outcomes[85], while those with high TG showed a decline in vocabulary over a 10-year period[46]. However, a recent study found that high normal TGs (mean level of TG in the 95th percentile equal to 2.15 mmol/l) were associated with a decreased risk of cognitive impairment independent of cognitive function[138]. Yet, others found no links between TG and the MMSE[129,139,171].

Lipid levels differ between males and females[76,174], thus sex differences in the association between lipoproteins and cognitive function has also been observed. Despite the lack of sex-stratified studies, a trend seems to exist indicating that the association between lipids and cognitive function may be stronger among women. For example, in the Swedish Adoption/Twin Study lipid levels were more indicative of cognitive aging in women than in men, with higher HDL-C and lower triglycerides related to better cognitive outcomes in women[85]. In women-only studies, high concentrations of LDL-C and TC were both associated with better memory[132] and better psychomotor speed[127]. More sex-stratified studies are needed to determine if the association between lipids and cognitive performance does vary between older males and females, and if so what are the intervening factors in this association.

Finally, variations in apolipoprotein ε4 allele (i.e., ε2/ε4, ε3/ε4, or ε4/ε4 vs. variants without any ε4) (APOE ε4 allele) have been associated with cognitive function. A meta-analysis showed that despite small effect sizes, those carriers of the APOE ε4 allele had lower cognitive function, including episodic memory and executive function[140]. A study over 3.2 years found a greater decline in memory among carriers of the APOE ε4 allele than non-carriers[133]. Although little is known about the association between APOE ε4 allele and its impact on lipoproteins and cognitive function, some studies have

associated APOE ε4 allele with lipid levels and cognition. De Frias et al (2007) found that higher TC was associated with greater decline in recognition only among carriers of the APOE ε4 allele. Yasuno et al (2012) reported that higher HDL-C was related to better cognition only for non-carriers of the APOE ε4 allele gene. Similarly, a study among older adults from New York reported that the associations found between high TC and LDL-C and better cognitive function only held for APOE ε4 non-carriers[126]. Therefore, further investigation of the role of being APOE ε4 carrier vs. non-carrier in the association between lipoproteins and cognitive performance in older ages seems warranted. If differences in the association exist based on variants of the APOE ε4 allele, perhaps future gene-targeted studies are needed to determine clear associations that can lead to gene-specific interventions in the future.

Research Aims

The current study has two main aims. The first aim explores the association between independent lipoproteins and cognitive performance in older adults. The second aim examines a possible moderation effect of age, sex and APOE ε4 allele on the association between lipids and cognitive performance.

Aim 1. The first aim was to examine the association between TC, LDL-C, TG and HDL-C and cognitive performance (measured as a composite cognitive score and separate cognitive domains: verbal and nonverbal memory; attention and working memory; language; visuospatial function; and executive function).

Hypothesis 1. Based on previous findings which suggest significant associations between lipoproteins and cognitive performance[39,41,42], it was hypothesized that high

levels of TC, LDL-C and HDL-C and low levels of TG would be associated with better cognitive function (higher composite cognitive scores and higher scores in each individual cognitive domain: nonverbal and verbal memory; visuospatial function; executive function; attention and working memory; and language).

Aim 2. The second aim was to investigate whether age, sex and/or APOE ε4 allele status moderated any statistically significant association between each independent lipoprotein (TC, LDL-C, TG and HDL-C) and the composite cognitive scores in model 1.

Hypothesis 2. It was hypothesized that age, sex and/or APOE ε4 allele status would moderate any statistically significant association between each independent lipoprotein and the composite cognitive score. Specifically, it was also hypothesized that the association between lipoproteins and cognitive performance would differ between men and women; with the expectation that the association would be more prevalent among women. It was also hypothesized that the association between lipoproteins and cognitive performance would be significant only among non-carriers of at least one APOE ε4 risk allele.

Methods

Study Sample

This cross-sectional study uses pooled data from participants recruited between 2005 and 2012 from the Memory Clinic at University Hospital Motol in Prague, Czech Republic participating in a longitudinal study. Participants in this study (a) came to the

memory clinic due to concern about their memory expressed by themselves or by a relative, (b) were recruited from the University of the Third Age, or (c) were relatives or caregivers of patients with MCI or AD. All participants underwent a thorough neuropsychological examination and provided medical history.

Figure 2 shows the sample included in this study. There were 215 adults with biomarker data ±60 days from the administration of the neuropsychological battery. After restricting the sample to those with Mini Mental State Examination (MMSE) scores ≥24, age ≥ 60 years, and information about education, 112 adults remained for analysis. A cut off of 24 on the MMSE was established based on criteria frequently used in clinical practice[175,176].

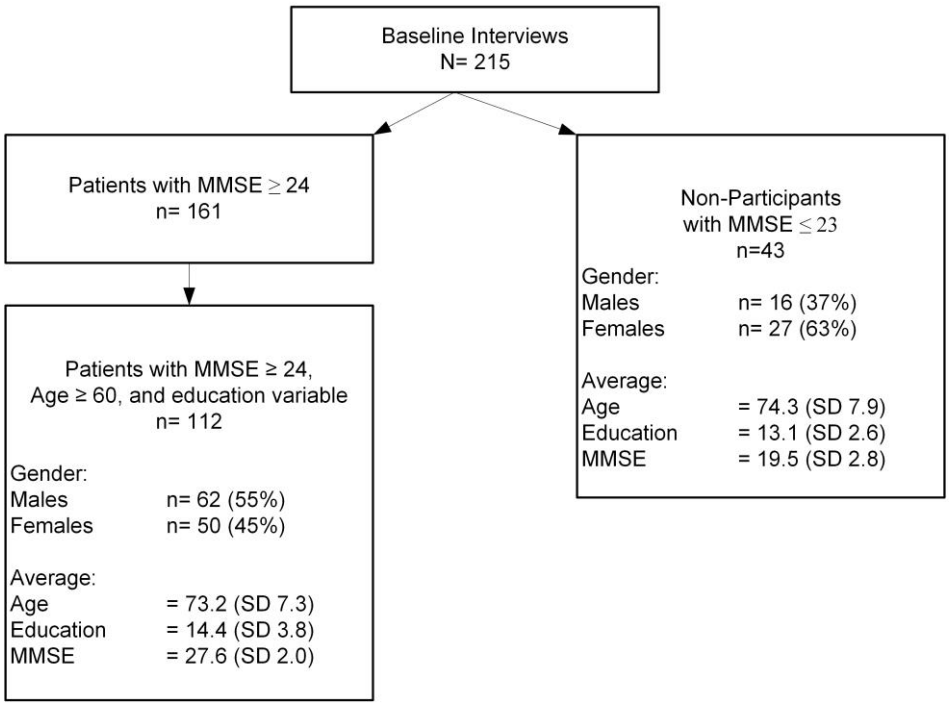

Figure 2. Study One Flow Diagram.

Note. MMSE = Mini-Mental State Exam; SD=Standard Deviation

Out of 215 participants, 54 had MMSE scores below 24; 50 were under the age of 60, and 2 were missing education variable. Those excluded from the sample were on average a year older, with one less year of education than the general sample and most were females. Due to the high education levels of the sample, no education effects or bias is anticipated. The study was approved by the institutional ethics committee from the Memory Clinic at 2nd Faculty of Medicine, Charles University and University Hospital Motol in Prague, Czech Republic and written informed consent was obtained from all subjects participating in the study. The database obtained for this study was completely anonymous (name and other identifiers were removed).

Neuropsychological Battery

The psychometric battery included the Mini-Mental State Exam which was used to screen for cognitive impairment, with a cut point greater or equal to 24 which is recommended for clinical practice[175], and the assessment of the following domains:

Visuospatial. Visuospatial function was evaluated with the Rey-Osterrieth Complex Figure Test – the Copy condition ROCFT-C[177-179]. This test, specifically the copy condition was developed to assess functions of the brain such as attention and concentration, fine-motor coordination, visuospatial perception, and organizational skills[177,179,180]. Although some age effects (e.g. older adults do not perform as well as their younger counterparts), some sex effects (males obtain higher scores than females) and education/IQ effects have been reported, it is a commonly used visuospatial test[179]. For the copy condition the participant is handed a piece of paper and a pencil and is told that he/she would be presented with a figure. A stimulus card with a geometric figure is presented in front of them and they are instructed to copy the figure to the best of their

ability. The participant is told there is no time limit to complete the task; however, the psychometrist starts timing as soon as the oral instructions are completed and keeps track of the respondent's executions of the figure. When the participant completes the figure, the stop time is recorded and the stimulus card removed. A specific protocol for the scoring system exists with raw scores ranging from 0.0 to 36.0; low scores are indicative of compromised or reduced visuo-perceptual and visuomotor skills[180].

Nonverbal Memory. Nonverbal memory, or visual memory, was evaluated using the Immediate Recall condition of the Rey-Osterrieth Complex Figure Test (ROCFT-R)[177,178]. The ROCFT-R is assessed immediately after the copy portion of the ROCFT is performed. The psychometrist removes the stimulus and the copy and the participant is asked to reproduce the image they just copied from memory[177]. This task evaluates nonverbal memory which is related to the hippocampus and associated regions in the right hemisphere[180]. The scoring protocol for the immediate recall also range from 0.0 to 36.0; low scores are indicative of compromised or reduced visuospatial recall ability, or non-verbal memory[180].

Verbal Memory. Verbal memory was tested using the Auditory Verbal Learning Test (AVLT)[181-183] trials 1-6, the AVLT-30 minute recall trial and the free and cued selective reminding test (FCSRT) or Total Recall Score[184,185]. Detailed instructions for each of the tests were given to each participant before each trial. The AVLT used in this study is the Czech version[186]. The AVLT is a neuropsychological test that determines the participant's ability to encode, associate, store, and retrieve verbal information previously encoded as well as the maximum amount of information able to retrieve from that learned in the trials[187,188]. In the AVLT trials 1-6 test, the participant hears a list of

15 semantically unrelated nouns read at a rate of one per second. When all the words have been read, the participant is asked to recall as many words from the list as possible. The psychometrist records all the words recalled correctly and any intrusions and/or perseverations (any additional words recalled that were not read or any repeated words). This is carried out 5 consecutive times with the order of the presentation and the words fixed across the trials. Then the examiner presents a second list of 15 new words; this time the participant is only allowed to recall them in one attempt. Then immediately the participant is asked to remember as many words as possible from the first list. The AVLT- 30 minute is when the participant is asked to recall the trial previously administered after 30 minutes to measure retention. Scoring for the AVLT is complex and calculations for the Czech version of this test used in the ongoing longitudinal study can be found elsewhere[186]. The recalled part (total recall) of the test after 30 minutes has a maximum score of 15. In this study, a modified version of the FCSRT called Enhanced Cued Recall (ECR test in Czech validated version) was used[188,189]. The FCSRT consists of asking the participant to search for a card, which contains line drawings of 4 objects and is asked to identify the one belonging to the category named by the psychometrist. After the item is correctly identified the card is removed. If it is incorrectly chosen, the error is corrected. This is done 12 additional times for a total of 16 items and/or possible points[188]. The total verbal memory score is calculated as the mean of the sum of the AVLT trials 1-6, AVLT-30 minute recall trial and the FCSRT[188].

Executive Function. Despite the disagreement in the literature as to how to best measure executive function[190], for this study it was measured with the Digit Symbol

Substitution Test (DSST)[191]. The DSST is used as a measure of attention, speed of processing, motor speed, visual scanning and memory in many protocols[192], especially among older adults as no education effects have been seen for younger or older adults[193]. Even though DSST is often included under the attention domain, it clearly overlaps with executive function[194]. For the purpose of this analysis it was thought most appropriate to include it under this category. In this assessment, the participant is given a piece of paper with 9 symbols corresponding to 9 digits; below it, are 4 rows of digits with empty spaces. The participant is asked to fill as many corresponding symbols as possible in 90 seconds[192]. The total number of correct digits completed was recorded and included in the study's analyses.

Executive function was also examined with Control Oral Word Association Test (COWAT)[195-197]. The COWAT is used for both language (verbal fluency) and executive function as a way to assess how a person communicates in daily life. It is important to note that some research has found age, sex and education effects with the COWAT (e.g., age-related declines, women slightly outperforming males and education beyond 12-years favoring scores)[197]. In this assessment, the participant is asked to say as many words as they can about a given category in 60 seconds. The total number of words recalled is recorded.

Attention and Working Memory. Attention and working memory was tested with the Backward Digit Span (BDS) and the Digit Span Forward Test (DSF)[198,199]. Both of these assessments date back to the 19th century when Wilhelm Wundt try to measure the scope of consciousness, now better known as working memory or retention[200]. The DSF is more indicative of short term auditory memory, while the BDS assesses more

the ability to manipulate verbal information while in temporary storage[201]. The digit span assesses working memory by asking the participant to recall digit sequences forward and backwards. The FDS is completed before the BDS. In the FDS the psychometrist tells the participant that he/she is going to say some numbers, to listen carefully and to repeat them back as soon as he/she is through. In the BDS, the participant hears the numbers and then is asked to repeat them backwards. Each correct response is worth 1 point for a maximum total of 14 for each sub-score and a total score of 28.

Language. Language was examined with the Boston Naming Test (30 item version)[202,203]. This is a classic confrontation naming test in psychology used to measure naming deficits[204]. Here, the participant is shown a series of 30 line-drawn pictures are presented to the participant (a maximum of 20 seconds are given per picture)[204]. If the participant has difficulty recalling the name of the picture, a stimulus cue is given. If the participant has difficulty recalling the name of the picture, a stimulus cue is given. If the participant incorrectly names the picture after a stimulus cue is given, a phonemic cue was provided. Several scores are estimated, including the total number of correct spontaneous responses, total number of correct responses following semantic cues, and total number of correct response following phonemic cues.

Each cognitive domain was converted to z-scores for standardization and ease of interpretation. To assess overall cognitive performance, a composite cognitive score (CCS) was constructed by taking the average of the z-scores from each of the six cognitive domains.

Biological Measures

Specimen collection of participants was performed at the University Hospital Motol in Prague, Czech Republic. Serum lipoprotein samples were collected in the morning after a 12-hour fasting period. Standard venipuncture methods were used. Specimens were stored and processed in-house within 1-3 hours after collection. Lipoproteins measured included in this study are: TC, LDL-C, TG and HDL-C. Continuous values of lipoproteins will be used in statistical models. Genotyping was performed by polymerase chain reaction (PCR) using oligonucleotide primers to identify the APOE gene polymorphism. The DNA from participants was obtained from blood leukocyte samples using standard technique[205]. For this analysis subjects with specimens collected ±60 days from the administration of the neuropsychological battery were included.

Covariates

Demographic variables were obtained at the time of cognitive testing and included sex, age (years), and maximum achieved education level. Age and education were analyzed as continuous variables. The Geriatric Depression Scale (GDS) was used as one of the covariates to assess depressive symptoms among participants, as it strongly correlates with cognitive performance[206]. This is a 30-item self-report assessment with scores 0-4 considered normal, 5-8 mild depression, 9-11 moderate and 12-15 severe depression.

Statistical analysis

Statistical analysis was performed using SAS software, version 9.4 (Copyright © 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.). This study examined baseline characteristics overall and for men and women separately by independent samples *t*-test and Pearson chi-square test. Scores for cognitive tests were standardized to z-scores (mean=0 and one unit standard deviation) to enable comparison across the cognitive measurements scored on different scales. Higher z-scores reflect better cognitive performance. APOE ε4 variable was coded to a dichotomous variable as ε4 carriers (ε2/ε4, ε3/ε4, or ε4/ε4) and non-carriers (ε2/ε2, ε2/ε3, ε3, ε3). Pearson correlation coefficients were obtained for all dependent and independent variables.

For the first aim, ordinary least square regressions (OLS) were employed to examine the relationship between continuous lipoprotein levels of TC, LDL-C, TG and HDL-C and cognitive performance measured by the composite cognitive score while controlling for age, sex, education, and depressive symptoms (model 1). Adjustment for these covariates was done because they are known to be correlated with cognitive performance. Models were subsequently also adjusted for APOE ε4 allele (model 2). All models were applied to each of the six individual cognitive domains. To aid interpretation of the results including the magnitude of the observed associations, standardized regression coefficients are presented along with unstandardized regression coefficients. In addition standard error and effect sizes (adjusted R^2) are provided for each of the models.

For the second aim, a moderation effect by age, sex and/or APOE ε4 allele status between each lipoprotein (TC, LDL-C, TG and HDL-C) and cognitive function was examined by adding the interaction term of the lipoprotein and the potential moderator in the regression model. Continuous variables in the interaction were centered as recommended[207]. Interaction effects were estimated with each potential moderator (age, sex, APOE) for all significant associations between a lipoprotein and a cognitive outcome. Stratification by moderator values was used in cases when the interaction is statistically significant. However, stratification by sex was performed regardless of the moderation results in order to better compare the study results to previous studies. Some figures for the stratification of the significant moderation results were obtained using the ModGraph program[207].

A post hoc power analysis was conducted using G*Power statistical software[208]. The sample size of 112 was used for statistical power analysis and an 8 predictor variable equation (TC, LDL-C, TG, HDL-C, age, sex, education, GDS score) was used as a baseline. The recommended effect sizes used for this assessment were as follows: small (f^2=.02), medium (f^2=.15), and a large (f^2=.35). The alpha levels used for the analysis was $p<.05$; critical F was 2.0295 and noncentrality parameter $\lambda = 24.8863$. Figure 3 shows that the post hoc analyses revealed the statistical power for this study was 0.95 for detecting an effect size of .22 medium effect, whereas the power exceeded .99 for the detection of a moderate to large effect size. Thus, there was more than adequate power (>0.80) at the moderate to large effect size level, but less than adequate statistical power at the small effect size level. The effect size obtain in this

study of 0.2 corresponds to a Cohen's d= 0.4. Cohen's d of 0.1-0.3 = small effect size, 0.3-0.5 = intermediate effect and ≥ 0.5 large effect[209].

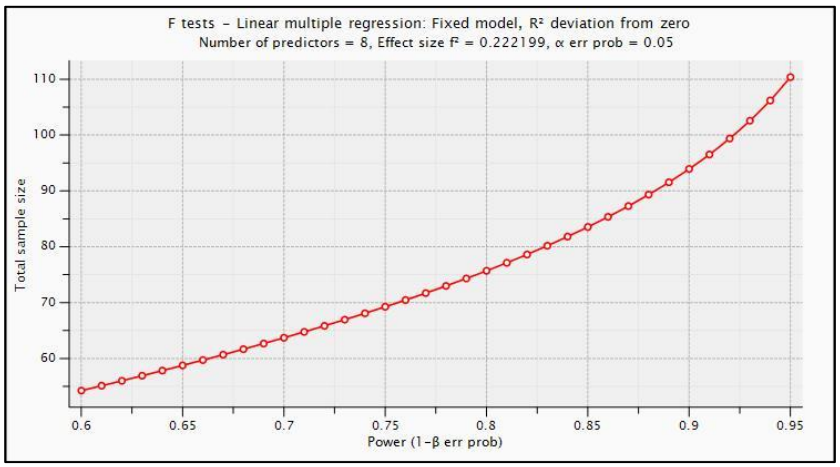

Figure 3. Linear Multiple Regression Plot of Power Analysis.

Results

Descriptive Statistics

Baseline characteristics of the sample stratified by sex are presented in Table 2. Overall, there were 6% more males than females included for analysis. The mean age was 73.2 years (SD 7.3); most were highly educated having some university education or above (79%, n=89). As expected for this cohort, males had higher levels of education than females (p=.006). The sample mean MMSE score was 27.6 (SD 2.0) and there were no significant differences in scores by sex (p=.840). The sample was borderline depressed with an average GDS score of 4.5 (scores of 0-4 are considered normal and 5-8 mildly depressed). Depressive symptom scores were significantly higher in women than in men (p=.007). In general, older adults in the study had borderline TC, near or

Table 2. Baseline Characteristics of the Participants.

	Total Sample (N=112) 100%	**Males (n=62) 53%**	**Females (n=50) 47%**	**p-value**
Mean Age (SD)	73.2 (7.3)	73.4 (7.4)	73.0 (7.2)	.733
Mean Education (SD)	14.4 (3.8)	15.3 (3.3)	13.2 (4.0)	.003
Education				
Secondary or below (< 11 years)	23 (20.5)	9 (14.5)	14 (28.0)	.006
Some University (12-15 years)	44 (39.3)	20 (32.3)	24 (48.0)	
Graduate Univ.+ (≥16 years)	45 (40.2)	33 (53.2)	12 (24.0)	
Apolipoprotein ε4 allele (n=100)				
Present	26 (26%)	15 (26.8)	11 (25.0)	.840
Absent	74 (74%)	41 (73.2)	33 (75.0)	
Mean Lipoprotein Levels mmol/l (SD)				
Total Cholesterol* (n=95)	5.41 (1.05)	5.09 (0.97)	5.78 (1.02)	.001
LDL-C* (n=93)	3.13 (0.95)	2.98 (0.89)	3.29 (1.00)	.113
Triglycerides* (n=95)	1.42 (0.71)	1.42 (0.64)	1.41 (0.79)	.940
HDL-C* (n=96)	1.40 (0.43)	1.27 (0.37)	1.54 (0.44)	.002
Mean Geriatric Depression Scale (SD) (n=111)	4.49 (3.45)	3.70 (3.15)	5.46 (3.59)	.007
Mean (SD)				
MMSE (n=112)	27.6 (2.00)	27.6 (2.03)	27.58 (1.98)	.931
Composite cognitive score†§(n=111)	0.08 (0.43)	0.05 (0.47)	0.13 (0.39)	.318
Verbal Memory	0.20 (0.75)	0.12 (0.71)	0.28 (0.81)	.283
AVLT 1-6 (n=111)	0.17 (0.90)	0.04 (0.11)	0.33 (0.94)	.093
AVLT 30 (n=110)	0.14 (0.95)	0.03 (0.88)	0.28 (1.03)	.180
Total Recall (n=109)	0.28 (0.71)	0.30 (0.70)	0.25 (0.72)	.727
Non-verbal (ROCFT-R) (n=80)	0.05 (0.93)	0.07 (0.97)	0.02 (0.90)	.808
Executive Function (n=111)	0.16 (0.75)	0.08 (0.74)	0.26 (0.74)	.189
COWAT (n=111)	0.23 (0.87)	0.14 (0.88)	0.33 (0.85)	.254
Digit Symbol (n=103)	0.09 (0.90)	0.01 (0.92)	0.18 (0.89)	.345
Visuospatial (ROCFT-C) (n=98)	0.09 (0.86)	0.06 (-0.15)	0.12 (-0.14)	.727
Language (BNT30) (n=101)	-0.24 (0.71)	-0.34 (0.66)	-0.12 (0.75)	.120
Attention & Working Memory (n=110)	0.21 (0.81)	0.24 (0.88)	0.17 (0.71)	.682
BDS (n=110)	0.21 (0.92)	0.27 (0.97)	0.14 (0.85)	.441
FDS (n=110)	0.20 (0.89)	0.20 (0.96)	0.021 (0.81)	.962

*Note. LDL-C = low-density lipoprotein; HDL-C = high-density lipoprotein; MMSE = Mini-Mental State Exam; AVLT 1-6 = Auditory Verbal Learning Test trials 1-6; AVLT 30 = Auditory Verbal Learning Test 30 minute recall; ROCFT-R = Rey-Osterrieth Complex Figure Test – the Immediate Recall condition; COWAT = Control Oral Word Association Test; ROCFT-C = Rey-Osterrieth Complex Figure Test – the Copy condition; BDS = Backward Digit Span; FDS = Forward Digit Span;.*Optimal range: TC< 5.2mmol/l; LDL-C<3.4mmol/l; Triglycerides<1.7mmol/l; HDL-C ≥1.5mmol/l † z-scores §Composite cognitive score=mean of the sum of cognitive domains*.

above optimal LDL-C, and normal levels of TG and HDL-C. Significant sex differences were observed for TC and HDL-C lipoproteins. Females had higher levels of TC (p=.001) and HDL-C (p=.002) than males, but no differences were observed for LDL-C (p=.113) or TG (p=.940). Table 2 also shows there were no significant sex differences in scores for the composite cognitive score or when assessing any of the specific cognitive domains. When composite cognitive scores were further examined, there were no statistically significant differences by sex (p=.318), age (p=.360), education (p=.393), or depressive symptoms score (p=.396).

Eighty nine percent of the older adults had information on their APOE. Two thirds were APOE ε4 allele non-carriers and this did not differ by sex (p=.840). In table 3 baseline characteristics are presented stratified by APOE ε4 allele group (carriers vs. non-carriers). In general non-carriers of the APOE ε4 allele scored higher in the MMSE (p=.047) and verbal memory (p<.001). Non-carriers also had a borderline significant advantage in non-verbal memory (p=.050) over the carriers. Furthermore, despite the lack of statistical significance, in the CCS and verbal memory tests, carriers of the APOE ε4 allele scored considerably lower than non-carriers of the gene.

Figure 4 shows the distribution of the lipids and the 95% Confidence Intervals (CI) for non-carriers and carriers of the APOE ε4 allele. No statistical significant differences were observed for any of the lipoprotein levels between carriers and non-carriers of the ε4 allele. However, carriers of the APOE ε4 allele had much higher levels of LDL-C and TG than non-carriers.

Table 3. Baseline Characteristics of Participants by APOE ε4 Allele group.

	APOE ε4 allele positive (n= 26)	APOE ε4 allele negative (n= 74)	p-value
	Mean (SD)		
Age	71.7 (6.4)	73.9 (7.4)	.184
Sex			
Males	15 (57.7)	41 (55.4)	
Females	11 (42.3)	33 (44.6)	.840
Education	13.3 (4.3)	14.6 (3.5)	.135
Total cholesterol (TC)*	5.5 (0.8)	5.4 (1.0)	.695
Low-density lipoprotein cholesterol (LDL-C)*	3.4 (0.8)	3.0 (0.9)	.067
Triglycerides (TG)*	1.6 (0.8)	1.3 (0.6)	.059
High-density lipoprotein cholesterol (HDL-C)*	1.3 (0.4)	1.4 (0.4)	.085
Geriatric Depression Scale	3.6 (2.9)	4.2 (3.2)	.424
Mini Mental State Exam	27.0 (2.1)	27.9 (1.9)	.047
Composite cognitive score***	-0.005(0.37)	0.17 (0.43)	.072
Verbal Memory	-0.23 (0.77)	0.41 (0.68)	<.001
Non-verbal Memory	-0.29 (0.96)	0.19 (0.90)	.050
Visuospatial	0.14 (0.74)	0.20 (0.77)	.750
Executive Function	0.14 (0.71)	0.23 (0.76)	.595
Language	-0.02(-0.34)	-0.33 (-0.50)	.067
Attention & Working Memory	0.23 (0.73)	0.25 (0.87)	.943

*Note. *Optimal range: TC< 5.2mmol/l; LDL-C<3.4mmol/l; Triglycerides<1.7mmol/l; HDL-C ≥1.5mmol/l ** z-scores ***Composite cognitive score=mean of the sum of cognitive domains.*

Correlations

In table 4, the Pearson correlation coefficients among demographic variables and lipoproteins are presented. Overall, it was observed that older ages yielded lower levels of TC, LDL and TG and higher levels of HDL-C, but none of these correlations were statistically significant (p's>.05). Female sex correlated with lower levels of education (p=.003) and higher levels of TC (p=.001) and HDL-C (p=.002). Higher MMSE scores correlated with higher levels of education (p=.023) and being non-carriers of the APOE ε4 allele (p=.047). TC was positively correlated with LDL-C (p<.001) and TG (p=.009)

and negatively with HDL-C (p=.005). Higher levels of LDL-C correlated with higher levels of TG (p=.002) and HDL-C correlated negatively with TGs (p<.001).

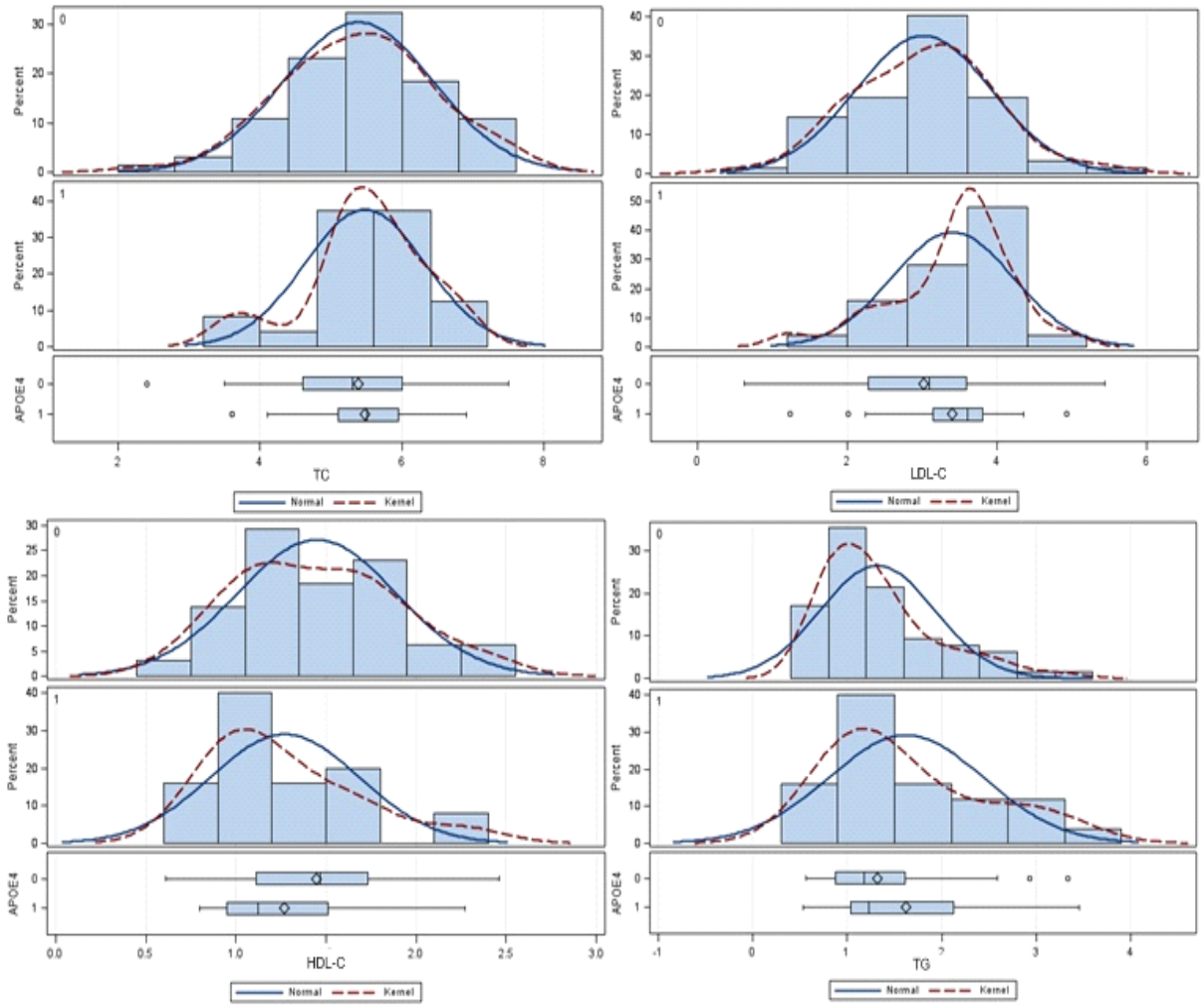

Figure 4. Distribution of the Lipoproteins by APOE ε4 allele.

*Note. *Optimal Range: Total Cholesterol (TC) < 5.2mmol/l; Low-density lipoprotein cholesterol (LDL-C) < 3.4mmol/l; Triglycerides (TG) < 1.7mmol/l; High-density lipoprotein cholesterol (HDL-C) > 1.5 mmol/l. Solid blue lines represent the normal distribution and the dashed red lines represent the Kernel density, or non-parametric. APOE4=0 for non-carriers of the APOE ε4 allele and APOE4=1 for carriers of the APOE ε4 allele.*

Table 4. Pearson Correlation Coefficients for Demographic Variables and Lipoproteins.

	1	2	3	4	5	6	7	8	9
1. Age (n=112)	1								
2. Sex (n=112)	-0.03	1							
3. Education (n=112)	0.14	-0.28**	1						
4. GDS (n=111)	-0.06	0.25**	-0.19*	1					
5. MMSE (n=112)	-0.10	-0.01	0.21*	-0.12	1				
6. APOE ε4 allele (n=100)	-0.13	-0.02	-0.15	-0.08	-0.20*	1			
7. TC (n=95)	-0.05	0.33**	-0.19	0.08	-0.001	0.04	1		
8. LDL-C (n=93)	-0.04	0.16	-0.13	0.004	-0.04	0.20	0.86***	1	
9. TG (n=95)	-0.10	-0.01	-0.29**	0.03	-0.01	0.20	0.27**	0.33**	1
10. HDL-C (n=96)	0.06	0.31**	0.04	0.09	0.04	-0.18	0.29**	-0.05	-0.42***

*Note. P-values: *p<.05, **p<.01, ***p<.001. GDS=Geriatric Depression Scale, MMSE=Mini Mental State Exam, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, TG= triglycerides, HDL-C=High-density lipoprotein cholesterol.*

Sex differences in the correlations within the lipoproteins and APOE ε4 allele is presented in table 5. A positive linear relationship was observed in both sexes between TC and LDL-C, both p's<.001 and between LDL-C and TGs (males (p=.041) and females (p=.016)). A negative correlation was found in both sexes between TG and HDL-C, meaning that low levels of HDL-C are correlated with high TG levels; however, 78% of the variation in females (r^2=.22) and 85% in males (r^2=.15) cannot yet be explained. In females, APOE ε4 allele correlated with higher levels of TG (p=.018) and lower levels of HDL-C (p=.047).

Table 5. Pearson Correlation Coefficients among Lipoproteins and APOE ε4 Allele Stratified by Sex.

		1	2	3	4
1.	**TC**				
	Males				
	Females	1			
2.	**LDL-C**				
	Males	0.83***			
	Females	0.88***	1		
3.	**TG**				
	Males	0.26	0.30*		
	Females	0.33*	0.36*	1	
4.	**HDL-C**				
	Males	0.29*	-0.005	-0.39**	
	Females	0.11	-0.20	-0.47**	1
5.	**APOE ε4 allele**				
	Males	0.11	0.26	0.04	-0.05
	Females	0.005	0.14	0.36*	-0.31*

*Note. *p<.05, **p<.01, ***p<.001. TC=Total Cholesterol, LDL-C=Low Density Lipoprotein cholesterol, TG=triglycerides, HDL-C=High Density Lipoprotein cholesterol.*

Table 6 presents the correlations for each of the cognitive function tests performed and lipoproteins. Higher CCS correlated with lower TG (p=.015) and higher HDL-C (p=.006) and these significant relationships were only statistically significant among women. Visuospatial skills correlated positively with HDL-C for the whole sample (p=.033). Overall, lower TG in women was significantly correlated with better verbal (p=.043) and non-verbal memory (p=.042) and visuospatial function (p=.010), but not in men. Additionally, only in women, higher levels of HDL-C correlated with better attention and working memory (p=.037). Being a carrier of the APOE ε4 allele had a linear relationship with lower verbal memory (p<.001) and borderline with non-verbal memory (p=.050). In women, carriers of the APOE ε4 allele showed linear relationships with lower scores in CCS (p=.003), verbal (p<.001) and non-verbal memory (p=.008).

Table 6. Pearson Correlation Coefficients between Lipoproteins and Cognitive Domains.

		CCS	Verbal Memory	Non-verbal	Visuo-spatial	Executive Function	Language	Attention & Working Memory
TC		0.15	0.02	-0.01	0.09	0.12	0.15	0.05
	Males	0.14	-0.07	0.08	0.16	0.02	0.21	0.07
	Females	0.13	0.08	-0.02	0.01	0.14	-0.02	0.09
LDL-C		0.03	-0.003	-0.07	0.01	0.02	0.07	-0.02
	Males	0.03	-0.05	-0.09	0.07	-0.05	0.14	0.01
	Females	0.01	0.02	-0.001	-0.04	0.06	-0.04	-0.04
TG		-0.25*	-0.16	-0.23	-0.21	-0.06	-0.03	-0.11
	Males	-0.11	0.01	-0.12	0.04	0.06	-0.23	-0.10
	Females	-0.42**	-0.30*	-0.36*	-0.40**	-0.18	0.14	-0.13
HDL-C		0.28**	0.15	0.13	0.23*	0.14	0.10	0.19
	Males	0.19	0.08	0.17	0.20	0.004	0.18	0.16
	Females	0.38**	0.17	0.18	0.26	0.21	-0.06	0.32*
APOE ε4 allele		-0.18	-0.37***	-0.23	-0.03	-0.05	0.19	-0.01
	Males	-0.02	-0.17	-0.06	0.04	0.03	0.14	0.62
	Females	-0.43**	-0.60***	-0.47**	-0.12	-0.16	0.25	-0.13

*Note. *p<.05, **p<.01, ***p<.001. TC=Total Cholesterol, LDL-C=Low Density Lipoprotein cholesterol, TG=triglycerides, HDL-C=High Density Lipoprotein cholesterol.*

Table 7 presents the Pearson Correlation Coefficients between demographics and cognitive domains among men and women. These correlations were done to determine if the linear associations seen particularly among women in each of the cognitive domains correlated with age, education or MMSE score.

With the exception of visuospatial and attention and working memory in women, all cognitive function tests showed a significant moderate linear relationship with MMSE for both men and women. Although age showed a negative correlation with CCS, verbal memory and executive function, these relationships were not statistically significant; however, among males age was negatively correlated with non-verbal abilities (p=.025). Among females, education positively correlated with verbal (p=.003) and non-verbal memory (p=.002).

Table 7. Pearson Correlation Coefficients between Demographics and Cognitive Domains by Sex.

		CCS	Verbal Memory	Non-verbal	Visuo-spatial	Executive Function	Language	Attention & Working Memory
AGE								
	Males	-0.02	-0.15	-0.34*	0.03	-0.04	0.02	0.14
	Females	-0.04	-0.14	-0.02	0.04	-0.04	0.12	-0.02
EDUCATION								
	Males	0.06	-0.01	-0.04	0.03	-0.01	0.007	0.15
	Females	0.21	0.41**	0.48**	-0.001	0.01	-0.40**	0.002
MMSE								
	Males	0.64***	0.56***	0.58***	0.46***	0.47***	-0.34*	0.45***
	Females	0.53***	0.66***	0.67***	0.29	0.36**	-0.45**	0.05

*Note. *p<.05, **p<.01, ***p<.001. CCS= Composite cognitive Score; MMSE=Mini-Mental State Exam.*

Ordinary Least Square Regression Results

An ordinary least square (OLS) regression analysis was conducted to test the hypothesis for the first aim which stated high levels of TC, LDL-C and HDL-C and low levels of TG are associated with better cognitive function (higher composite cognitive scores and higher scores in each individual cognitive domain: nonverbal and verbal memory; visuospatial function; executive function; attention and working memory; and language). Associations between lipoproteins and each cognitive domain are shown in Table 8. In model 1 better CCS was associated with lower levels of TG (p=.036) and higher levels of HDL-C (p=.008). When examining specific cognitive domains, participants with higher levels of HDL-C performed better in visuospatial function (p=.028) and attention/working memory (p=.037). In model 2, when additional adjustment was performed for APOE ε4 allele, significance between high levels of HDL-

Table 8. Ordinary Least Square Regressions Modeling the Association between each Lipoprotein and Cognitive Function.

	Model 1						Model 2					
	b	SE	β	p	AdjR^2	n	b	SE	β	p	AdjR^2	n
Composite cognitive score*												
TC	0.06	0.046	0.154	.158	.03	94	0.08	0.048	0.180	.102	.07	88
LDL-C	0.01	0.049	0.282	.790	.01	92	0.01	0.049	0.028	.790	.01	92
TG	-0.13	0.064	-0.224	.036	.07	94	-0.11	0.068	-0.174	.115	.09	89
HDL-C	0.29	0.108	0.283	.008	.10	95	0.26	0.109	0.262	.018	.11	89
Verbal Memory												
TC	0.02	0.080	0.024	.821	.03	94	-0.005	0.078	-0.007	.947	.20	88
LDL-C	0.004	0.084	0.005	.962	.03	92	0.02	0.084	0.026	.796	.21	86
TG	-0.12	0.115	-0.107	.312	.08	94	-0.03	0.114	-0.023	.814	.25	89
HDL-C	0.19	0.196	0.105	.327	.07	95	0.09	0.181	0.052	.607	.23	89
Non-Verbal Memory												
TC	0.03	0.114	0.035	.779	.09	68	0.01	0.127	0.013	.918	.14	64
LDL-C	-0.02	0.121	-0.029	.853	.07	66	-0.04	0.135	-0.040	.752	.13	62
TG	-0.27	0.156	-0.214	.083	.19	67	-0.15	0.177	-0.114	.383	.20	64
HDL-C	0.34	0.276	0.150	.226	.12	69	0.27	0.28	0.123	.335	.16	65
Visuospatial												
TC	0.07	0.097	0.089	.444	.01	84	0.10	0.103	0.119	.327	-.02	78
LDL-C	0.002	0.101	0.003	.981	.01	81	0.02	0.109	0.023	.850	-.04	75
TG	-0.23	0.125	-0.213	.069	.06	83	-0.15	0.132	-0.145	.258	-.01	78
HDL-C	0.47	0.211	0.250	.028	.07	84	0.42	0.204	0.247	.043	.03	78
Executive Function												
TC	0.05	0.079	0.069	.526	.02	94	0.11	0.086	0.144	.200	.02	88
LDL-C	-0.002	0.087	-0.003	.980	-.005	92	0.07	0.098	0.083	.459	-.003	86
TG	-0.08	0.115	-0.073	.508	-.009	94	-0.02	0.128	-0.021	.854	-.01	89
HDL-C	0.24	0.196	0.133	.228	.01	95	0.19	0.203	0.108	.355	-.003	89
Language												
TC	0.06	0.085	0.085	.483	.04	86	0.08	0.094	0.104	.365	.06	80
LDL-C	0.005	0.083	0.007	.951	.06	84	-0.01	0.089	-0.011	.918	.15	78
TG	-0.11	0.114	-0.107	.346	.06	86	-0.23	0.123	-0.216	.070	.11	81
HDL-C	0.11	0.182	0.066	.555	.05	87	0.19	0.178	0.118	.298	.12	81
Attention & Working Memory												
TC	0.07	0.091	0.092	.420	-.03	93	0.08	0.101	0.092	.434	-.05	87
LDL-C	-0.01	0.098	-0.008	.943	-.05	91	-0.01	0.112	-0.013	.910	-.06	85
TG	-0.01	0.132	-0.094	.400	-.03	93	-0.11	0.148	-0.087	.463	-.05	88
HDL-C	0.46	0.217	0.233	.037	.01	94	0.46	0.226	0.237	.044	-.003	88

Note. * *TC=Total Cholesterol, LDL-C=Low Density Lipoprotein cholesterol, TG=triglycerides, HDL-C=High Density Lipoprotein cholesterol. Composite cognitive score=mean of the sum of cognitive domains. β= standardized regression coefficient. Results in model 1 were adjusted for age, sex, education, and depressive symptoms. Results in model 2 were additionally adjusted for APOE4.*

C, and cognitive measures (i.e., CCS (p=.018), visuospatial function (p=.043) and attention and working memory (p=0.44)) remained.

Moderation Analysis Results

To test the hypothesis that age, sex and/or APOE ε4 allele moderate the relationship between the lipoproteins and the cognitive tests (Aim 2) a moderation analysis was performed by inserting an interaction term in the equation for all significant cognitive associations. Unstandardized betas were used to calculate the figures, but standardized betas are reported in the text to ease the interpretation of the results.

Moderations on the Association of TG and HDL-C on CCS. Multiple regression models were tested to investigate whether the association between TG and the CCS and between HDL-C and CCS was moderated by age, sex, or APOE ε4 allele. As illustrated in figure 5, APOE ε4 allele did modify the association between TG and the CCS (b=0.27, SE_b=0.134, β=0.28; p=.044) and between HDL-C and the CCS (b=-0.56, SE_b=0.236, β=-0.28; p=.020). However, the age-by-TG interaction term was not significant (b=0.001, SE_b=0.008, β=0.01; p=.910), nor was the age- by-HDL- C (b=-0.009, SE_b=0.015, β=-0.07; p=.526). Sex also had no moderation effect on the relationship between TG and CCS (b=-0.11, SE_b=0.123, β=-0.31; p=.356) or between HDL-C and CCS (b=0.034, SE_b=0.217, β=0.05; p=.875).

Moderation on the Association of HDL-C on Visuospatial Function. To investigate whether the association between HDL-C and visuospatial function was moderated by age, sex, or APOE ε4 allele, an interaction term with these variables was added separately to the first multiple regression model. Results indicated that neither

the age-by-HDL-C interaction term (b=-0.0006, SE_b=0.03, β=-0.002; p=.984), the sex-by-HDL-C interaction term (b=0.02, SEb=0.426, β=0.02; p=.953), nor the APOE ε4 allele-by-HDL-C interaction term (b=-0.52, SEb=0.449, β=-0.16; p=.247) were significant on visuospatial function.

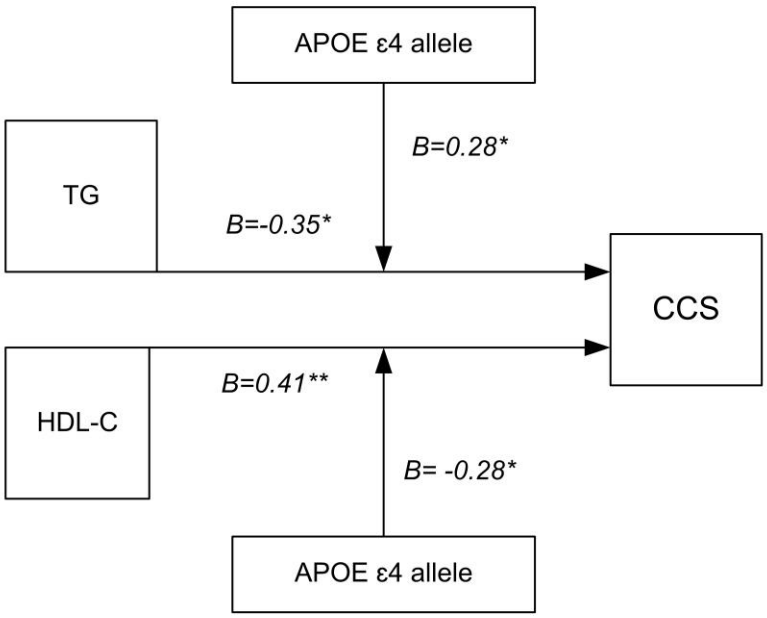

Figure 5. Standardized Regression Coefficients for the Moderation of APOE ε4 on the Relationship between: TG and CCS and HDL-C and CCS, Controlling for Age, Sex, Education and Depressive Symptoms.

Moderation on the Association of HDL-C on Attention and Working Memory. To examine whether the association between HDL-C and attention and working memory was moderated by age, sex, or APOE ε4 allele, the model 1 of the multiple regression models were applied adding separate interaction terms (e.g. age*HDL-C, sex*HDL-C, APOE ε4 allele*HDL-C). Results indicated that none of the

interactions were significant: age-by-HDL-C interaction term on attention and working memory was (b=-0.03, SE_b=0.030, β=-0.13; p=.250), the sex-by-HDL-C (b=0.12, SE_b=0.433, β=0.10; p=.783) and the APOE ε4-by-HDL-C interaction term was (b=-0.59, SE_b=0.500, β=-0.16; p=.237).

Sex-Stratified Results. Despite the fact that no interaction was detected by sex, sex-stratification was performed on those cognitive tests that had statistically significant results in the first regression model in order to match this study with recent previous research on lipoproteins and cognition [45,85] in which separate results for men and women were presented. Table 9 shows the significant findings of the exploratory sex-stratified analysis conducted, in which significant results were only seen among women. Lower levels of TG were associated with better CCS in women (p=.013), but not in men (p=.550). Additionally higher levels of HDL-C were also associated with better CCS in women only (p=.019), not men (p=.118). For the significant individual cognitive domains reported in model 1, lower levels of TG were also linked with better visuospatial function in women only (p=.006), not men (p=.799) and higher levels of HDL-C were related to better attention and working memory among women (p=.039), not men (p=.297).

The lack of interaction of sex by lipoproteins is important put into the context of the sex-stratified results presented in the ordinary least square regression models. It appears that while the associations were stronger for women, they were also present for men, just not at the same magnitude, hence deeming the sex-by-lipoprotein interactions non-significant.

Table 9. Ordinary Least Square Regressions Modeling the Association between each Lipoprotein and Cognitive Function among Men and Women Adjusting for Age, Education, and Depressive Symptoms.

	Males (n=62)						Females (n=50)					
	b	SE	β	p	Adj R^2	n	b	SE	β	p	Adj R^2	n
Composite cognitive score*												
TC	0.097	0.075	0.193	.204	.01	50	0.044	0.058	0.115	.458	.02	44
LDL-C	0.018	0.084	0.033	.834	-.02	48	0.002	0.060	0.007	.966	.01	44
TG	-0.065	0.109	-0.089	.550	-.08	49	-0.195	0.075	-0.403	.013	.15	45
HDL-C	0.299	0.188	0.226	.118	.05	50	0.300	0.123	0.349	.019	.14	45
Visuospatial												
TC	0.209	0.146	0.232	.161	.03	43	-0.029	0.143	-0.034	.837	-.04	41
LDL-C	0.078	0.158	0.084	.625	-.02	41	-0.071	0.147	-0.081	.631	-.03	40
TG	0.045	0.177	0.041	.799	-.01	42	-0.531	0.182	-0.499	.006	.16	41
HDL-C	0.485	0.312	0.242	.128	.04	43	0.484	0.304	0.250	.120	.04	41
Attention & Working Memory												
TC	0.145	0.146	0.152	.324	-.02	50	0.088	0.123	0.118	.480	-.08	43
LDL-C	0.052	0.165	0.050	.752	-.07	48	-0.013	0.126	-0.018	.917	-.09	43
TG	-0.113	0.218	-0.078	.607	-.05	49	-0.152	0.165	-0.163	.363	-.08	44
HDL-C	0.389	0.369	0.157	.297	-.04	50	0.545	0.255	0.330	.039	.02	44

*Note. *Composite cognitive score=mean of the sum of cognitive domains. Stand β= standardized regression coefficient.*

Stratification by APOE ε4 Allele. Stratification by carriers vs. non-carriers of the APOE ε4 allele was also performed for the association between TG and CCS and between HDL-C and the CCS as these were the only statistically significant results in the moderation analysis. Table 10 presents the results for the stratification by carriers vs. non-carriers of the APOE ε4 allele. The significant associations between the lipoproteins and the cognitive domains predominated only among non-carriers of the APOE ε4 allele. Lower levels of TG and higher levels of HDL-C are only associated with cognitive function among non-carriers of the APOE ε4 allele. Figures 6 and 7 show the interaction of APOE ε4 allele and the stratification results by carriers or non-carriers of

the ε4 allele. Low TG yielded higher CCS (p=.022) on non-carriers of the APOE ε4 allele, but not on carriers (p=.470). Furthermore, figures 8 and 9 show the APOE ε4 allele moderation, non-carriers of the APOE ε4 allele with high HDL-C levels also obtained higher CCS (p=.003), but not APOE ε4 allele carriers (p=.289). Additionally, it is interesting to note that in each of the significant findings the levels of lipoproteins were in opposite directions among carriers vs. non-carriers.

Table 10. Ordinary Least Square Regressions Modeling the Association between each Lipoprotein and Cognitive Function among Carriers vs. Non-Carriers of the APOE ε4 Allele Adjusting for Age, Sex, Education, and Depressive Symptoms.

	APOE ε4 carriers (n=26)						**APOE ε4 non-carriers (n=74)**					
	b	SE	β	p	AdjR^2	n	b	SE	β	p	AdjR^2	n
Composite cognitive score*												
TG	0.085	0.115	0.190	.470	-.14	25	-0.206	0.087	-0.288	.022	.12	64
HDL-C	-0.222	0.203	-0.249	.289	-.10	25	0.401	0.130	0.388	.003	.17	64

*Note. *Composite cognitive score=mean of the sum of cognitive domains. B= non-standardized regression coefficient. Stand β= standardized regression coefficient.*

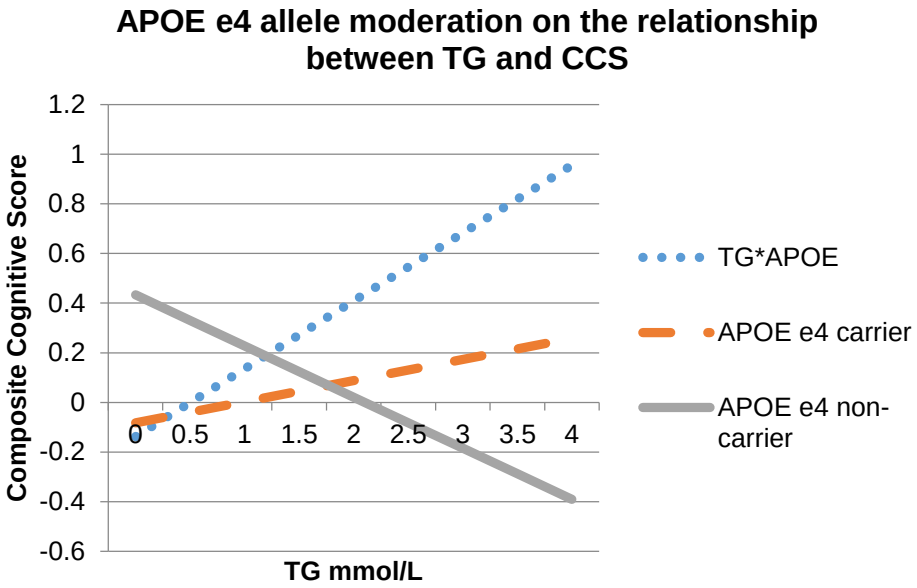

Figure 6. Moderation of the Effect of TG on CCS by Carriers or Non-Carriers of the APOE ε4 Allele.

Note. TG = triglycerides, APOE = APOE ε4 allele.

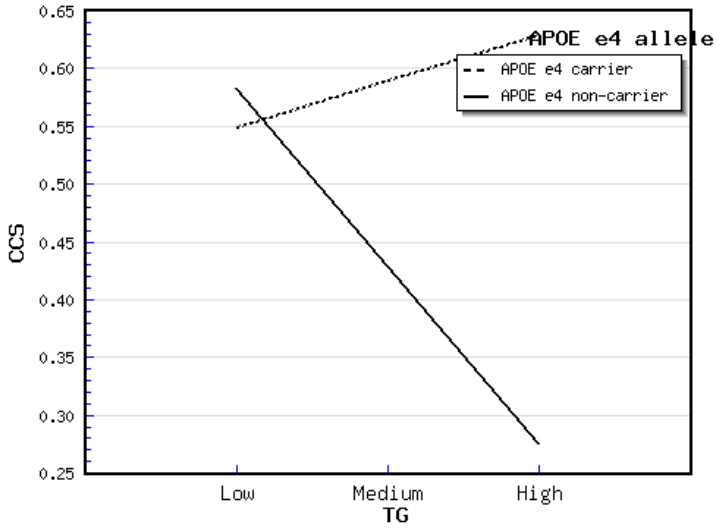

Figure 7. Moderation of the Effect of TG on CCS by APOE ε4 Allele.

Note. TG = triglycerides, APOE = APOE ε4 allele.

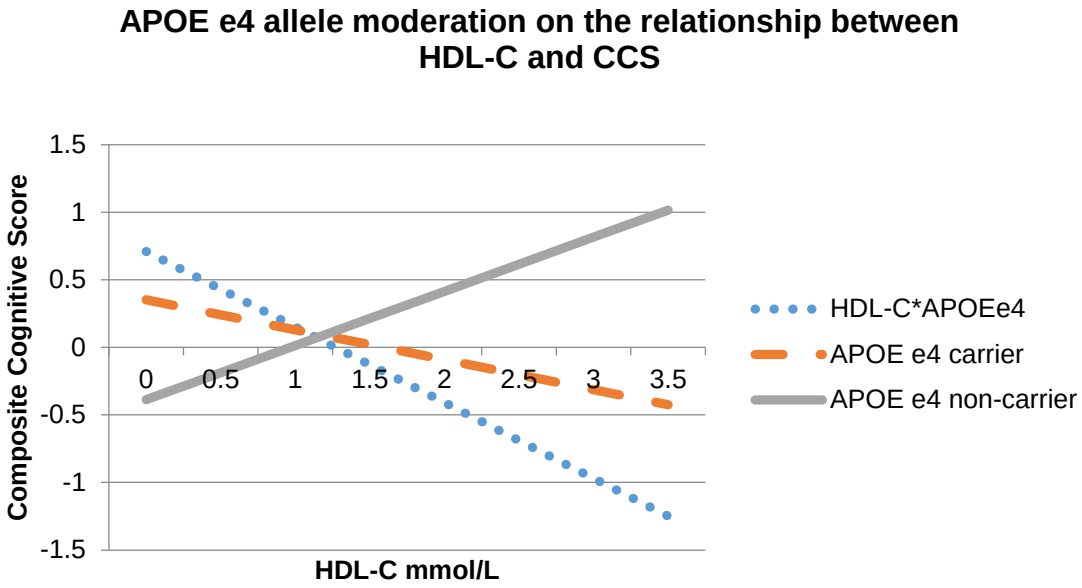

Figure 8. Moderation of the Effect of HDL-C on CCS by Carriers or Non-Carriers of the APOE ε4 allele.

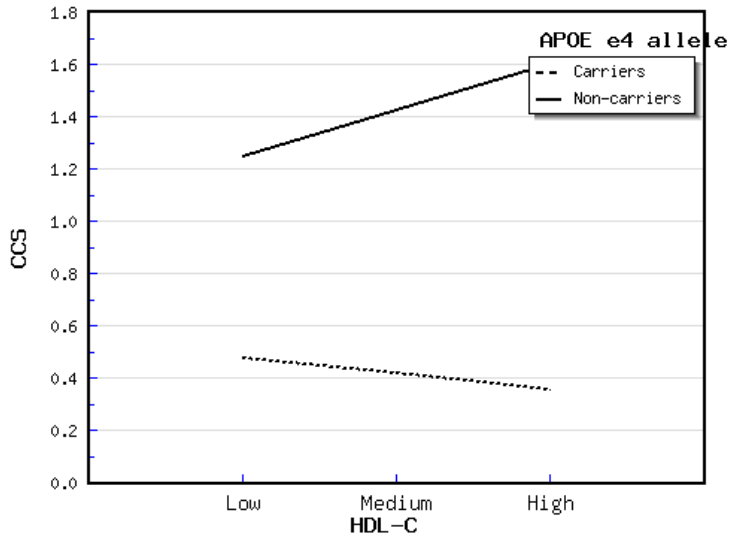

Figure 9. Moderation of the Effect of HDL-C on CCS by APOE ε4 Allele.

Note. HDL-C = High-density lipoprotein cholesterol, APOE = APOE ε4 allele.

Discussion

Using a volunteer sample of older adults tested at a memory clinic in Prague, Czech Republic, this study addressed the first aim assessing the association of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) in relation to overall cognitive performance measured through a composite cognitive score as well as individual scores on six well-established cognitive domains (verbal memory, non-verbal memory, visuospatial, executive function, attention/working memory, and language). Results obtained indicate an association between lower TG and higher levels of HDL-C with better overall cognitive performance after adjustment for age, sex, education, and depressive symptoms with only high HDL-C results remaining significant after additionally adjustment for APOE ε4 allele. Results also show that high levels of HDL-C were associated with better visuospatial function and attention and working memory. However, this study was not able to detect any association between other lipoproteins and cognitive performance measures. Furthermore, when addressing the second aim of this study, results indicated that only APOE ε4 allele had a moderating effect on the association between low TG and better CCS and between high HDL-C and better CCS.

Specific Discussion of the Regression Findings

Triglycerides and CCS. Few studies in the literature have looked at TG and cognitive function[46,85,138,210,211], but overall these studies seem to show a non-linear association, whereby very low or very high TGs are associated with cognitive function. The relationship found in this study between low TG and better cognitive function

measure as a composite cognitive score is supported by several studies. An earlier cross-sectional study by Kilander and colleagues (1997) studied men 69-74 years of age from Uppsala, Sweden and found a similar association between high plasma TG and poor cognitive performance[210]. Another earlier study in diabetics found that higher TG levels were associated with decrease cognitive performance measure by the digit substitution test, digit span backwards and a measure of reaction time[211]. More recent findings from a 16-year longitudinal study of health and cognition found an association between high TG and worse cognitive performance only among men before the age of 65 before controlling for variables of interest, but not among women[85]. However, some have found contrasting findings.

A recent analysis of 836 participants from the Chinese Longitudinal Healthy Longevity Survey observed that high normal TG levels were associated with better preserved cognitive function (measured with the MMSE) after adjusting the models for covariates[138]. These inconsistent findings between the studies are not surprising. Differences in methodologies, samples, and statistical analyses may partially explain differences in the results. A recently completed clinical trial in the United Kingdom looking at the effects of TG on age-related cognitive function decline in older adults may be able to provide further understanding of this association in the near future (https://clinicaltrials.gov/show/NCT01702480). This cross-over assignment study looked at 14-day treatment periods investigating cognitive performance and tolerability (gastrointestinal side effects) of the drug GSK2981710, expected to lower medium-chain TG in adults between 55 and 80 years of age. This gold-standard type of study

may bring further insight into the association between TG and cognitive performance in older adults.

HDL-C and CCS. Since the 1980's HDL-C has been known to be a protective factor for atherosclerosis and cardiovascular disease[212]. But only more recently have higher levels of HLD-C been associated with better cognitive performance, especially among older adults[49,85,127,137,213]. Results from this study agree with these previous findings, higher levels of HDL-C were found associated with better cognitive performance. Moreover, the association between higher HDL-C levels and better overall cognitive performance was maintained after additional adjustment for APOE ε4 allele, which is consistent with previous research findings[45,48,85,165].

Low levels of HDL-C have been found associated with low gray matter volume in cognitively normal adults[214] and grey matter is also present in the spinal cord. Studies have found that among all the circulating serum lipoproteins, HDL-C is the only one found in cerebrospinal fluid[215,216]. HDL-C is known to help maintain the homeostasis of intracellular cholesterol and is involved in reverse cholesterol transport of other lipids from the tissues, including the brain to the liver, which may explain why people with low HDL-C levels are displaying lower cognitive function than those with higher HDL-C levels. Perhaps the lack of a more efficient reverse cholesterol transport system compromises brain homeostasis and prompts for an accumulation of toxic brain byproducts such as amyloid-β yielding lower cognitive performance.

HDL-C and Visuospatial Function. Results from this study indicated high levels of HDL-C were related to better visuospatial function, even adjusting for APOE ε4 allele. Although not many studies have addressed this association in the literature, a previous

study from the third National Health and Nutrition Examination Survey, 1988-1994, was not able to find a statistically significant association between visuomotor speed and HDL-C , the only association found was in men with low serum TC and non-HDL cholesterol (TC minus HDL-C)[217]. Future research should be inclusive of visuospatial function to supplement these findings.

HDL-C and Attention and Working Memory. In this study high levels of HDL-C yielded better attention and working memory performance. This result is in agreement with some studies reported in the literature. An analysis from the Whitehall II Study also showed high levels of HDL-C associated with better attention and working memory[213]. Károssy and colleagues (2007) also found that the highest levels of HDL-C yielded better working memory performance in postmenopausal women using the digit span backwards. These authors suggested that HDL-C might perhaps be protecting frontal lobe functions on which working memory is dependent[165]. Future studies looking at the association between HDL-C and working memory could benefit of functional magnetic resonance imaging (fmRI) protocols to further understand the physiological aspects of this association.

Specific Discussion on Moderation

Few studies have been performed looking at the interaction between age, sex and APOE ε4 allele on the relationship between lipids and cognitive function. In this study, moderation was performed on all significant findings from the first regression model. However, no moderation effect was found between age or sex and any of the lipoproteins and the CCS. In addition, none of the moderators were found to have an

effect on the association between TG and HDL on any of the individual cognitive domains that were statistically significant in model 1. Several possible explanations for this may be posed. First, the nature of the neuropsychological test may have influenced the moderation, as most of these tests have been shown to have age and/or sex effects. Second, sex moderation analysis was underpowered due to the low number of participants in the stratified sex groups. In addition, only 26 individuals in this study were carriers of the APOE ε4 allele, therefore interactions with the individual cognitive test may have also been difficult to detect. Overall, these findings suggest that further moderation analysis with cognitive tests may be needed; as it is likely that cognitive tests currently used may also have APOE ε4 allele effects.

Moderation of APOE ε4 Allele in the Association between TG and Cognitive Performance. APOE ε4 allele was found to moderate the association between low TG and better CCS in this study. This suggests that having at least one APOE ε4 allele strengthens the association between high TGs and lower cognitive performance in older adults. Unfortunately to the author's knowledge only one study has looked at APOE ε4 allele moderation in the association of TG and cognitive performance[46]. In a sample of participants over the age of 65 from the Betula project, de Frias and colleagues were not able to find any significant interactions between APOE4 and TG for any of the cognitive domains they tested. Further stratification of the association between TG and CCS among carriers and non-carriers of the APOE ε4 allele in this study showed a significant association between high TG and lower CCS in non-carriers only[46]. Understanding the moderation effect of not only APOE ε4 allele, but age and sex as well on the cognitive function of a cognitively normal older adult population, may provide

insight into the need to develop different preventive interventions to address the needs of diverse genetic populations[218].

Moderation of APOE ε4 Allele in the Association between HDL-C and Cognitive Performance. This study found that only APOE ε4 allele moderated the association between high HDL-C and better CCS. Moderation analysis for age and sex did not yield any significant results. A study by Atzmon and colleagues (2012) was also not able to see any interaction between HDL-C and sex[45]. When the sample was stratified by APOE ε4 allele carriers versus APOE ε4 allele non-carriers, high levels of HDL-C were associated with higher composite cognitive scores in non-carriers of the APOE ε4 allele only, suggesting that the differences between HDL-C-cognition associations were larger for APOE4 carriers. This is consistent with previous findings[172]. In a study of 1,395 adults over the age of 65 participating in the "Tone Project" in Japan, investigators divided the group into carriers (n=277) and non-carriers (n=1,118) of the APOE ε4 allele and tested cognitive function with a CCS and individually in attention, memory, language ability, and reasoning. They found that among non-carriers of the APOE ε4 allele high levels of HDL-C yielded higher scores in all the domains tested, but not among carriers of the gene[172]. This finding is very important as HDL-C may be targeted to prevent the loss of cognitive function on non-carriers of the APOE ε4 allele.

Sex-Stratified Results. Furthermore, in the current study sex-stratified results indicate a female predominated association between low TG, high HDL-C and better cognitive performance. In addition, the link between high HDL-C and better attention and working memory also prevailed among women only. Overall, the associations observed for HDL-C and cognition were more slightly pronounced for women, which is

in agreement with previous research[85,127,219]. Though it is important to note, no sex-by-HDL-C interactions were statistically significant. Still, one possible explanation for the stronger associations among women may be that a greater range of HDL-C levels tends to be observed in women compared to men. Though a relationship was observed between lower TG levels and better visuospatial skills only among women, which is in accordance with Reynolds et al. (2010) who found that lower TG levels were predictive of spatial ability, the contrast between the strength of the associations for men vs. women was not great enough to allow for a statistical significant interaction of sex-by-TG in relation to cognition. It can be speculated that the relationship between low TG and better CCS and visuospatial function among women may be somewhat influenced by the level of education achieved given that lower TG showed a linear relationship with higher education. However, this can be questioned since women in this sample had statistically significant lower education level than the males. Further studies are needed to confirm/refute these findings.

Limitations

Despite the inclusion of all commonly used measures of blood lipids in the analyses, only TG and HDL-C showed consistent association with cognition. Theoretically, it is not completely surprising that HDL-C was the main lipoprotein driving the association with cognitive performance given that only the relatively small HDL-C particles are known to actively pass the brain barrier, prevent the formation of amyloid-β in the brain[216] and have anti-inflammatory properties[220,221]. Additionally, this study did not take into consideration any genetic disorders affecting lipoproteins such as familial

hypoalphalipoproteinemia in which levels of HDL-C are extremely low[69,222] or familial hypertriglyceridemia[223] in which very high levels of TG remain constant. Perhaps, to better capture the combined effects of these blood lipids on cognitive function, longitudinal analysis with multiple consistent lipoproteins and cognitive measures are needed from mid adulthood into older ages. The lack of association between other measures of blood lipids and cognition has also been observed in other cross-sectional studies[49,129].

Some additional limitations should be mentioned. Due to the cross-sectional nature of this study, it is not possible to indicate whether lipoprotein levels relate to change in cognitive functioning. Further, the sample was homogeneous (white) and highly educated. Although the neuropsychological battery used in this study is very comprehensive, it must be noted that using digit symbol as part of the executive function may be questionable by some neuropsychologists and may pose some measurement limitations. However, since many cognitive test overlap in domains, the best and most accurate method of measuring overall cognitive function is through the use of a global standardized score, as the one presented in this study. It is also important to note that the associations of HDL-C with verbal, non-verbal, language or executive function measures were not significant, nor were levels of TG associated with any other specific cognitive domain. The finding that the composite measure was significantly associated with HDL-C while most individual cognitive measures were not provides additional evidence that the effect of HDL-C may occur mainly on the global level[45]. This study also lacked data in some important socio-demographic variables such as income, medical comorbidities and medications, and 11% of the sample (12

people) did not have data regarding APOE ε4 allele status. Finally, sex-specific analyses were underpowered.

Conclusion

The cardiovascular benefits of HDL-C and the detrimental effects of hypertriglyceridemia have been known for some time now, but their role in cognitive function had not been explored until recent years and is still not well understood. The results of this study point to HDL-C as the main lipoprotein associated with cognitive performance. In addition, lipid profile may be more indicative of cognitive functioning in women than in men. Moderation by APOE ε4 allele clearly indicates that lipoprotein studies need to account for genetics in studies of cognitive function.

Future Implications. Blood lipid levels are modifiable through simple changes in lifestyle habits. Existing cardiovascular research suggests that lowering TGs and raising HDL-C can be done relatively easily through a diet containing monounsaturated and polyunsaturated fats, exercise, eliminating smoking, reducing alcohol consumption and using medications such as niacin, nicotinic acid, statins, fibrates and omega-3 fatty acid (fish oil capsules) among others when necessary[224,225]. Therefore, strategies to maintain TG levels low and especially increase HDL-C levels may be a viable population-wide intervention strategy to help maintain cognitive function with age. Future research aimed at understanding the factors underlying the role of lipoproteins, as well as the sex-based differences in the link between lipids and cognition, is needed especially from a life course perspective. Additionally, the possibility that boosting HDL-C levels may promote cognition should be investigated.

CHAPTER 3: STUDY 2: SERUM LIPIDS, HEALTH OUTCOMES AND CHANGE IN FUNCTION AMONG OLDER COSTA RICAN ADULTS: THE CRELES STUDY

Abstract

Sustaining physical function into older age is vital for maintaining independence and a good quality of life. Decreases in physical function are often associated with functional limitations and disability. Furthermore, physical function is often compromised by comorbidity in older adulthood. Cardiovascular disease is a main contributor to disease burden, limitation of functional abilities and decreased quality of life. However, the association between cardiovascular risk factors such as serum lipoproteins and physical function in older adults is less clear, especially over time. To date, no previous publications were identified in Latino populations. With Latin American countries growing older faster than North American or European countries, studying the underpinnings of lipoproteins and the pooled effect of risk factors and comorbidity on physical function in this group of older adults is necessary.

This study explored the longitudinal association between baseline total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) and physical function. Random effects models were used to assess whether lipoprotein levels are associated with subsequent change in physical function adjusting for demographics, cardiovascular risk factors and

comorbidity. Results indicated that lower baseline TC and HDL-C scores had cross-sectional associations with more ADL disability; but not across the three study waves. In addition, higher baseline TGs were also associated with better grip strength, but not across time. Moreover, there was a significant moderation by cognitive disability on the cross-sectional association between TC and ADL disability. Further stratification by cognitive disability indicated that the previous association was only significant for participants with cognitive disability. Future research should strive to determine if maintaining optimal recommended lipid levels delays physical function decline to as long as possible.

Introduction

Physical function is a reflection of health status, the impact of chronic diseases, and a crucial determinant of quality of life. It is well known that a decrease in physical function leads to functional limitations (e.g., strength, mobility, balance and coordination) and disability (e.g., self-reported activities of daily living or instrumental activities of daily living) especially among older adults[226-231]. Moreover, changes in physical function may be due to established cardiovascular morbidity. Recent studies have shown that cardiovascular disease (CVD) contributes greatly to disease burden and decreased quality of life as they are often accompanied by limitation in functional abilities[86,154]. Disruption in lipoproteins such as total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C) and high-density-lipoprotein cholesterol (HDL-C) are influential factors for atherosclerosis and subsequent complications such as CVD[9-11] and functional decline[13,87].

With CVD being one of the most common chronic diseases in the old[232,233] understanding the association between lipids and physical function in aging populations may be of great importance to maintain healthy functional populations longer. However, few studies have explored the association between individual serum lipoproteins and physical function altogether[44,86,87,137,154,158,234]. A small number of longitudinal studies in community dwelling older adults have been published examining the relationship between lipoproteins and physical function[44,234]. Reuben and colleagues investigated the effects of albumin and TC in 937 community living adults 70-79 years of age; they observed that low serum cholesterol levels over a 3 and 7-year period increased the risk of functional decline[234]. The Longitudinal Aging Study Amsterdam (LASA) is an ongoing population-based study looking at changes in physical, cognitive, emotional, and social functioning in older adults every 3 years[235]. An analysis from the LASA study examined TC and functional performance decline in adults 55-85 years of age over a 3-year change and found that after adjustment for lifestyle and disease-related factors, women with lower TC were 2.5 times more likely to decline than women with higher TC (95% CI: 1.07-5.84); the association was not observed in men[44].

Recent cross-sectional investigations have also been able to link lower levels of TC and HDL-C with mobility limitations and disability. High levels of HDL-C have been significantly associated with reduced risk of functional impairment even after accounting for other lifestyle-based CVD risk factors (e.g., smoking, exercise) and cardiovascular diseases such as stroke or coronary heart disease[86,158]. A recent study on adults 60 years and over found that those with functional limitations and dependence had higher TC[87].

Despite these important findings, research on lipoproteins and physical function has been limited and overall ethnically homogeneous. For example, to date no research has been found in the literature examining lipids and physical outcomes in a solely Latino cohort. Studies with cross-ethnic comparisons have observed that while Hispanics living in the United States have less CVD and less cardiovascular mortality than non-Hispanic Whites[97,236-238], they tend to have a high prevalence of CVD risk factors[29,51,97,239,240]. Hispanics have also been reported to be at a disadvantage in physical function as they experience greater disabilities than non-Hispanic Whites in the United States[241-244]. A recent investigation comparing a physical function questionnaire in participants of the Patient-Reported Outcomes Measurement Information System (PROMIS®) project found that Spanish speakers with the same underlying conditions as English speaking participants reported more physical limitations; this was reflected in the fact that Spanish speakers reported 50 of the 114 items of the questionnaire differently than English speakers[245].

Although acculturation may play a role in these differences, many underlying health factors within each population may account for the differentials. Latinos are often collapsed into a single group, but are in fact a heterogeneous group composed of multiple ethnicities[246]. Within-group or nativity differentials are important when measuring health behaviors and outcomes[246,247]. Once within population, or nativity differences in Latinos are adequately captured, it may be easier to understand between-group health differences in the United States or other countries. It has been suggested that future studies with ethnically diverse populations need to not only statistically adjust for the lack of equivalence in the measures, but also differentiate and stratify their

analysis by ethnicity[245,248]. This way, future public health interventions for the ethnically diverse population would be evidence based.

With a projected 31% Hispanic population in the United States by 2060[249] and Latin American countries aging faster than North American or European countries[250], it is extremely important to understand the factors affecting physical function in this group. In Costa Rica, for example, 11.5% of the country's population is expected to surpass 65 years of age by the year 2025[251]. With this population aging so quickly, the expected economic and social burden to the United States and Latin American countries may turn unsustainable.

Additionally, there are significant sex differences in physical function. It has been long described that women experience more disability than males[252,253]. According to results obtained from a 10-year analysis from the National Health Interview Survey, in each of all racial-ethnic categories, females had more functional limitations than males overall[254]. A study looking at sex differences in physical health found a significant higher number of functional limitations among older women, with the difference increasing with age[255]. One study looking at motor performance in relation to serum lipid characteristics in women found that high triglycerides (TG) and low HDL-C showed poor motor skills, indicative of functional limitations[256]. Additionally, Hispanic women tend to have physical function more compromised from comorbidity than males[250,257]. A recent study that pooled data from various countries in Latin America and the Caribbean observed that women were 1.6 times more likely to have disability in ADLs and 2 times more likely to have disability in IADLs compared to Latin men, even after adjusting for age, childhood

conditions, adult socio-economic status and current social conditions[257]. However, with such few longitudinal studies, more research is needed to assess the association.

Moreover, cognitive health is another major determinant of functional abilities. Thus cognitive decline/cognitive disability is highly correlated with functional decline[14,258,259]. Results from the Aging, Demographics, and Memory Study (ADAMS) found 45% prevalence of IADL limitations in those with cognitive impairment[14]. However, no study was found in the literature associating lipoproteins with both physical function and cognitive disability. Additional research is needed to assess this relationship.

Currently, there are many unanswered questions in the association between cardiovascular risk factors and physical function across time in older adults. This study will contribute to this gap in knowledge in several important ways. First, it will identify the lipoproteins associated with disability and functional limitation in older Latino adults. Second, the study will pinpoint which cardiovascular risk factors are indicative of disability and functional limitations. Third, it may be able to detect which forms of comorbidity are directly associated with physical function when accounting for demographics and cardiovascular risk factors. Additionally, this study will be the first longitudinal study of lipoproteins and physical function among older Latinos, specifically Costa Ricans a population yet to be explored in this respect. Understanding the relationship between lipids and physical function and determining which lipids are key in older ages, may help clinicians suggest treatment needs and anticipate treatment response specific to this aging Latino population.

Research Aims

The current study had two aims. The first aim explored the association between baseline TC, LDL-C, TG and HDL-C and decline in physical function over time. The second aim examined if sex and cognitive disability moderated either of the associations. The population-based study from Costa Rican Longevity and Healthy Aging Study (CRELES) was used for this analysis. Based on previous studies, it was hypothesized that those older adults with sustained lower levels of TC, LDL-C and HDL-C and high levels of TG over the study period will have more physical function decline (more functional limitations and disability) even after adjusting for demographics and possible confounders. It was expected that being female and having cognitive disability would moderate the association between the lipoproteins and physical function.

Aim 1. The main purpose of this study was to determine if baseline measures of independent lipoproteins TC, LDL-C, TG and HDL-C are associated with change in physical function taking into account demographics, cardiovascular risk factors and comorbidity in adults over the age of 60 participating in the CRELES. Physical function measured as (a) disability and (b) functional limitations.

Hypothesis 1. It was hypothesized that those older adults with lower baseline levels of TC, LDL-C and HDL-C and high levels of TG would have worse physical function decline (more disability and functional limitations) over the study period even after adjusting for demographics and possible confounders.

Aim 2. The second aim was to investigate whether sex and/or cognitive disability moderated any statistically significant association between baseline lipoproteins (TC, LDL-C, TG and HDL-C) and change in physical function over time.

Hypothesis 2. It was hypothesized that sex and/or cognitive disability would moderate any statistically significant association between each independent lipoprotein and physical function. Specifically, it was also hypothesized that the association between lipoproteins and physical function would differ between men and women; with the expectation that physical function decline would be more prevalent among women. It was also hypothesized that the association between lipoproteins and physical function would be significant only among participants with cognitive disability.

Methods

This study included all three waves of data collection from CRELES. A total of 2,827 residents of Costa Rica aged 60 and older in 2005 (oversample with the oldest old) were initially included in the first wave of the study between November 2004 and September 2006[260]. The initial CRELES sample was selected based on the 2000 census database using a multistage sampling design and complemented with a 100% sample of near centenarians and centenarians[260]. Lost to follow-up between wave 1 and 2 was 7%. Wave 2 includes all 2,364 participants that were still alive and were willing to participate between October 2006 and July 2008. There was a 16% attrition rate at wave 2 (10% deceased, 6% could not be located). Details of the study design, sampling distribution, weights, and non-response rates for waves 1 and 2 can be found elsewhere[260,261]. The third wave took place from February 2009 to January 2010. There are 1855 surviving and completed interviews; loss of follow up between waves 2 and 3 thus represented 9% of the baseline sample and there was 10% attrition of the wave 2 sample[262]. On average, a quarter of the interviews were conducted using proxies at all

three waves; 95% of the sample provided blood samples and 91% had anthropometric measures. Figure 10 shows the study composition used in this analysis. All individuals consented underwent in person interviews conducted by trained personnel. The "Committee on Science and Ethics" of the University of Costa Rica approved the CRELES study. The three waves were approved March 17, 2004 in session reference VI-763-CEC-23-|-04. The databases are completely anonymous (name and other identifiers were removed).

Measures

Demographic variables were obtained from each participant at the time of initial interview. For this analysis, age was analyzed as a continuous variable. Sex was categorized as males=1 and females=2. Education was coded continuously as the highest year of schooling achieved. Socioeconomic status was measured through perceived economic situation, participants were asked to describe their current economic situation; this was measured and coded in the following scale: 1=Excellent, 2=Very good, 3= Good, 4=Average/Normal, 5=Poor or 9=Did not know or did not respond.

Dependent Variables

Physical function for older adults was assessed through measures of physical limitations and disability. Functional measures of physical limitation included (a) maximum grip strength, (b) ability to stand with no arms, which measures balance and equilibrium and (c) the time-up and go test, or walking ability. Grip strength was

assessed having the participant sit for at least 3 minutes before doing the first measurement on the dominant hand using a Creative Health Products Inc. dynamometer, model T-18[260]. Participants were asked to stand with dominant arm extended beside their body, the first measurement was taken; and then sit again for another 3 minutes before the second measurement was taken. Two measures were obtained but only the highest whole value of the dominant hand is used in this analysis. This method has been previously used in epidemiological studies[263].

For mobility assessments, participants were asked if they had any impairment from doing a mobility and flexibility test, if the response was negative the measures for flexibility and mobility were obtained to quantify equilibrium and balance, and walking ability. All mobility assessments were coded 1=able to complete, 2=tried but unable, and 3= those that could not performed the test or refused. Similar coding has been previously used in the literature[234,264]. The description of each functional test is as follows: (a) equilibrium and balance were assessed asking the participant to remain standing with feet together for 10 seconds and to stand up five times from a sitting position with arms crossed on the chest[260]; (b) walking was measured by asking the participant to rise off a chair (from a sitting position) and walk a distance of 3 meters at normal walking speed. The variable is known as the Timed Up and Go Test (TUG) test and was coded as stated above.

Self-reported disability was coded as suggested in the literature[155] and measured in the study using ADL and IADLs. ADLs included walking, bathing, eating, going to bed, using the toilet, and grooming. IADLs comprised preparing food, managing money, shopping, and managing medications. For general comparisons of the data each

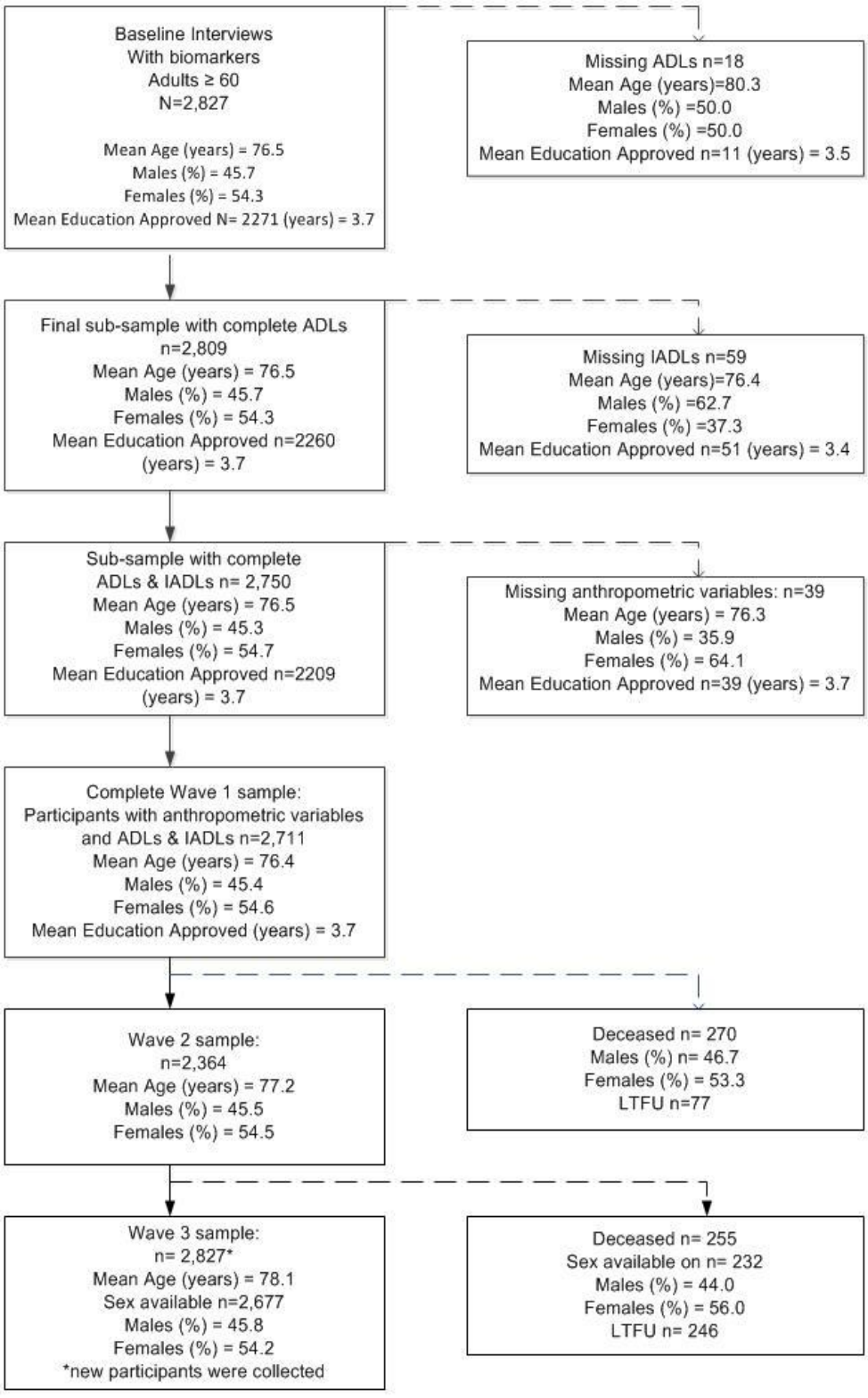

Figure 10. Study Flow Chart of All Waves Included in the Analysis for Study 2.

ADL/IADL was categorized as: 1=No, I never need help; 2=Yes, I have difficulty but can do without help; 3=Yes, I have difficulty and need help; and 4=Never do or cannot do the activities. Disability was coded following the International Classification of Functioning, Disability and Health (ICF)[155,265] as either 1=no self-reported difficulty or limitation or 2=had some degree of difficulty or could not do the activity. If the subject reported one or more limitation in ADL or IADL then the subject was labeled as being disabled or having ADL disability or IADL disability in that given category. This dichotomized classification is clinically applicable and has been previously used in similar analyses[86]. For the statistical model analysis, the summary score (continuous variable) for ADLs and IADLs were included in the models as previously done in the literature[266]. The score for ADLs ranged from 0 to 20 and for IADLs from 0 to 24 in the study period, with 0 indicating no disability on any of the ADL/IADL domains.

Independent Variables

Blood samples for lipoproteins were measured from fasting serum the day after the baseline interview. All blood specimens were collected after a 14-hour fasting period in participants' homes by venipuncture, normally during the second visit (the day after the main interview) and sent immediately to the participant laboratories for analysis. Three tubes of blood samples were collected: one was a vacutainer with (EDTA) of approximately 3-4 ml which was centrifuged later to separate the plasma of the cells and two 5 milliliter tubes were vacutainers without anticoagulant (SST) with coagulum activator for obtaining serum. A fraction of the serum was separated in a conical tube type Eppendorf to obtain the measures for the TC, LDL-C, TG, HDL-C and 1 ml of complete blood in the tube EDTA for the analysis of glycosylated hemoglobin. Additional

specific protocol for laboratory samples and quality control measures can be found elsewhere[260]. Specific levels of lipoproteins TC, LDL-C, TG, and HDL-C were also examined and converted to mmol/l for comparison with previous studies using the standard international measurement system.

Covariates. Cardiovascular risk factors included in this study were based on definitions suggested by the American Heart Association[56]. Covariates for comorbidity included here were those known to correlate with both cardiovascular disease and physical function.

- Hypertension. Sitting systolic and diastolic blood pressure was measured twice during the interview and the average reading was used. If the participant had systolic ≥140 mmHg, or diastolic ≥90 mmHg, or they reported being diagnosed with hypertension, taking antihypertensive and/or diuretic medication, they were categorized as having hypertension (hypertension=1), otherwise hypertension=0.
- Antihyperlipidemics. This variable was dichotomized as: 1= the participant was taking medications to lower cholesterol; 0=the participant said no or do not know.
- Diabetes. Accounted for by including the participant's levels of glycosylated hemoglobin (HbA1c) in mg/dl to cover those with high glucose levels that did not know they were diabetics.
- Smoking status. Coded (0) never smoked, (1) previous smoker or (2) current smoker.
- Self-report Exercise. Participants were asked if in the last 12 months they exercised regularly or did other physically rigorous activities like sports, jogging, dancing, or heavy work, 3 times per week. If they answer yes, exercise=1, otherwise exercise=0.

- Chronic health conditions known to add to the burden of functional limitations and disability are included in the analysis. These comprised current or medical history of:
- Heart disease. If participants were ever told by a physician they had heart disease with or without myocardial infarction, then coronary heart disease was marked positive (CHD=1), otherwise CHD= 0.
- Stroke. Coded as 1 if participants were ever told by a physician they had a stroke or 0 if not, or they did not know.
- Arthritis. If in the last 2 years participants were told by a physician they had arthritis, rheumatism or arthrosis, then arthritis=1, otherwise arthritis=0.
- Osteoporosis. If in the last 2 years participants were told by a physician they had osteoporosis or frail bones, then osteoporosis=1 or if the participant said no or did not know, then osteoporosis=0.
- Pulmonary pathology. If in the last 2 years participants were told by a physician of having a respiratory disease or chronic pulmonary disease (emphysema, tuberculosis, asthma or chronic bronchitis), then the variable was coded as lung=1, otherwise lung=0.
- Cancer. If in the last 2 years participants had been told they had cancer or a malignant tumor, not inclusive of small skin tumors, then cancer=1; otherwise cancer=0.
- Psychiatric conditions. If in the last 2 years participants were told by a physician they had any nervous or psychiatric problems such as depression, then psych=1,otherwise psych=0.

- Insomnia. This dichotomized variable, participants were asked if in the last 12 months they have or had any problems with insomnia. If they answer positively insomnia=1, otherwise insomnia=0.
    - Severe cognitive disability. This variable was coded as a categorical value, where 0 meant not having a cognitive disability and 1 stated that the participant had severe cognitive impairment determined by a short modified Spanish version of the MMSE with a maximum of 15 points. The participant was coded as having severe cognitive if the participant scored less than or equal to 11 items incorrectly (4/15 questions correct).

Statistical Analysis

Random effects modeling (REM), also known as mixed-effects or multilevel models[267], were performed utilizing SAS software, version 9.4 (Copyright © 2002-2012 SAS Institute Inc., Cary, NC). Mixed models have the ability to measure and account for random variability in scores that can ultimately bias results[268,269]. The means are modeled by fixed effects (identical for all individuals) and the residuals and variances by random effects[270]. REMs share some basic characteristics with repeated measures analysis of variance (rANOVA); however, mixed models have a number of advantages. First, REM include all individuals for whom complete data is not available[268]. Second, rANOVA treats time as a categorical variable, while multilevel growth curves treat time as continuous, which better reflects reality[270]. Third, REM also has the advantage that individuals are assumed to follow a curve shape but can vary in the parameters (random effects)[270].

This study first examined baseline demographics at wave 1 and presented them separately for males and females. Participant's characteristics were also analyzed comparing them to each study outcome by wave. Gender characteristics were analyzed by independent samples *t*-test and Pearson chi-square test. Continuous variables were reported as means with standard deviation (SD) and were compared using the t-test. Pooled p-values were used for equal variances and Satterthwaite for unequal variances. Categorical variables were analyzed using Chi-square test for equal proportions. Pearson correlation coefficients were also obtained for all dependent and independent variables.

REM was used to examine lipoproteins TC, LDL-C, TG and HDL-C at baseline in relation to physical function and change in function over three measurement occasions while taking into account demographics, cardiovascular risk factors and comorbidity. The equilibrium and TUG variables were explored in the descriptive analysis, but most of values were zero, not allowing us to use inferential statistics on these two variables. Therefore, to study the association between lipids and physical function outcomes, ADL disability, IADL disability, and grip strength were utilized as the outcomes. Each outcome was analyzed separately for each of the lipids. The REMs estimate overall fixed effects, or average effects for the group, as well as random effects, which are reflective of the person's deviation from the fixed effect. Random effects were calculated using an unstructured correlations matrix, the most commonly used matrix for these types of data, and included the baseline outcome/physical function (intercept) and rate of decline (slope). All study covariates were included in the main models, which also provided the best model fit. At level 1, an individual's development is represented by

each person's growth trajectory (within-person model) with an intercept (X_{0i}) and a slope (β_{1i}); it provides information on whether participants changed over time. Level 2 represents the inter-individual change in linear time (across waves 1, 2 and 3). The three study waves were coded as an ordinal variable with wave 1 coded as time zero. Continuous variables were grand-mean centered. Dichotomous variables were contrast centered (i.e., -1 vs. 1) as suggested[271]. The alpha levels used for the analysis was $p<.05$.

The REMs were estimated as two-level models. For example, in the case of ADL as the outcome, the level 1 intra-individual change in predictors is based on an individual's baseline ADL score (Y_{ij}) as a function of the average ADLs across all participants at baseline, X_{0i} (or fixed effect), the average group difference in the lipoproteins and demographic variables for the ADLs. These estimates provide the cross-sectional association between the predictor and ADL scores. At level 2, the model estimates if there are significant inter-individual differences in change of ADLs after controlling for variables of interest. In other words, level 2 describes the average rate of change of ADLs over time or longitudinally (random effect of how the individual varies around the mean ADL) and how it is systematically related to the predictor variable(s) being tested. The equation used was as follows:

$$Y_{ij} = X_{0i} + \beta_{1i}\,(Time) + \beta_{2i}\,(Lipoprotein) + \beta_{3i}\,(Time*Lipoprotein) + \beta_{4i}\,(Age) + \beta_{5i}\,(Age*Time) + \beta_{6i}\,(Sex) + \beta_{7i}\,(Sex*Time) + \beta_{8i}\,(Education) + \beta_{9i}\,(Education*Time) + \beta_{10i}\,(Perceived\ economic\ situation) + \beta_{11i}\,(Perceived\ economic\ situation*Time) + \beta_{12i}(Hypertension) + \beta_{13i}(Hypertension*Time) + \beta_{14i}(Antilipidemics) +$$

β_{15i}(*Antilipidemics*Time)* + β_{16i}(*Glycated hemoglobin)* + β_{17i}(*Glycated hemoglobin*Time)* + β_{18i}(*Smoking)* + β_{19i}(*Smoking*Time)* + β_{20i}(*Exercise)* + β_{21i}(*Exercise*Time)* + β_{22i}(*Coronary heart disease*) + β_{23i}(*Coronary heart disease*Time*) + β_{24i}(*Stroke*) + β_{25i}(*Stroke*Time*) + β_{26i}(*Arthritis*) + β_{27i}(*Arthritis*Time*) + β_{28i}(*Osteoporosis*) + β_{29i}(*Osteoporosis*Time*) + β_{30i}(*Pulmonary*) + β_{31i}(*Pulmonary*Time*) + β_{32i}(*Cancer*) + β_{33i}(*Cancer*Time*) + β_{34i}(*Psychiatric*) + β_{35i}(*Psychiatric*Time*) + β_{36i}(*Insomnia*) + β_{37i}(*Insomnia*Time*) + β_{38i}(*Cognitive disability*) + β_{39i}(*Cognitive disability*Time*) + b_i + ε_{ij}

where *Y* represents the outcome (physical function) for the *i*th subject during the *j*th observation. The X_{0i} is the intercept (when a participant's value on the predictors are both zero), β_{1i} the slope (time representing the wave of the study), which is the difference between the observed measure of the outcome and the expected measure of the outcome based on the model. The within-person slope (β_{ij}) is the fixed effect for the lipoproteins and demographics and b_i is the subject-specific random effect that allows for the baseline value of the predictor to vary for each subject and the ε_{ij} is the within-subject error term.

To test the second aim, interaction terms for sex and cognitive disability were performed for all statistically significant lipoproteins in the first aim. Further, stratification was done for those statistically significant interactions.

Results

Sample Characteristics

Baseline characteristics of the sample with complete variables of interest are presented in table 11. The mean age of the sample was 76.4 (SD10.2), with 4th grade of elementary school being the average grade completed. Half of the sample self-reported their health as better than good, 41% thought it was average and only 9% thought their health was bad. Most thought their perceived economic situation was average or better. Most of the participants owned their home (84%); 60% reported residing in an urban area.

Over half of the sample at baseline had never smoked and only 8% were current smokers. Most did not exercise regularly (76%), but men were more physically active than women. Figure 11 shows the sample's lipid distribution. Levels were on the borderline high category for TC, LDL-C and TG[32,33]. Refer to table 1 for lipid ranges. The mean blood pressure for the sample was 145.9/82.6 mmHg, which is considered to be hypertensive for younger older adults, but in target values for those between 70-90 years of age[272,273]. Women had significantly more hypertension than men. The percentage of glycated hemoglobin for the sample was 5.8% and it was in the normal range (4.0-6.0%). Women had significantly higher levels of HbA1c. With the exception of myocardial infarctions, women had significantly more comorbidities than men. An important 44.3% of older adults reported sleeping problems and almost a quarter (23%) were reported to have cognitive disability. There were no differences in the percentage of stroke or cancer between males and females.

Physical function was examined through ADL/IADLs and grip function in the REM models, but a description of equilibrium, and the TUG test is also provided. When disability was examined at baseline, it was found that 56% of participants did not report any problems with ADLs such as bathing, eating, going to bed, using toilet, or grooming. However, of those that did report problems, 60% had difficulty with walking, 44% with grooming and 15% problems bathing. Three quarters of the sample did not report problems with IADLs, but disabilities presented included: shopping (33%), managing medications (25%), preparing food (24%), and managing money (21%). Those with ADL and IADL disabilities were on average 11 years older (p's<.001); less educated (ADLS p=.002; IADLs p=.004); and had significantly lower levels of TC and LDL-C (p's<.001).

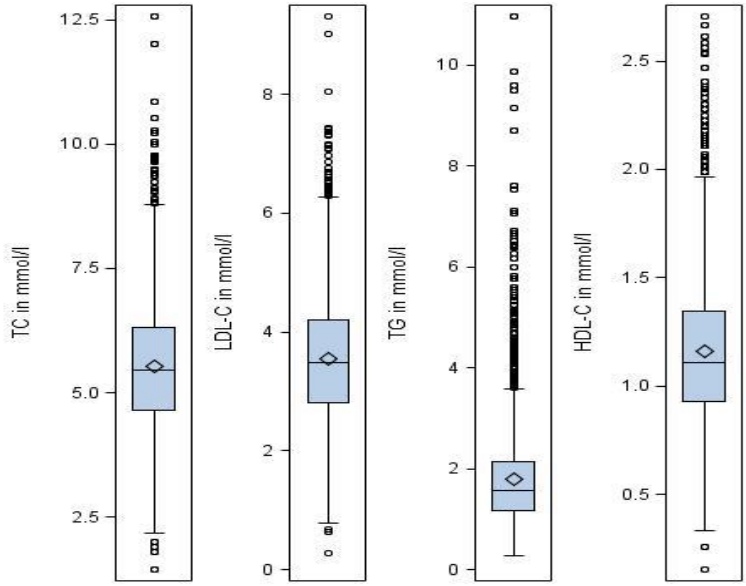

Figure 11. Box-plots of Lipoprotein Range in the Sample.

Note: TC=total cholesterol; LDL=low-density lipoprotein cholesterol; TG=triglycerides; HDL-C= high-density lipoprotein cholesterol

Table 11. Baseline Characteristics of Participants by Gender.

	Total Sample (N=2677) 100%	Males (n=1227) 45.8%	Females (n=1450) 54.2%	p-value
Mean Age (SD)	76.4 (10.2)	76.4 (10.3)	76.4 (10.2)	.869
Mean Education (SD)	3.7 (1.8)	3.7 (1.8)	3.7 (1.7)	.382
Perceived Current Economic Situation				
Excellent	88(3.2)	40 (3.3)	48 (3.3)	
Very Good	156 (5.8)	67 (5.5)	89 (6.2)	
Good	792 (29.6)	319 (26.0)	473 (32.6)	
Average/Normal	1231 (46.0)	587 (47.8)	644 (44.4)	
Poor	402 (15.0)	211 (17.2)	191 (13.2)	
Do not know/No response	8 (0.3)	3 (0.2)	5 (0.3)	.002
Mean Lipoprotein Levels mmol/l (SD)				
Total Cholesterol	5.5 (1.3)	5.3 (1.2)	5.7 (1.3)	<.001
LDL-C*	3.5 (1.1)	3.4 (1.0)	3.7 (1.1)	<.001
Triglycerides	1.8 (1.0)	1.7 (1.0)	1.8 (1.0)	.001
HDL-C*	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	<.001
Cardiovascular Risk Factors				
Mean Systolic Blood Pressure mmHg (SD)	145.9 (24.7)	144.6 (24.0)	147.0 (25.3)	.012
Mean Diastolic Blood Pressure mmHg (SD)	82.6 (12.8)	81.8 (12.8)	83.2 (12.7)	.007
Have Hypertension %	49.0	41.4	55.5	<.001
Taking Medications for Hypertension %	45.5	39.3	50.7	<.001
Taking Diuretics %	23.3	20.2	25.9	<.001
Hypercholesterolemia %	34.5	27.3	40.6	<.001
Taking Medication for Hypercholesterolemia %	18.7	15.5	21.5	<.001
Diabetics	19.3	15.3	22.8	<.001
Glycated Hemoglobin (HbA1c) %	5.8 (1.1)	5.7 (1.0)	5.9 (1.2)	<.001
Exercise %	24	32.6	16.8	<.001
Smoking %	8.1	13.6	3.2	<.001
Current Smoker	35.1	54.5	18.5	
Previous Smoker	56.8	31.9	78.2	
Never Smoked				
Comorbidity %				
Stroke	5.4	5.1	5.6	.547
Myocardial Infarction	5.3	6.2	4.5	.009
Pulmonary Problems	18.0	14.9	20.6	<.001
Cancer	6.8	6.3	7.2	.273
Arthritis	16.6	12.3	20.6	<.001
Osteoporosis	9.4	2.0	15.6	<.001
Psychiatric (nervous problems)	18.6	12.3	24.0	<.001
Insomnia	44.3	37.5	50.4	<.001
Cognitive Disability	22.7	250 (20.4)	348 (24)	.026

*Note: *LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol; SD=Standard Deviation. Optimal range: Total Cholesterol< 5.2mmol/l; LDL-C<3.4mmol/l; Triglycerides<1.7mmol/l; HDL-C >1.5mmol/l*

When looking at the associations between disability and functional limitations, those with ADL and IADL disabilities had significantly more difficulty with equilibrium (standing with no arms) and walking (TUG test) (p's<0.001). Table 12 shows participant characteristics with respect to physical function status for the overall sample and by sex. Females had significantly more ADL disability than males (p<0.001) and more functional limitations in grip strength (p<.001) and equilibrium (p=0.001); the sex difference was not significant for IADLs (p=0.251) and for the TUG (p=0.344).

Table 12. Participant Characteristics at Baseline for Physical Function by Sex.

	Disability and/or Functional Limitation %			
	Total Sample (N=2677) 100%	Males (n=1227) 45.8%	Females (n=1450) 54.2%	p-value
Mean Disability in Activities of Daily Living (SD)	8.5 (3.4)	8.1 (3.3)	8.8 (3.5)	<.001
Mean Disability in Instrumental Activities of Daily Living (SD)	6.2 (3.2)	6.1 (3.3)	6.2 (3.1)	.244
Mean Grip Strength (SD)	22.3 (8.6)	27.8 (8.0)	17.5 (5.7)	<.001
Equilibrium				
Able and completed	2068 (91.7)	982 (94.0)	1059 (89.7)	
Tried but unable	61 (2.7)	17 (1.6)	43 (3.6)	
Not attempted/refused	126 (5.6)	46 (4.4)	79 (6.7)	
Time up and go test				
Able and completed	2233 (99.0)	1038 (99.3)	1166 (98.7)	
Tried but unable	4 (0.2)	1 (0.1)	3 (0.3)	
Not attempted/refused	18 (0.8)	6 (0.6)	12 (1.0)	

Note: SD=Standard Deviation

Table 13 presents the baseline lipid and HbA1c levels by disability. Overall, participants with ADL disability had lower TC, LDL-C HDL-C and higher HbA1c than those without ADL disabilities; while those with IADL disabilities had lower TC, LDL-C

and TG than those without IADL disabilities. Older adults with cognitive disability had lower levels of TC, LDL-C, TG and HbA1c, but surprisingly had slightly higher HDL-C. Results also indicated that older adults with disabilities have lower lipid levels than those without disabilities.

Table13. Baseline Lipid Characteristics by Disability Status.

	ADL disability			IADL disability			Cognitive Status		
	Without disability	With disability		Without disability	With disability		Without cognitive disability	With cognitive disability	
	Mean (SD)	Mean (SD)	p	Mean (SD)	Mean (SD)	p	Mean (SD)	Mean (SD)	p
TC*	5.6 (1.2)	5.4 (1.3)	<.001	5.6 (1.3)	5.3 (1.3)	<.001	5.6 (1.3)	5.3 (1.3)	<.001
LDL-C*	3.6 (1.1)	3.4 (1.1)	<.001	3.6 (1.1)	3.4 (1.1)	<.001	9.7 (29.5)	6.8 (20.8)	<.001
TG*	1.8 (1.0)	1.8 (1.0)	.592	1.8 (1.0)	1.7 (1.0)	.001	1.8 (1.0)	1.6 (0.9)	<.001
HDL-C*	1.2 (1.1)	1.1 (1.1)	.123	1.1 (0.3)	1.2 (0.4)	.165	1.1 (0.3)	1.2 (0.4)	<.001
HbA1C**	5.7 (1.1)	5.9 (1.2)	<.001	5.8 (1.1)	5.9 (1.2)	.131	5.8 (1.2)	5.7 (1.0)	<.001

Note. *Optimal range: Total Cholesterol (TC) < 5.2mmol/l; Low-density lipoprotein cholesterol (LDL-C) <3.4mmol/l; Triglycerides (TG) <1.7mmol/l; High-density lipoprotein cholesterol (HDL-C) ≥1.5mmol/l; P-values are based on t-test statistics. SD= Standard deviation.

Correlations

A Pearson correlation analysis was performed to first observe and better understand the data; second, to examine whether the dependent variables and covariates were associated; and last to determine the strength of the associations. As illustrated in table 14, older age was significantly correlated with lower levels of TC, LDL-C and TG, but with higher levels of HDL-C. Being a woman was associated with higher level of lipids, specifically significant were TC, TG and HDL-C. Education and perceived economic situation did not correlate with any of the lipoproteins of interest.

When cardiovascular risk factors were examined, having high levels of HbA1c, being hypertensive and taking medication for cholesterol was associated with higher levels of LDL-C, TG and low levels of HDL-C. People who did not exercise were linked with higher levels of TC and lower HDL-C, while smoking was linked with lower levels of both TC and HDL-C. When comorbidities were assessed, having had a stroke correlated with higher levels of LDL-C. In general, those with a history of osteoporosis or depression had higher levels of TC and HDL-C. Lower levels of TC, LDL-C and TG and higher levels of HDL-C were linked with cognitive disability.

Table 14. Correlations between Lipoproteins, Demographic Characteristics, Cardiovascular Risk Factors and Comorbidities.

	TC	**LDL-C**	**TG**	**HDL-C**
Age	-0.11***	-0.06**	-0.13***	0.08***
Sex	0.18***	0.02	0.06**	0.21***
Max Education Achieved	-0.02	0.02	0.03	0.01
Perceived Economic Situation	-0.04	0.01	-0.01	0.00
HbA1c	0.01	0.05*	0.19***	-0.13***
Hypertension	-0.004	0.05**	0.09***	-0.08***
Cholesterol Medications	-0.01	0.07***	0.13***	-0.06**
Exercise	0.04*	0.01	0.04	-0.05**
Smoking	-0.05*	0.01	0.01	-0.08***
CHD	-0.04	-0.01	0.003	-0.02
Stroke	-0.03	0.04*	0.01	-0.02
Rheumatoid Arthritis	-0.01	0.02	-0.003	0.03
Osteoporosis	0.06***	0.0003	0.02	0.07***
Pulmonary Pathology (e.g. COPD)	0.01	-0.01	0.001	0.01
Cancer	-0.001	0.02	0.03	-0.01
Psychiatric (e.g. Depression)	0.04*	-0.01	0.01	0.07***
Insomnia	0.01	0.01	-0.001	0.03
Cognitive disability	-0.10***	-0.05*	-0.09***	0.05*

Note: <.05, <.01**, <.001*** TC=Total cholesterol, LDL-C=Low-density lipoprotein cholesterol, TG=Triglycerides, HDL-C=High density-lipoprotein cholesterol.*

Table 15 shows the correlations between the lipoproteins and functional outcomes. At baseline, lower levels of TC correlated with increased ADL/IADL disability. Lower levels of LDL-C were related to more IADL disability. Lower TG were significantly associated with more disability overall and lower HDL-C was related to lower grip strength. However, by the third wave only lower levels of HDL-C correlated with an outcome (grip strength).

Table 15. Correlations between Functional Outcomes and Lipoproteins by Wave.

	ADL	IADL	Grip
Wave 1			
TC	-0.11***	-0.10***	-0.04
LDL-C	-0.01	-0.04*	0.02
TG	-0.07***	-0.09***	0.03
HDL-C	0.01	0.04*	-0.17***
Wave 2			
TC	-0.07***	-0.06**	-0.08***
LDL-C	-0.03	-0.04*	-0.002
TG	-0.06**	-0.09***	0.03
HDL-C	0.03	0.05*	-0.21***
Wave 3			
TC	-0.05	-0.04	-0.02
LDL-C	-0.003	-0.02	-0.002
TG	-0.02	-0.03	-0.0004
HDL-C	0.04	0.04	-0.09***

Note: <.05, <.01**, <.001*** TC=Total cholesterol, LDL-C=Low-density lipoprotein cholesterol, TG=Triglycerides, HDL-C=High density-lipoprotein cholesterol, ADL=Activities of daily living, IADL=instrumental activities of daily living.*

Table 16 displays the correlation analysis of the association between demographics and functional outcomes. At baseline, age and education were significantly related to all functional outcomes examined. Older ages were associated with more ADL and IADL disability and lower grip strength. Sex (being female) was also related to more ADL disability and lower grip strength. Higher education was associated

with better grip strength, while lower levels of education achieved were related to more ADL/IADL disability. Higher income correlated with more reported ADL and IADL disability.

Table 16. Correlations between Functional Outcomes and Demographics by Wave.

	ADL	IADL	Grip
Wave 1			
Age	0.47***	0.54***	-0.43***
Sex	0.10***	0.02	-0.60***
Max Education Achieved	-0.04*	-0.12***	0.08***
Perceived Economic Situation	0.10***	0.12***	-0.01
Wave 2			
Age	0.48***	0.56***	-0.42***
Sex	0.11***	0.04*	-0.60***
Max Education Achieved	-0.04	-0.11***	0.08***
Perceived Economic Situation	0.05*	0.08***	-0.01
Wave 3			
Age	0.47***	0.51***	-0.23***
Sex	0.14***	0.05*	-0.42***
Max Education Achieved	-0.07*	-0.12***	0.07**
Perceived Economic Situation	0.10***	0.09***	0.01

Note: <.05, <.01**, <.001*** Note: TC=Total cholesterol, LDL-C=Low-density lipoprotein cholesterol, TG=Triglycerides, HDL-C=High density-lipoprotein cholesterol.*

The association between the functional outcomes and cardiovascular risk factors is illustrated in table 17. Hypertension was associated with lower grip strength throughout the study. Taking medications for cholesterol was related to less difficulty with IADLs in at waves 1 and 2. Exercise correlated to all outcomes at baseline, such that not exercising was associated with more ADL/IAD disability. Furthermore, those who did exercise performed better in grip function throughout the study.

Table 17. Correlations between Functional Outcomes and Cardiovascular Risk Factors by Wave.

	ADL	IADL	Grip
Wave 1			
HbA1c	0.004	-0.003	-0.04
Hypertension	-0.01	-0.03	-0.05*
Cholesterol Medications	-0.03	-0.07**	0.02
Exercise	-0.27***	-0.28***	0.29***
Smoking	-0.07***	-0.01	0.28***
Wave 2			
HbA1c	0.04*	0.001	-0.05*
Hypertension	0.04	0.01	-0.05*
Cholesterol Medications	-0.02	-0.08***	0.01
Exercise	-0.26***	-0.26***	0.26***
Smoking	-0.07**	-0.001	0.26***
Wave 3			
HbA1c	0.06*	0.002	-0.05*
Hypertension	0.06**	0.03	-0.07**
Cholesterol Medications	-0.03	-0.05*	-0.01
Exercise	-0.26***	-0.23***	0.15***
Smoking	-0.07**	0.01	0.21***

Note: <.05, <.01**, <.001*** ADL=Activities of daily living, IADL=instrumental activities of daily living, HbA1c=hemoglobin A1c.*

Table 18 shows the relationship between functional outcomes and comorbidities. All comorbid conditions were significantly associated with more ADL disability throughout the study waves. With the exception of osteoporosis, IADLs were also associated with all comorbidities. Lower grip strength was associated with the majority of comorbidity in the first two study waves.

Table 18. Correlations between Functional Outcomes and Comorbidities by Wave.

	ADL	IADL	Grip
Wave 1			
CHD	0.08***	0.07***	-0.06**
Stroke	0.24***	0.21***	-0.11***
Rheumatoid Arthritis	0.11***	0.04*	-0.13***
Osteoporosis	0.06**	-0.01	-0.13***
Pulmonary Pathology (e.g. COPD)	0.09***	0.06**	-0.08***
Cancer	0.08***	0.05**	-0.05**
Psychiatric (e.g. Depression)	0.08***	0.06**	-0.10***
Insomnia	0.12***	0.09***	-0.14***
Cognitive disability	0.58***	0.71***	-0.34***
Wave 2			
CHD	0.06**	0.07***	-0.05*
Stroke	0.22***	0.19***	-0.10***
Rheumatoid Arthritis	0.10***	0.06**	-0.16***
Osteoporosis	0.05*	-0.001	-0.15***
Pulmonary Pathology (e.g. COPD)	0.09***	0.07**	-0.09***
Cancer	0.06**	0.08***	-0.04
Psychiatric (e.g. Depression)	0.08***	0.06**	-0.09***
Insomnia	0.10***	0.09***	-0.16***
Cognitive disability	0.56***	0.71***	-0.29***
Wave 3			
CHD	0.11***	0.10***	0.01
Stroke	0.20***	0.18***	-0.02
Rheumatoid Arthritis	0.16***	0.07**	-0.05*
Osteoporosis	0.07**	-0.005	-0.13***
Pulmonary Pathology (e.g. COPD)	0.07**	0.09***	-0.04
Cancer	0.05*	0.07**	-0.01
Psychiatric (e.g. Depression)	0.08**	0.06**	-0.11***
Insomnia	0.12***	0.08***	-0.09***
Cognitive disability	0.46***	0.51***	-0.08**

Note: <.05, <.01**, <.001*** ADL=Activities of Daily Living, IADL=Instrumental Activities of Daily Living, CHD=Coronary Heart Disease.*

Random Effect Model (REM) Results

Intraclass correlations (ICCs) were calculated for ADLs, IADLs, and grip strength to find out whether there was a sufficient amount of within- and between-person variance in the three outcomes to conduct the REM, as suggested previously [274]. Between-person variance (expressed as ICC value) indicates how much participants vary in their actual outcome scores. For example, a low value for between-person variance would mean that participants have about the same functional limitations. Within-person variance (expressed as 1-ICC value) indicates how much participants vary with respect to each participant's trajectory of change. Low values for within-person variance would indicate that participants change in about the same way (e.g., all decline at about the same rate) across the three measurement occasions. The ICC results suggested that 70% to 72% of the total variance was due to between-person variance. The 1-ICC results suggested that 28% to 30% was due to within-person variance.

To assess whether TC, LDL-C, TG and HDL-C were associated with functional outcomes, REM models for each dependent variable were estimated adjusting for demographics, cardiovascular risk factors, and comorbidity. Table 19a-19d presents the results of the REM analyses for all three outcome variables of interest. The fixed effect for each of the intercepts represents the average baseline outcome score. The fixed effect for time represents average change in the outcome per one wave. The fixed effect for predictor shows the average change in the outcome per one unit change in the predictor. The fixed effect for the time by predictor interaction shows the average change in the outcome per wave when the value of the predictor increases by one unit.

REM Results for Intercept and Slope. To summarize, the results for the intercept (the average value for the outcome at baseline when controlling for all independent variables in the model) and the slope (the average change in the outcome scores per one wave, controlling for all independent variables in the model) are first discuss. For ADLs, the average value at baseline after adjusting for all covariates (e.g., the intercept) was consistently above 4 for all lipoproteins. There was not a significant change in ADLs such that the ADL scores increased by an average of just under 0.06 points with each wave. For IADLs, the average covariate adjusted scores at baseline were almost 3.8 for all lipids, and the participants IADL score declined on average by about additional 0.09 points per wave, but this decrease was also not significant. For grip, the average adjusted baseline scores were around 39 and these scores did not change significantly across the three waves.

REM Results for Random Effects. This section summarizes the results for random effects (i.e., the variability in scores at the intercept and in change over time, as well as covariance between the scores at the intercept and over time) across the reported models. The significant random effects for the variance in the intercept across all outcome models indicated that baseline outcome scores varied significantly, providing a good reason to use REM (where adjustment for the potential effect of baseline values on subsequent trajectory of change is incorporated). The significant variance of time demonstrated that there were significant individual differences in the rate of change for disability and functional limitations. In other words, participants were changing with respect to outcome scores at different rates when scores for all study covariates were controlled. Last, there was no significant covariance between the

intercept and the years in the study period, which means that, after accounting for all study covariates, the rate of decline in each outcome was not different among participants with different outcome baseline levels.

Total Cholesterol. Table 19a displays the results from the REMs for the association between TC and all three the outcomes of interest. With respect to the cross-sectional results, there was a statistical significant fixed effect for TC in ADLs, which indicates lower TC was associated with significantly more ADL disability. No other significant fixed effects were observed for TC in IADLs or grip function, which suggests that scores for IADLs and grip function were not significantly associated with TC scores. With respect to the longitudinal results, none of the TC-by-time interactions were statistically significant which indicated that baseline TC scores did not have a significant impact on the rate of decline over time for the measured outcomes. In this fully adjusted model, the explained variance across the physical limitations and disability measures was 67%-81% for the ICC (between-person) and 25%-43% for the 1-ICC (within-person) values.

Low-density Lipoprotein Cholesterol. Table 19b displays the results from the REMs for the association between LDL-C and the outcomes of interest. When examining the cross-sectional results, there was no significant fixed effect for LDL-C on any of the outcomes, which indicated that scores for physical function measures were not significantly associated with LDL-C scores. None of the interactions by time were statistically significant which indicated that baseline LDL-C measures were not significantly associated with rate of change in the physical function outcomes. In this fully adjusted model, the explained variance across the physical limitations and disability

measures was 68%-79% for the ICC (between-person) and 24%-43% for the 1-ICC (within-person) values.

Table 19a. Random Effect Models for all Outcomes and Total Cholesterol.

	ADLs		IADLs		Grip	
FIXED EFFECTS	b	SE	b	SE	b	SE
Intercept	4.29***	0.32	3.78***	0.25	39.14***	0.80
Time	0.08	0.22	-0.08	0.19	-1.07	0.69
TC	-0.16***	0.04	-0.05	0.03	0.07	0.10
TC*Time	-0.0002	0.03	0.01	0.02	0.17	0.09
RANDOM EFFECTS						
Variance of the intercept	3.01***	0.21	1.41***	0.14	15.87***	1.08
Variance of time	0.44***	0.10	0.31***	0.07	8.43***	0.71
Covariance of intercept, time	0.15	0.11	0.11	0.13	0.04	0.06
Residual variance	2.75***	0.11	2.26***	0.09	14.38***	0.56
-2 log likelihood	22941.8		21144.7		29247.6	

*Note: *p<.05; **p<.01; ***p<.001; TC=Total cholesterol; Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML. Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Table 19b. Random Effect Models for all Outcomes and Low-density Lipoprotein Cholesterol.

	ADLs		IADLs		Grip	
FIXED EFFECTS	b	SE	b	SE	b	SE
Intercept	4.38***	0.32	3.77***	0.25	38.92***	0.80
Time	0.04	0.22	-0.11	0.20	-1.20	0.69
LDL-C	0.001	0.002	-0.001	0.001	0.002	0.004
LDL-C*Time	-0.001	0.001	0.0001	0.001	0.001	0.003
RANDOM EFFECTS						
Variance of the intercept	3.01***	0.20	1.42***	0.14	15.68***	1.09
Variance of time	0.44***	0.10	0.30***	0.07	8.59***	0.72
Covariance of intercept, time	0.15	0.11	0.12	0.14	0.03	0.06
Residual variance	2.75***	0.11	2.28***	0.09	14.47***	0.57
-2 log likelihood	22941.8		20841.6		29298.0	

*Note: *p<.05; **p<.01; ***p<.001; LDL-C=Low-density lipoprotein cholesterol; Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML. Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Triglycerides. Table 19c displays the results from the REMs for the association between TG and all three outcomes of interest. Regarding the cross-sectional results, there was a significant positive fixed effect for grip function, which indicates that higher TG scores were associated with significantly better grip function. No other significant cross-sectional effects were observed for TG in disability, which suggests that scores for disability were not significantly associated with baseline TG scores. In regards to the longitudinal results, none of the TG-by-time interactions were statistically significant, which indicated that baseline TG scores were not significantly associated with rate of change in the measured outcomes. In this fully adjusted model, the explained variance across the physical limitations and disability measures was 66%-79% for the ICC (between-person) and 25%-43% for the 1-ICC (within-person) values.

Table 19c. Random Effect Models for all Outcomes and Triglycerides.

	ADLs		IADLs		Grip	
FIXED EFFECTS	b	SE	b	SE	b	SE
Intercept	4.29***	0.32	3.75***	0.25	39.18***	0.80
Time	0.06	0.22	-0.08	0.19	-1.13	0.69
TG	-0.02	0.06	-0.04	0.04	0.26*	0.13
TG*Time	-0.01	0.04	0.003	0.03	0.08	0.11
RANDOM EFFECTS						
Variance of the intercept	3.04***	0.21	1.41***	0.13	15.79***	1.07
Variance of time	0.44***	0.10	0.31***	0.07	8.48***	0.71
Covariance of intercept, time	0.15	0.11	0.11	0.13	0.03	0.06
Residual variance	2.75***	0.11	2.26***	0.09	14.38***	0.57
-2 log likelihood	22948.2		21135.6		29232.5	

*Note: *p<.05; **p<.01; ***p<.001; TG=Triglycerides; Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML. Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

High-density Lipoprotein Cholesterol. Table 19d displays the results from the REMs for the association between HDL-C and the outcomes of interest. With respect to the cross-sectional results, there was a statistical significant fixed effect for HDL-C in ADLs, which indicates that lower HDL-C scores were associated with significantly more ADL disability. No other significant fixed effects were observed for HDL-C in IADLS or grip function, which suggests that scores for IADLs and grip function were not significantly associated with HDL-C scores. With regard to the longitudinal results, none of the HDL-C-by-time interactions were statistically significant, which indicated that baseline HDL-C scores were not significantly associated with rate of change in the measured outcomes. In this fully adjusted model, the explained variance across the physical limitations and disability measures was 68%-81% for the ICC (between-person) and 25%-43% for the 1-ICC (within-person) values.

Table 19d. Random Effect Models for all Outcomes and High-density Lipoprotein Cholesterol.

	ADLs		IADLs		Grip	
FIXED EFFECTS	b	SE	b	SE	b	SE
Intercept	4.27***	0.32	3.77***	0.25	39.04***	0.80
Time	0.07	0.11	-0.08	0.19	-1.12	0.69
HDL-C	-0.44**	0.16	-0.06	0.12	-0.31	0.38
HDL-C*Time	0.10	0.11	0.02	0.09	0.23	0.33
RANDOM EFFECTS						
Variance of the intercept	3.03***	0.21	1.41***	0.13	15.88***	1.08
Variance of time	0.41***	0.10	0.31***	0.07	8.48***	0.71
Covariance of intercept, time	0.15	0.11	0.11	0.13	0.04	0.06
Residual variance	2.75***	0.11	2.26***	0.09	14.39***	0.57
-2 log likelihood	22937.3		21134.6		29566	

*Note: *p<.05; **p<.01; ***p<.001; HDL-C=High density-lipoprotein cholesterol; Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML. Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Interactions

In order to examine the second aim of the study, which was to examine whether the previous significant lipid associations with their respective outcomes were moderated by sex or cognitive disability, REM models were carried out with additional interaction terms. To assess moderation on the cross-sectional associations, separate two-way-interaction terms were included (e.g. sex*lipid, cognitive disability*lipid). Furthermore, to examine whether the association between the lipoprotein and the outcomes was moderated by sex or cognitive disability across the three study waves, the REM model included three-way interaction terms (e.g. sex*lipid*time, cognitive disability*lipid*time).

Total Cholesterol. Tables 20a and 20b present the models testing the moderation of sex and cognitive disability on the relationship between lower TC and greater ADL disability. With respect to the cross-sectional results, there was no statistical significant moderation by sex. However, cognitive disability did moderate the association between TC and ADLs. With regard to the longitudinal results, none of the sex or cognitive disability interactions were statistically significant, which indicated that the association between baseline TC scores and the rate of ADL decline over time was not moderated by sex or cognitive disability.

Triglycerides. Tables 21a and 21b present the models testing the moderation of sex and cognitive disability on the relationship between TG and grip function. There was no statistical significant moderation by sex or cognitive disability for either the cross-sectional or the longitudinal associations between higher TG and better grip function.

Table 20a. Models for Moderation of Sex on the Association between TC and Activities of Daily Living.

	ADLs	
FIXED EFFECTS	b	SE
Intercept	4.29***	0.32
Time	0.08	0.22
TC	-0.16***	0.04
TC*Sex	-0.01	0.04
TC*Sex*Time	-0.006	0.03
RANDOM EFFECTS		
Variance of the intercept	3.02***	0.20
Variance of time	0.44***	0.10
Covariance of intercept, time	0.15	0.11
Residual variance	2.75***	0.11
-2 log likelihood	22941.5	

*Note: *p<.05; **p<.01; ***p<.001; ADLs= Activities of Daily Living; TC=Total cholesterol. Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML; Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Table 20b. Models for Moderation of Sex and Cognitive Disability on the Association between TC and Activities of Daily Living.

	ADLs	
FIXED EFFECTS	b	SE
Intercept	4.27***	0.31
Time	0.08	0.22
TC	-0.08	0.04
TC*Cognitive Disability	-0.40***	0.09
TC*Cognitive Disability*Time	0.14	0.08
RANDOM EFFECTS		
Variance of the intercept	2.94***	0.20
Variance of time	0.44***	0.10
Covariance of intercept, time	0.16	0.11
Residual variance	2.75***	0.11
-2 log likelihood	22922.1	

*Note: *p<.05; **p<.01; ***p<.001; ADLs= Activities of Daily Living; TC=Total cholesterol. Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML; Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Table 21a. Models for Moderation of Sex on the Association between TG and Grip Function.

Grip		
FIXED EFFECTS	b	SE
Intercept	20.59***	0.77
Time	1.25	0.68
TG	0.26*	0.13
TG*Sex	0.13	0.12
TG*Sex*Time	0.09	0.11
RANDOM EFFECTS		
Variance of the intercept	15.77***	1.07
Variance of time	8.47***	0.71
Covariance of intercept, time	0.03	0.06
Residual variance	14.38***	0.56
-2 log likelihood	29229.8	

*Note: *p<.05; **p<.01; ***p<.001; TG=Triglycerides. Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML; Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disabilitv.*

Table 21b. Models for Moderation of Cognitive Disability on the Association between TG and Grip Function.

Grip		
FIXED EFFECTS	b	SE
Intercept	20.53***	0.77
Time	1.30	0.68
TG	0.18	0.14
TG*Cognitive Disability	0.54	0.32
TG*Cognitive Disability*Time	-0.28	0.28
RANDOM EFFECTS		
Variance of the intercept	15.77***	1.07
Variance of time	8.45***	0.71
Covariance of intercept, time	0.04	0.06
Residual variance	14.37***	0.56
-2 log likelihood	29229.6	

*Note: *p<.05; **p<.01; ***p<.001; TG=Triglycerides. Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML; Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

High-density Lipoprotein Cholesterol. Tables 22a and 22b display the results of the models testing the moderation of sex and cognitive disability on the relationship between HDL-C and ADLs. None of the cross sectional or longitudinal interactions were statistically significant for any of the moderators. This indicated that the significant cross-sectional association between lower HDL-C and more ADL disability was not dependent on sex or cognitive disability.

Table 22a. Models for Moderation of Sex on the Association between HDL-C and Activities of Daily Living.

	ADLs	
FIXED EFFECTS	b	SE
Intercept	4.24***	0.32
Time	0.06	0.22
HDL-C	-0.49**	0.16
HDL-C*Sex	-0.21	0.16
HDL-C*Sex*Time	-0.11	0.11
RANDOM EFFECTS		
Variance of the intercept	3.03***	0.20
Variance of time	0.44***	0.10
Covariance of intercept, time	0.15	0.11
Residual variance	2.75***	0.11
-2 log likelihood	22932.8	

*Note: *p<.05; **p<.01; ***p<.001; ADLs=Activities of Daily Living; HDL-C=High-density lipoprotein cholesterol. Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML; Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Table 22b. Models for Moderation of Sex and Cognitive Disability on the Association between HDL-C and Activities of Daily Living.

	ADLs	
FIXED EFFECTS	b	SE
Intercept	4.27***	0.32
Time	0.06	0.22
HDL-C	-0.46**	0.17
HDL-C*Cognitive Disability	0.13	0.34
HDL-C*Cognitive Disability*Time	-0.29	0.28
RANDOM EFFECTS		
Variance of the intercept	3.04***	0.20
Variance of time	0.44***	0.10
Covariance of intercept, time	0.15	0.11
Residual variance	2.75***	0.11
-2 log likelihood	22936.2	

*Note: *p<.05; **p<.01; ***p<.001; ADLs=Activities of Daily Living; TC=Total cholesterol. Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML; Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Stratification

Since cognitive disability moderated the association between ADLs and TC, stratification by cognitive disability was carried out. There were 1725 subjects without cognitive disability and 474 with cognitive disability in this analysis. The mean age for those without cognitive disability was 74.8 (SD=8.3) and for those cognitively disabled was 85.9 (SD=10.0). Table 23 presents the lipid distribution by cognitive status. Overall, participants with cognitive disability had lower lipid levels (all p's<.001). Table 24 presents the stratification of the mixed effects models that were carried out to determine if the association between ADL disability and TC for participants with and without cognitive disability differed. The relationship between low TC scores and more ADL disability was only significant for the cross-sectional association on participants with

cognitive disability, but not the longitudinal association. In other words, at baseline, low TC scores were related to greater ADL disability mainly in the presence of cognitive disability.

Table 23. Frequency Distribution of Lipoproteins by Cognitive Status.

	TC	LDL-C	TG	HDL-C
	Means in mmol/l (SD)			
No Cognitive disability	5.59 (8.3)	9.68 (29.5)	1.83 (1.0)	1.15 (0.33)
Cognitive disability	5.31 (1.3)	6.80 (20.8)	1.61 (0.9)	1.19 (0.4)

Note: TC=total cholesterol; LDL=low-density lipoprotein cholesterol; TG=triglycerides; HDL-C= high-density lipoprotein cholesterol; mmol/l=millimole per liter SD=Standard deviation.

Table 24. Models Stratifying by Cognitive Disability the Association between TC and Activities of Daily Living.

	ADLs for No Cognitive Disability		ADLs for Cognitive Disability	
FIXED EFFECTS	b	SE	b	SE
Intercept	1.72***	0.33	5.37**	1.82
Time	-0.05	0.03	-0.22	1.29
TC	-0.05	0.03	-0.47**	0.15
TC*time	-0.02	0.03	0.12	0.11
RANDOM EFFECTS				
Variance of the intercept	1.26***	0.12	9.76***	1.29
Variance of time	0.60***	0.07	0.34	0.57
Covariance of intercept, time	0.18	0.09	-0.11	0.31
Residual variance	1.73***	0.07	6.07***	0.69
-2 log likelihood	17278.1		4476.2	

*Note: *p<.05; **p<.01; ***p<.001.TC=Total cholesterol. Values based on SAS PROC Mixed. Entries show parameter estimates (b) with standard errors (SE). Estimation Method = ML; Model adjusting for age, sex, education, perceived economic situation, hypertension, cholesterol medications, HbA1c, smoking, exercise, coronary heart disease, stroke, arthritis, osteoporosis, pulmonary problems, cancer, psychiatric/depression, Insomnia, cognitive disability.*

Discussion

The present study examined the longitudinal association between physical function and TC, LDL-C, TG and HDL-C taking into account demographics, cardiovascular risk factors and comorbidity inclusive of cognitive disability in adults over the age of 60 participating in the CRELES study. Physical function was measured as disability and functional limitations. In this population sample, it was found that there was a cross-sectional association between lower TC, and lower HDL-C scores specifically, and higher ADL disability after adjusting for all covariates. These findings are partly supportive of previous research studies evaluating comparable outcomes [44,86,87,137,157,158,234].

Canavan and colleagues looked at the cross-sectional association between both vascular risk factors and established cardiovascular diseases and disability in community-dwelling adults from West Ireland and also found that older adults with lower levels of HDL-C had more functional impairment even after full adjustment for demographics, cardiovascular risk factors and comorbidity [86]. Furthermore, results from the NonaSantfeliu Study in Spain studying the association between HDL-C and physical and cognitive performance in adults over the age of 90 with a low level of education showed a 1.03 times better ADL performance in those with normal baseline HDL-C ($p<.006$) [137]. A study performed in institutionalized older adults also described severe disability associated with low levels of TC and HDL-C [157]. Moreover, Landi and colleagues (2007) examined older adults from the ilSIRENTE study and reported that higher HDL-C levels were associated with better physical performance. These results

support the study findings and suggest that maintaining optimal HDL-C levels into very old age may be protective of physical function. However, contrary associations have also been described. Welmer and colleagues (2014) reported that older adults with high TC had more functional dependence; however, this association was no longer significant after adjusting for demographics and cardiovascular risk factors (p=.087).

Although this study identified significant cross-sectional effects between TC and ADL disability, it did not identify any longitudinal effects, whereby changes in the functional outcomes would be a function of baseline lipoprotein scores. Nevertheless, a study from the Longitudinal Aging Study Amsterdam (LASA) did describe time effects. Their study assessed the association between TC and a 3-year decline in performance and found that older women with lower baseline TC levels had 11.1% more functional decline than those with higher TC; however, not among males [44].

Previous research has reported using hand grip strength as a reliable and valid proxy for muscle strength [158] and also as a health and/or disability predictor [275-277]. The current study found that older adults with higher levels of TG performed significantly better in grip strength function. These results are in conflict with those found in a population based sample from the Hertfordshire Cohort Study where higher fasting TG yielded a 0.5 standard deviation decrease in grip strength after adjusting for covariates [278]. Similar findings were observed by a very recent study conducted on data collected between 2002 and 2009 among older Japanese men and women where no grip strength associations were observed for those with elevated TGs [276]. In the current study, no other significant associations were found between the other lipoproteins (e.g. TC, LDL-C, and HDL-C) and grip strength. However, this lack of association disagrees

with other recent studies who have observed significant associations between decreased levels of TC in males with lower grip strength [279], or low HDL-C levels associated with declines in grip strength [276].

There were no additional associations observed between lipoproteins and physical function among older Latino adults in this study. One possible explanation for the lack of associations may perhaps be an over-adjustment of the models. All clinically variables related to dyslipidemia and disability were taken into account without discriminating variables that may have been confounds versus those that may have been collinear with the lipoprotein measures. Although the full model had the best fit, inclusion of potential mediators at level-1 could be considered over-adjustment [280]. Another possibility may be the origin of the data. Costa Rica ranks among the top countries in Latin America on longevity [281] and the country's health status is often compared to that of developed nations. Additionally, the CRELES study sampled 100% of older adults over the age of 95 from the Nicoya area, a north-western region of Costa Rica globally known for exceptional longevity, also known as a blue zone [282]. Nicoyans, specifically males, have lower cardiovascular risk markers and less disabilities than their counterparts in other areas of the country [283]. This perhaps, may have influence the overall analysis and caused an underestimate of the associations sought.

When sex and cognitive disability were tested as moderators in the significant associations between lipoproteins and physical function, only cognitive disability had a two-way interaction between lower levels of TC and ADL disability. Stratification by cognitive status showed that the association between lower levels of TC and more ADL disability was only significant for those with cognitive disability. It has been theorized

that oxidized cholesterol is the driving force behind the development of cognitive problems. This is a reasonable theory providing the brain's lipid content is high and thus very vulnerable to oxidation by free radicals. A recent review of the literature describes how despite pathological advancements, it is still unclear whether the oxidative stress is the cause or the consequence of dementia; furthermore other proposed causal mechanisms for the association between TC and cognitive disability such as inflammation cannot be ruled out [284].

However, the literature has been consistent in reporting cognitive disability associated with the disablement process among older adults. Cognitive decline and/or impairment are highly correlated with functional decline [14,258,259]. A recent study among older South Koreans participating in the Suwon Longitudinal Aging Study (SLAS) tested whether cognitive disability was associated with the rate of change in physical functional status (inclusive of ADLs) and found that older adults with cognitive disability were 0.6 times more likely to have a disability at baseline and 1.4 times more likely to have a disability at year 2 even after adjusting for potential confounders [258]. However, contradicting reports have been published regarding the association between TC and cognitive disability and/or dementia. Many agree that lower TC levels are associated with cognitive decline and higher risk of dementia in older adults [124,161,285]. A recent meta-analysis showed inconsistent results among the studies analyzed; although 3 out of the 5 studies looking at TC and cognitive decline found no association, 2 of the 5 studies reviewed did find high levels of TC associated with a reduced risk of cognitive decline [136]. To the author's knowledge, no other study has reported the moderating effect of cognitive disability on the association between TC and ADL disability.

This study examined the association between lipids and physical function in a population study of older Latino adults participating in CRELES. The study covered 59% of the Costa Rican territory, making it generalizable for the entire population of Costa Rican older adults. Despite the robustness of a population study, several limitations need be mentioned. First of all, given the nature of the study, extrapolation of results outside the country may be limited. The Costa Rican economy ranks in the average range compared to other Latin American countries, many social determinants of health places the country among the highest in the continent [286] possibly hampering comparability with Latin countries with lower economies. A recent study compared the association between several cardiovascular risk factors such as lipids, with education (a proxy for SES) among older adults participating in the CRELES and the US National Health and Nutrition Examination Survey (NHANES) and found little evidence for the association; suggesting that the biological underpinnings of CVD risk factors rests beyond racial and SES factors [287]. Crimmins and colleagues [96] examined biological risk profiles by race, ethnicity and nativity among adults over the age of 40 from the National Health and Nutrition Examination Surveys (1999-2002) from the United States and found that although US Hispanics had higher average biological risk indicator scores (including metabolic risk factors such as TC, HDL-C, and glycated hemoglobin) than non-Hispanic Whites, once socioeconomic status (SES) was accounted for in the models, their high-risk levels in biological systems did not differ. This suggests that if SES is properly accounted for in other studies, comparison across cultures may be somewhat valid.

In addition, lipoprotein levels may be reflective of certain dietary patterns not accounted for in this analysis. Lipids were only measured at baseline and this may have underestimated the association between lipids and physical function across time. Moreover, lipids accounted for were analyzed in mmol/l; normalizing the values to a z-score, may have made all the lipid effects on the same outcome more comparable. Furthermore, many of the variables used in the analysis are self-reported, so these should be interpreted with some caution. Most comorbidity questions asked the participant if in the last 2 years they were told by a physician they had a specific condition; this may have introduced some recall bias in the data. Another obvious limitation is the lack of subclinical cardiovascular disease measures, such as radiographic atherosclerotic measures, which may have reflected better the cardiovascular status of participants. Additionally, some may find the use of the maximum value for grip strength of the dominant hand a limitation. It has been reported by some that the mean measure is the most reliable [288]. However, the maximum grip value has been previously used in population studies [263,289]. A recently study measured the prognostic value of grip strength and health outcomes across several countries and they reported that maximum grip strength was a strong indicator and a moderately strong predictor of cardiovascular mortality and incident cardiovascular disease respectively across country-income strata [263]. A last valid limitation in this study is the measurement of cognitive disability. A small number of questions are used to evaluate cognition in the CRELES study, which may not fully capture cognitive changes over the study period. A quarter of respondents were proxies, which may have affected results via inaccurate reporting.

This study was able to identify potential specific lipoproteins associated with physical function in an older Latino population, although lipoprotein scores did not appear to be associated with change in function over the three measurements. Furthermore, TC seemed to be of particular importance among people with cognitive disability. Further aging research should focus in understanding lipid metabolism in aging populations and its implications in maintaining physical function as means of sustaining independence and a high quality of life. Studying the association of lipoproteins, cardiovascular risk factors and comorbidity with physical function in older adults for longer periods of time may better determine a causal association. Future studies ought to consider analyzing the association between lipoproteins and physical function with cardiovascular risk factors and comorbidity as composite covariate scores. Research shows that when health factors are aggregated in the old, these are more indicative of physical disability [13,87,264]. The Zutphen Elderly Study from Netherlands, used an aggregate of cardiovascular risk factors (BMI, smoking status, hypertension, serum TC and diabetes) in older adults living in the community and found that a high cardiovascular risk score was predictive of functional disability, specifically mobility-related disability in men [154]. Another study among older Chinese also found that the odds of disability increased when aggregated vascular risk factors were considered [87]. Further, Van Peet and colleagues concluded that cardiovascular risk factors even at advanced ages are prognostic of functional decline [13].

Additionally, analyzing physical function in sex-stratified cohorts may be more indicative for specific health outcomes given the fact that in general, men's physical function had a very different life trajectory than that of females for older cohorts,

especially in developing countries like Costa Rica. Comparing the association of lipids and physical function across other Latino populations may better identify the heterogeneity of the associations across Latino subpopulations as well as within subpopulations. Often the research has collapsed Latinos populations into one category, such an approach may underestimate unique mechanisms that may explain associations. Future interventional approaches should be designed to adequately address physical functioning limitations across all Latino groups. In addition, further molecular and/or cell biological studies should look into the overall metabolic changes that are happening from mid to older ages, which are responsible for the underlying association between lipoproteins and health outcomes.

As the population continues to age and the demographic shift becomes more evident, finding ways to prevent or postpone disability becomes imperative. If the positive association between high TC and HDL-C and better physical function found in this study is replicated in intervention trials treating cardiovascular risk factors, lipids may become an easy predictive marker of functional health for aging cohorts and especially for those with cognitive disability. Lipoproteins along with cardiovascular risk factors may become easily accessible modifiable targets to help compress morbidity, decrease healthcare burden and slow functional decline for future aging populations.

CHAPTER 4: GENERAL DISCUSSION OF LIPOPROTEINS AND HEALTH OUTCOMES

Cardiovascular, cognitive and functional health remains major determinants of quality of life for aging populations. These health domains often coexist leading to disability and to what is refer to as geriatric syndrome [290]. Despite important declines in mortality from CVD in the last decades, the burden of disease remains high, especially for older adults [56]. Dyslipidemia is an important risk factor for cardiovascular disease and recent research lean towards an influence in mobility as well. This dissertation was conducted with the purpose of addressing the possible relationships between lipoproteins and cognitive and physical function among older adults using two secondary data sets from populations in which these issues had not been addressed. This chapter summarizes the main findings of the two studies with a brief discussion. In addition, limitations of the dissertation and future directions are addressed.

The first study addressed the association between lipoproteins, TC, LDL-C, TG and HDL-C and cognitive function among older cognitively normal adults from the Czech Republic. This study offered novel information in several aspects. First, it addressed cognitive function through a composite cognitive score as well as accounting for individual cognitive domains. Second, it described sex difference in the mentioned associations, which allowed for identification of significant observations that would have not been otherwise known. Third, cognitive function studies are scarce among older

adults, most of the literature focuses on cognitive decline or dementia. Findings of this first study showed significantly better cognitive function among older adults with high HDL-C and lower TG levels. Furthermore, older adults with higher levels of HDL-C performed better in visuospatial function and attention and working memory tests. Moreover, when APOE ε4 allele was accounted for in the statistical models, high levels of HDL-C remained significantly associated with composite cognitive measures, visuospatial function and attention and working memory. These results are consistent with previous studies accounting for TG [210 211 85] and HDL-C [49,85,127,137,213], even after adjusting for APOE ε4 allele [45,48,85,165]. Further interaction analysis indicated APOE ε4 allele as a moderator in the above-mentioned associations. DeFrias and colleagues (2007) similarly observed that TG moderated the effect of the APOE ε4 allele on the memory of older adults. Furthermore, stratification analysis in the current study by carriers and non-carriers of the gene revealed that the associations were only significant for carriers of the APOE ε4 allele. Further genetic analyses are needed to explore these interactions.

Based on the health-related quality of life conceptual model of Wilson and Cleary (1985), additional determinants of health must be addressed as to further evaluate the association between lipoproteins and the overall health of the older adult. Social determinants of health such as cultural or social and economic factors seem to play a major role in the associations with CVD [291]. Older Latinos are one of the fastest growing minority in the United States and in all Latin America. Thus, it is important to understand the association between lipids and health outcomes across diverse Latino

subpopulations, such as the older native Latino populations to examine whether similar underlying mechanisms account for risk of disability across these subpopulations.

Therefore, the second study of this dissertation examined the association between lipoproteins and physical function among older Latinos. This study used a population dataset of older adults residing in Costa Rica. Results showed lower levels of TC and HDL-C associated with ADL disability, but not across time. This agrees with three previous studies in very different populations [86,137,157,158]. Furthermore, this study found higher levels of TG related to better left grip function. Interaction analysis indicated that cognitive disability moderated the association between TC and ADLs and further stratification revealed that the association was only pertinent for participants with cognitive disability. Independent of cardiovascular risk factors and an extensive list of comorbidities, older Latino adults living in the community with higher levels of TC, TG and HDL-C were associated with better physical function outcomes. To the author's knowledge, this was the first known analysis of the association between lipids and physical function in a Latino population and the first study to provide the within and between-person variances for each of the outcomes, which is important information not provided in other studies.

Serum cholesterol is known to be essential in the aging process for cell division, brain and central nervous function as well as for numerous biological immune processes [26]. However, a buildup of esterified forms of circulating cholesterol, or oxidized cholesterol not only forms plaque and vascular disease [292,293] but may also lead to cognitive deterioration [284]. On the other hand, HDL-C has been known to battle oxidation, inflammation, endothelial dysfunction and help modulate the immune function

[294]. Higher levels of HDL-C are not only associated with CVD protection [1,47] but have also been associated with better cognitive performance [45,48,49] as well as physical function [158]. Results found in this dissertation support these previous findings.

Limitations

Despite the novel aspects of both studies, several limitations ought to be addressed. Due to the cross-sectional nature of the first study looking at the association between lipoproteins and cognitive function, it is not possible to indicate whether lipoproteins relate to change in cognitive functioning. Further, the sample was not racially or ethnically diverse and was overall highly educated. Inclusion of some caregivers in the analysis cannot be ruled out and this may have introduced a healthy bias effect, or the contrary, overloaded caregivers may reflect higher biomarker load. The data also lacked some important socio-demographic variables such as income, medical comorbidities and medications, which limit the generalizability of the results. Plus allocation of the measurement instruments may not fully reflect or encompass each specific cognitive domain. Additionally, the timing of biomarkers collection was not ideal and thus may not reflect a factual association with cognition. In the second study, despite being a representative population longitudinal study, three time points for data collection in a five year period may not have been ideal and/or suffice to either observe metabolic and functional changes in this older population. In very old cohorts data collection may need to be adjusted (narrower windows) in order to decrease reporting bias and see more acute associations in the latter part of life. Both studies may also be subject to survival and participant bias. The samples may have been selectively

healthier than the general population. Last, both studies used secondary data analysis, which by nature are subject to a number of inherent limitations such as appropriateness of the data and quality issues.

Study Implications

Despite the standing limitations in this dissertation, important contributions were made to the literature. Both studies showed important associations between similar lipoproteins with cognitive and physical outcomes among older adults of very diverse backgrounds. Higher levels of TC and HDL-C yielded healthier outcomes in both studies. Maintaining optimal lipids throughout the lifespan may prove to be a compelling preventive measure for maintenance of cardiovascular and physical health. Addressing these combined health outcomes may support the compression of disability, increased the overall quality of life for older adults and may help guide clinicians in predicting health decline and prompt age-appropriate interventions to preserve health for as long as possible.

Conclusion and Future Directions

Dyslipidemia is a major cardiovascular disease risk factor that shares some pathophysiological pathways between cognitive and physical function. This dissertation work was undertaken to assess how lipids are associated to cognitive and physical performance in adults over the age of 60. Identifying shared mechanisms of these

diseases, such as the important role of TC, TG and HDL-C in both cognitive and physical function as seen in this dissertation, may provide the foundation to design future age appropriate interventions, optimize clinical care and perhaps in the future advocate for policy changes with evidence-based data. Nonetheless, several questions beyond the scope of this dissertation remain unanswered. The underlying pathways/mechanisms that explain the association between lipoproteins and cognitive/functional outcomes remain unclear. Although an interactive concentric model of analysis has been proposed as an ideal mechanism to address multifactorial conditions in older adults [290], no conceptual model has been designed to assist in the development of future studies to identify/elucidate the potential underlying mechanisms. However, this might be a beneficial first step to understanding the association. Future studies should also try to address these associations in more racially and ethnically inclusive populations accounting for additional psychosocial, economical and physiological constructs, as well as quality of life measures, which may be mediating some of the associations. Including ethnically diverse samples in scientific investigations may better validate the associations sought, increase external validity, and better address outcome differences/disparities. The question also remains as to how high or how low lipoproteins levels should be among different older age groups to obtain cognitive and physical function benefits. Future studies should try to address these associations using: (a) age groups, (b) quartiles or quintiles of lipid levels and (c) quadratic analysis to determine non-linear relationships. Furthermore, studies should include common genetic components, such as the APOE gene.

LIST OF REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the american heart association. *Circulation.* 2015;131(4):e29-e322.

2. Ortman J, Velkoff V, Hogan H. *An Aging Nation: The Older Population in the United States. Population Estimates and Projections.* U.S, Department of Commerce. Economics and Statistics Administration;2014. P25-1140.

3. Colby S, Ortman J. *Projections of the Size and Composition of the U.S. Population: 2014 to 2060.* Washington, DC: U.S. Census Bureau;2014.

4. 2015 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2015;11(3):332-384.

5. Disability Characteristics. American Community Survey 1-year Estimates. Source: U.S. Census Bureau; 2013.

6. Chaves PH, Kuller LH, O'Leary DH, Manolio TA, Newman AB. Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. *Am. J. Geriatr. Cardiol.* 2004;13(3):137-151.

7. Wang M, Jiang L, Monticone RE, Lakatta EG. Proinflammation: the key to arterial aging. *Trends Endocrinol. Metab.* 2014;25(2):72-79.

8. Lakatta E, Wang M, Najjar S. Arterial aging and subclinical arterial disease are fundamentally intertwined at macroscopic and molecular levels. 2009;93(3):583-604.

9. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation.* 2002;105(9):1135-1143.

10. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Atherosclerosis.* 2012;223(1):1-68.

11. Libby P. Inflammation in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 2012;32(9):2045-2051.

12. Nation D, Wierenga C, Delano-WOOD L, et al. Elevated pulse pressure is associated with age-related decline in language ability. *J. Int. Neuropsychol. Soc.* 2010;16(5):933-938.

13. van Peet PG, Drewes YM, de Craen AJ, Westendorp RG, Gussekloo J, de Ruijter W. Prognostic value of cardiovascular disease status: the Leiden 85-plus study. *Age (Dordrecht, Netherlands).* 2013;35(4):1433-1444.

14. Gure TR, Langa KM, Fisher GG, Piette JD, Plassman BL. Functional limitations in older adults who have cognitive impairment without dementia. *J. Geriatr. Psychiatry Neurol.* 2013;26(2):78-85.

15. Dantas AP, Jimenez-Altayo F, Vila E. Vascular aging: facts and factors. *Front. Physiol.* 2012;3:325.

16. Laurent S. Defining vascular aging and cardiovascular risk. *J. Hypertens.* 2012;30 Suppl:S3-8.

17. Stauffer ME, Weisenfluh L, Morrison A. Association between triglycerides and cardiovascular events in primary populations: a meta-regression analysis and synthesis of evidence. *Vascular health and risk management.* 2013;9:671-680.

18. Arsenault BJ, Rana JS, Stroes ES, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. *J Am Coll Cardiol.* 2009;55(1):35-41.

19. Anderson TJ, Mancini GB, Genest J, Jr., Gregoire J, Lonn EM, Hegele RA. The New Dyslipidemia Guidelines: What Is the Debate? *Can. J. Cardiol.* 2014.

20. Liu HH, Li JJ. Aging and dyslipidemia: a review of potential mechanisms. *Ageing Res Rev.* 2015;19:43-52.

21. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA.* 1995;273(1):59-65.

22. Higgins C. *Understanding Laboratory Investigations : A Text for Nurses and Other Health Care Professionals.* Blackwell Science; 2000.

23. Benfield R. *Biochemistry.* Global Media; 2009.

24. Powar CB, Chatwal GR. *Biochemistry [electronic resource].* 2nd ed: New Delhi : Himalaya Publishing House; 2008.

25. Cullis PR, Fenske DB, Hope MJ. Chapter 1 Physical properties and functional roles of lipids in membranes. In: Dennis EV, Jean EV, eds. *New Comprehensive Biochemistry.* Vol Volume 31: Elsevier; 1996:1-33.

26. McLean KJ, Hans M, Munro AW. Cholesterol, an essential molecule: diverse roles involving cytochrome P450 enzymes. *Biochemical Society transactions.* 2012;40(3):587-593.

27. Cox R, García-Palmieri M. Cholesterol, Triglycerides, and Associated Lipoproteins In: Walker H, Hall W, Hurst J, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston: Butterworths1990.

28. Warnick GR, Knopp RH, Fitzpatrick V, Branson L. Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. *Clin. Chem.* 1990;36(1):15-19.

29. Rodriguez CJ, Daviglus ML, Swett K, et al. Dyslipidemia patterns among Hispanics/Latinos of diverse background in the United States. *Am. J. Med.* 2014;127(12):1186-1194.e1181.

30. Ray KK, Kastelein JJ, Matthijs Boekholdt S, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. *European heart journal.* 2014.

31. Kenik J, Jean-Jacques M, Feinglass J. Explaining racial and ethnic disparities in cholesterol screening. *Preventive medicine.* 2014.

32. Pasternak RC. Report of the Adult Treatment Panel III: the 2001 National Cholesterol Education Program guidelines on the detection, evaluation and treatment of elevated cholesterol in adults. *Cardiology clinics.* 2003;21(3):393-398.

33. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486-2497.

34. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA.* 2007;298(7):776-785.

35. Emerging Risk Factors C, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA.* 2009;302(18):1993-2000.

36. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2935-2959.

37. Preiss D, Kristensen SL. The new pooled cohort equations risk calculator. *Can. J. Cardiol.* 2015;31(5):613-619.

38. Salthouse T. Relations between age and cognitive functioning. *Major Issues in Cognitive Aging*. Ipswich, MA: Oxford : Oxford University Press; 2010:pp. 3-34.

39. Elias PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA. Serum cholesterol and cognitive performance in the Framingham Heart Study. *Psychosomatic medicine.* 2005;67(1):24-30.

40. Panza F, D'Introno A, Colacicco A, et al. Lipid metabolism in cognitive decline and dementia. *Brain Res Rev.* 2006;51(2):275-292.

41. Mielke MM, Zandi PP, Sjogren M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology.* 2005;64(10):1689-1695.

42. Schreurs B. The effects of cholesterol on learning and memory. *Neurosci. Biobehav. Rev.* 2010;34(8):1366-1379.

43. Lippi G, Sanchis-Gomar F, Montagnana M. Biological markers in older people at risk of mobility limitations. *Curr. Pharm. Des.* 2014;20(19):3222-3244.

44. Schalk BW, Visser M, Deeg DJ, Bouter LM. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam. *Age Ageing.* 2004;33(3):266-272.

45. Atzmon G, Gabriely I, Greiner W, Davidson D, Schechter C, Barzilai N. Plasma HDL levels highly correlate with cognitive function in exceptional longevity. *J. Gerontol. Ser. A-Biol. Sci. Med. Sci.* 2002;57(11):M712-M715.

46. de Frias C, Bunce D, Wahlin A, et al. Cholesterol and triglycerides moderate the effect of apolipoprotein E on memory functioning in older adults. *The journals of gerontology. Series B, Psychological sciences and social sciences.* 2007;62(2):P112-118.

47. Eren E, Yilmaz N, Aydin O. High density lipoprotein and it's dysfunction. *The open biochemistry journal.* 2012;6:78-93.

48. van den Kommer T, Dik M, Comijs H, Jonker C, Deeg D. The role of lipoproteins and inflammation in cognitive decline: Do they interact? *Neurobiology of Aging.* 2012;33(1):196.e191-196.e112.

49. van Exel E, de Craen AJ, Gussekloo J, et al. Association between high-density lipoprotein and cognitive impairment in the oldest old. *Annals of Neurology.* 2002;51(6):716-721.

50. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *European heart journal.* 2014.

51. Frank AT, Zhao B, Jose PO, Azar KM, Fortmann SP, Palaniappan LP. Racial/ethnic differences in dyslipidemia patterns. *Circulation.* 2014;129(5):570-579.

52. Kataoka Y, St John J, Wolski K, et al. Atheroma progression in hyporesponders to statin therapy. *Arterioscler. Thromb. Vasc. Biol.* 2015;35(4):990-995.

53. Deano R, Sorrentino M. Lipid effects of antihypertensive medications. *Curr Atheroscler Rep.* 2012;14(1):70-77.

54. Krone W, Nagele H. Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am. Heart J.* 1988;116(6 Pt 2):1729-1734.

55. Whayne TF, Mukherjee D. Medications not intended for treatment of dyslipidemias and with a variable effect on lipids. *Curr. Pharm. Des.* 2014.

56. Go A, Mozaffarian D, Roger V, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation.* 2014;129(3):e28-e292.

57. Tilvis RS, Valvanne JN, Strandberg TE, Miettinen TA. Prognostic significance of serum cholesterol, lathosterol, and sitosterol in old age; a 17-year population study. *Ann. Med.* 2011;43(4):292-301.

58. Fontana L, Klein S. Aging, adiposity, and calorie restriction. *JAMA.* 2007;297(9):986-994.

59. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol.* 2014;63(8):747-762.

60. Fontana L, Addante F, Copetti M, et al. Identification of a metabolic signature for multidimensional impairment and mortality risk in hospitalized older patients. *Aging Cell.* 2013;12(3):459-466.

61. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. *J Am Coll Cardiol.* 2014;63(19):1935-1947.

62. Surakka I, Horikoshi M, Magi R, et al. The impact of low-frequency and rare variants on lipid levels. *Nat. Genet.* 2015;47(6):589-597.

63. Maxwell TJ, Ballantyne CM, Cheverud JM, Guild CS, Ndumele CE, Boerwinkle E. APOE modulates the correlation between triglycerides, cholesterol, and CHD through pleiotropy, and gene-by-gene interactions. *Genetics.* 2013;195(4):1397-1405.

64. Pablos-Mendez A, Mayeux R, Ngai C, Shea S, Berglund L. Association of apo E polymorphism with plasma lipid levels in a multiethnic elderly population. *Arterioscler. Thromb. Vasc. Biol.* 1997;17(12):3534-3541.

65. Zende PD, Bankar MP, Kamble PS, Momin AA. Apolipoprotein e gene polymorphism and its effect on plasma lipids in arteriosclerosis. *Journal of clinical and diagnostic research : JCDR.* 2013;7(10):2149-2152.

66. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis.* 1988;8(1):1-21.

67. Suwalak T, Srisawasdi P, Puangpetch A, et al. Polymorphisms of the ApoE (Apolipoprotein E) gene and their influence on dyslipidemia in HIV-1-infected individuals. *Jpn. J. Infect. Dis.* 2015;68(1):5-12.

68. Gronroos P, Raitakari OT, Kahonen M, et al. Influence of apolipoprotein E polymorphism on serum lipid and lipoprotein changes: a 21-year follow-up study from childhood to adulthood. The Cardiovascular Risk in Young Finns Study. *Clinical chemistry and laboratory medicine : CCLM / FESCC.* 2007;45(5):592-598.

69. Weissglas-Volkov D, Pajukanta P. Genetic causes of high and low serum HDL-cholesterol. *J. Lipid Res.* 2010;51(8):2032-2057.

70. Novella S, Dantas AP, Segarra G, Medina P, Hermenegildo C. Vascular aging in women: is estrogen the fountain of youth? *Front. Physiol.* 2012;3:165.

71. Lopes RA, Neves KB, Carneiro FS, Tostes RC. Testosterone and vascular function in aging. *Front. Physiol.* 2012;3:89.

72. Aiman U, Najmi A, Khan RA. Statin induced diabetes and its clinical implications. *J. Pharmacol. Pharmacother.* 2014;5(3):181-185.

73. Marengoni A, Pasina L, Concoreggi C, et al. Understanding adverse drug reactions in older adults through drug-drug interactions. *Eur. J. Intern. Med.* 2014;25(9):843-846.

74. John SG, Thorn J, Sobonya R. Statins as a potential risk factor for autoimmune diseases: a case report and review. *Am J Ther.* 2014;21(4):e94-96.

75. Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia: a clinical review. *JAMA.* 2014;312(11):1136-1144.

76. Gobal FA, Mehta JL. Management of dyslipidemia in the elderly population. *Ther. Adv. Cardiovasc. Dis.* 2010;4(6):375-383.

77. Warsch JR, Wright CB. The aging mind: vascular health in normal cognitive aging. *J Am Geriatr Soc.* 2010;58 Suppl 2:S319-324.

78. Pavlik VN, Hyman DJ, Doody R. Cardiovascular risk factors and cognitive function in adults 30–59 years of age (NHANES III). *Neuroepidemiology.* 2005;24(1-2):42-50.

79. Tamosiunas A, Baceviciene M, Reklaitiene R, et al. Cardiovascular risk factors and cognitive function in middle aged and elderly Lithuanian urban population: results from the HAPIEE study. *BMC Neurol.* 2012;12:149.

80. O'Donnell M, Teo K, Gao P, et al. Cognitive impairment and risk of cardiovascular events and mortality. *European heart journal.* 2012;33(14):1777-1786.

81. de Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. *Diabetologia.* 2009;52(11):2328-2336.

82. Elkins JS, Knopman DS, Yaffe K, Johnston SC. Cognitive function predicts first-time stroke and heart disease. *Neurology.* 2005;64(10):1750-1755.

83. Flaker GC, Pogue J, Yusuf S, et al. Cognitive function and anticoagulation control in patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes.* 2010;3(3):277-283.

84. van den Kommer T, Dik M, Comijs H, Fassbender K, Lutjohann D, Jonker C. Total cholesterol and oxysterols: early markers for cognitive decline in elderly? *Neurobiol. Aging.* 2009;30(4):534-545.

85. Reynolds C, Gatz M, Prince J, Berg S, Pedersen N. Serum lipid levels and cognitive change in late life. *Journal of the American Geriatrics Society.* 2010;58(3):501-509.

86. Canavan M, Glynn L, Smyth A, et al. Vascular risk factors, cardiovascular disease and functional impairment in community-dwelling adults. *Gerontology.* 2014.

87. Welmer AK, Liang Y, Angleman S, et al. Vascular risk factor burden, atherosclerosis, and functional dependence in old age: a population-based study. *Int. J. Behav. Med.* 2014;21(4):597-604.

88. Carroll M, Kit B, Lacher D. *Total and high-density lipoprotein cholesterol in adults, 2009-2010* Hyattsville, MD: National Center for Health Statistics;2012.

89. Cabrera MA, de Andrade SM, Dip RM. Lipids and all-cause mortality among older adults: a 12-year follow-up study. *TheScientificWorldJournal.* 2012;2012:930139.

90. Tuikkala P, Hartikainen S, Korhonen MJ, et al. Serum total cholesterol levels and all-cause mortality in a home-dwelling elderly population: a six-year follow-up. *Scandinavian journal of primary health care.* 2010;28(2):121-127.

91. Spada RS, Toscano G, Cosentino FI, et al. Low total cholesterol predicts mortality in the nondemented oldest old. *Arch. Gerontol. Geriatr.* 2007;44 Suppl 1:381-384.

92. Akerblom JL, Costa R, Luchsinger JA, et al. Relation of plasma lipids to all-cause mortality in Caucasian, African-American and Hispanic elders. *Age Ageing.* 2008;37(2):207-213.

93. Schupf N, Costa R, Luchsinger J, Tang MX, Lee JH, Mayeux R. Relationship between plasma lipids and all-cause mortality in nondemented elderly. *J Am Geriatr Soc.* 2005;53(2):219-226.

94. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *The Lancet.* 2001;358(9279):351-355.

95. Weiss A, Beloosesky Y, Schmilovitz-Weiss H, Grossman E, Boaz M. Serum total cholesterol: A mortality predictor in elderly hospitalized patients. *Clinical Nutrition.* 2013;32(4):533-537.

96. Crimmins EM, Kim JK, Alley DE, Karlamangla A, Seeman T. Hispanic paradox in biological risk profiles. *Am. J. Public Health.* 2007;97(7):1305-1310.

97. Cortes-Bergoderi M, Goel K, Murad MH, et al. Cardiovascular mortality in Hispanics compared to non-Hispanic whites: a systematic review and meta-analysis of the Hispanic paradox. *Eur. J. Intern. Med.* 2013;24(8):791-799.

98. Abraido-Lanza AF, Dohrenwend BP, Ng-Mak DS, Turner JB. The Latino mortality paradox: a test of the "salmon bias" and healthy migrant hypotheses. *Am. J. Public Health.* 1999;89(10):1543-1548.

99. Heijmans BT, Beekman M, Houwing-Duistermaat JJ, et al. Lipoprotein particle profiles mark familial and sporadic human longevity. *PLoS Med.* 2006;3(12):e495.

100. Barzilai N, Atzmon G, Schechter C, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA.* 2003;290(15):2030-2040.

101. Vaarhorst AA, Beekman M, Suchiman EH, et al. Lipid metabolism in long-lived families: the Leiden Longevity Study. *Age (Dordrecht, Netherlands).* 2011;33(2):219-227.

102. Finkel J, Duffy D. 2013 ACC/AHA cholesterol treatment guideline: Paradigm shifts in managing atherosclerotic cardiovascular disease risk. *Trends Cardiovasc. Med.* 2015;25(4):340-347.

103. Stein E, Raal F. Targeting LDL: is lower better and is it safe? *Best Pract. Res. Clin. Endocrinol. Metab.* 2014;28(3):309-324.

104. Bhattacharya P, Chaturvedi S. Dyslipidemia management. *Continuum (Minneapolis, Minn.).* 2011;17(6 2ndary Stroke Prevention):1242-1254.

105. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation.* 2013.

106. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.

107. Ericsson S, Berglund L, Frostegard J, Einarsson K, Angelin B. The influence of age on low density lipoprotein metabolism: effects of cholestyramine treatment in young and old healthy male subjects. *Journal of internal medicine.* 1997;242(4):329-337.

108. Paik JK, Chae JS, Kang R, Kwon N, Lee SH, Lee JH. Effect of age on atherogenicity of LDL and inflammatory markers in healthy women. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2012.

109. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol--United States, 1999-2002 and 2005-200. *MMWR. Morbidity and mortality weekly report.* 2011;60(4):109-114.

110. Williams PT. Low high-density lipoprotein 3 reduces the odds of men surviving to age 85 during 53-year follow-up. *J Am Geriatr Soc.* 2012;60(3):430-436.

111. Gonzalez-Covarrubias V. Lipidomics in longevity and healthy aging. *Biogerontology.* 2013;14(6):663-672.

112. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *The New England journal of medicine.* 2007;357(13):1301-1310.

113. Cooney MT, Dudina A, De Bacquer D, et al. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. *Atherosclerosis.* 2009;206(2):611-616.

114. Pinto X, Millan J, Munoz A, et al. A very high prevalence of low HDL cholesterol in Spanish patients with acute coronary syndromes. *Clin Cardiol.* 2010;33(7):418-423.

115. Amarenco P, Labreuche J, Touboul P-J. High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: A systematic review. *Atherosclerosis.* 2008;196(2):489-496.

116. Araujo AB, Chiu GR, Christian JB, Kim HY, Evans WJ, Clark RV. Longitudinal changes in high-density lipoprotein cholesterol and cardiovascular events in older adults. *Clin. Endocrinol. (Oxf.).* 2014;80(5):662-670.

117. Carroll M, Lacher D, Sorlie P, et al. Trends in serum lipids and lipoproteins of adults, 1960-2002. *JAMA.* 2005;294(14):1773-1781.

118. Gremeaux V, Gayda M, Lepers R, Sosner P, Juneau M, Nigam A. Exercise and longevity. *Maturitas.* 2012;73(4):312-317.

119. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. *Circ. Res.* 2012;110(8):1097-1108.

120. Laudisio A, Marzetti E, Pagano F, et al. Association of metabolic syndrome with cognitive function: The role of sex and age. *Clinical Nutrition.* 2008;27(5):747-754.

121. Reis JP, Loria CM, Launer LJ, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. *Annals of Neurology.* 2013;73(2):170-179.

122. van Vliet P. Cholesterol and late-life cognitive decline. *J Alzheimers Dis.* 2012;30 Suppl 2:S147-162.

123. van Vliet P, van de Water W, de Craen A, Westendorp R. The influence of age on the association between cholesterol and cognitive function. *Experimental Gerontology.* 2009;44(1-2):112-122.

124. Solomon A, Kareholt I, Ngandu T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. *Neurology.* 2007;68(10):751-756.

125. Panza F, Capurso C, D'Introno A, et al. Serum total cholesterol as a biomarker for Alzheimer's disease: Mid-life or late-life determinations? *Experimental Gerontology.* 2006;41(9):805-806.

126. West R, Beeri MS, Schmeidler J, et al. Better memory functioning associated with higher total and low-density lipoprotein cholesterol levels in very elderly subjects without the apolipoprotein e4 allele. *Am J Geriatr Psychiatry.* 2008;16(9):781-785.

127. Mielke MM, Xue QL, Zhou J, Chaves PHM, Fried LP, Carlson MC. Baseline serum cholesterol is selectively associated with motor speed and not rates of cognitive decline: The Women's Health and Aging Study II. *J. Gerontol. Ser. A-Biol. Sci. Med. Sci.* 2008;63(6):619-624.

128. Solomon A, Kareholt I, Ngandu T, et al. Serum total cholesterol, statins and cognition in non-demented elderly. *Neurobiology of Aging.* 2009;30(6):1006-1009.

129. Reitz C, Luchsinger J, Tang MX, Manly J, Mayeux R. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. *Neurology.* 2005;64(8):1378-1383.

130. Tan ZS, Seshadri S, Beiser A, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. *Arch Intern Med.* 2003;163(9):1053-1057.

131. Vicario A, Del Sueldo M, Fernandez RA, Enders J, Zilberman J, Cerezo GH. Cognition and vascular risk factors: an epidemiological study. *International journal of hypertension.* 2012;2012:783696.

132. Henderson V, Guthrie J, Dennerstein L. Serum lipids and memory in a population based cohort of middle age women. *Journal of neurology, neurosurgery, and psychiatry.* 2003;74(11):1530-1535.

133. Packard CJ, Westendorp RG, Stott DJ, et al. Association between apolipoprotein E4 and cognitive decline in elderly adults. *J Am Geriatr Soc.* 2007;55(11):1777-1785.

134. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. *Archives of neurology.* 2004;61(5):705-714.

135. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology.* 1995;45(6):1161-1168.

136. Anstey K, Lipnicki D, Low L. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am. J. Geriatr. Psychiatry.* 2008;16(5):343-354.

137. Formiga F, Ferrer A, Chivite D, Pinto X, Cuerpo S, Pujol R. Serum high-density lipoprotein cholesterol levels, their relationship with baseline functional and cognitive status, and their utility in predicting mortality in nonagenarians. *Geriatrics & Gerontology International.* 2011;11(3):358-364.

138. Yin ZX, Shi XM, Kraus VB, et al. High normal plasma triglycerides are associated with preserved cognitive function in Chinese oldest-old. *Age Ageing.* 2012;41(5):600-606.

139. Huang CQ, Dong BR, Wu HM, et al. Association of cognitive impairment with serum lipid/lipoprotein among Chinese nonagenarians and centenarians. *Dement Geriatr Cogn Disord.* 2009;27(2):111-116.

140. Small B, Rosnick C, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychology and aging.* 2004;19(4):592-600.

141. Barnes L, Arvanitakis Z, Yu L, Kelly J, De Jager P, Bennett D. Apolipoprotein E and change in episodic memory in blacks and whites. *Neuroepidemiology.* 2013;40(3):211-219.

142. Wilson R, Bienias J, Berry-Kravis E, Evans D, Bennett D. The apolipoprotein E epsilon 2 allele and decline in episodic memory. *J Neurol Neurosurg Psychiatry.* 2002;73(6):672-677.

143. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. *Neurobiol. Aging.* 2011;32(1):63-74.

144. Phillips MC. Apolipoprotein E isoforms and lipoprotein metabolism. *IUBMB life.* 2014;66(9):616-623.

145. Oh JE, Shin JW, Sohn EH, et al. Effect of cardiac function on cognition and brain structural changes in dementia. *Journal of clinical neurology (Seoul, Korea).* 2012;8(2):123-129.

146. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* 2011;42(9):2672-2713.

147. Daulatzai M. Quintessential risk factors: their role in promoting cognitive dysfunction and Alzheimer's disease. *Neurochem Res.* 2012;37(12):2627-2658.

148. de la Torre J. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovascular psychiatry and neurology.* 2012;2012:367516.

149. Kovacic JC, Castellano JM, Fuster V. The links between complex coronary disease, cerebrovascular disease, and degenerative brain disease. *Ann. N. Y. Acad. Sci.* 2012;1254:99-105.

150. Muqtadar H, Testai FD, Gorelick PB. The dementia of cardiac disease. *Current cardiology reports.* 2012;14(6):732-740.

151. Gharacholou S, Reid K, Arnold S, et al. Cognitive impairment and outcomes in older adult survivors of acute myocardial infarction: Findings from the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health Status registry. *American Heart Journal.* 2011;162(5):860-869.e861.

152. Go A, Mozaffarian D, Roger V, et al. Heart disease and stroke statistics--2013 update: A report from the American Heart Association. *Circulation.* 2013;127(1):e6-e245.

153. Purnell C, Gao S, Callahan CM, Hendrie HC. Cardiovascular risk factors and incident Alzheimer disease. A systematic review of the literature. *Alzheimer Dis Assoc Disord.* 2009;23:1-10.

154. Giltay EJ, Zitman FG, Kromhout D. Cardiovascular risk profile and subsequent disability and mental well-being: the Zutphen Elderly Study. *Am J Geriatr Psychiatry.* 2008;16(11):874-882.

155. Verbrugge LM, Jette AM. The disablement process. *Soc. Sci. Med.* 1994;38(1):1-14.

156. Stump TE, Johnson RJ, Wolinsky FD. Changes in physician utilization over time among older adults. *The journals of gerontology. Series B, Psychological sciences and social sciences.* 1995;50(1):S45-S58.

157. Zuliani G, Romagnoni F, Bollini C, Leoci V, Soattin L, Fellin R. Low levels of high-density lipoprotein cholesterol are a marker of disability in the elderly. *Gerontology.* 1999;45(6):317-322.

158. Landi F, Russo A, Cesari M, Pahor M, Bernabei R, Onder G. HDL-cholesterol and physical performance: results from the ageing and longevity study in the sirente geographic area (ilSIRENTE Study). *Age Ageing.* 2007;36(5):514-520.

159. Hyttinen L, Strandberg TE, Strandberg AY, et al. Effect of cholesterol on mortality and quality of life up to a 46-year follow-up. *Am J Cardiol.* 2011;108(5):677-681.

160. Scott KM, Collings SC. Gender differences in the disability (functional limitations) associated with cardiovascular disease: a general population study. *Psychosomatics.* 2012;53(1):38-43.

161. Zuliani G, Cavalieri M, Galvani M, et al. Relationship between low levels of high-density lipoprotein cholesterol and dementia in the elderly. The InChianti study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2010;65(5):559-564.

162. Purser JL, Fillenbaum GG, Pieper CF, Wallace RB. Mild cognitive impairment and 10-year trajectories of disability in the Iowa Established Populations for Epidemiologic Studies of the Elderly cohort. *J Am Geriatr Soc.* 2005;53(11):1966-1972.

163. Wadley VG, Crowe M, Marsiske M, et al. Changes in everyday function in individuals with psychometrically defined mild cognitive impairment in the Advanced Cognitive Training for Independent and Vital Elderly Study. *J Am Geriatr Soc.* 2007;55(8):1192-1198.

164. Chanti-Ketterl M, Andel R, Lerch O, Laczo J, Hort J. Cholesterol and cognitive performance among community volunteers from the Czech Republic. *International psychogeriatrics / IPA.* 2015:1-9.

165. Károssy K, Kerekes Z, Horváth D, Gőocze P, Kállai J. Association of high and low density serum cholesterol, cognitive performance and emotional well-being in menopausal women. *Review of Psychology.* 2007;14(1):13-23.

166. Yaffe K, Vittinghoff E, Pletcher MJ, et al. Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation.* 2014;129(15):1560-1567.

167. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology.* 2001;56(1):42-48.

168. Parale GP, Baheti NN, Kulkarni PM, Panchal NV. Effects of atorvastatin on higher functions. *Eur. J. Clin. Pharmacol.* 2006;62(4):259-265.

169. Xia W, Zhang B, Yang Y, Wang P, Yang Y, Wang S. Poorly controlled cholesterol is associated with cognitive impairment in T2DM: a resting-state fMRI study. *Lipids Health Dis.* 2015;14:47.

170. Oberlin LE, Manuck SB, Gianaros PJ, et al. Blood pressure interacts with APOE epsilon4 to predict memory performance in a midlife sample. *Neuropsychology.* 2015.

171. Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. *Archives of neurology.* 2002;59(3):378-384.

172. Yasuno F, Tanimukai S, Sasaki M, et al. Association between cognitive function and plasma lipids of the elderly after controlling for apolipoprotein E genotype. *Am J Geriatr Psychiatry.* 2012;20(7):574-583.

173. Cheng Y, Jin Y, Unverzagt FW, et al. The relationship between cholesterol and cognitive function is homocysteine-dependent. *Clin. Interv. Aging.* 2014;9:1823-1829.

174. Abbott RD, Garrison RJ, Wilson PW, et al. Joint distribution of lipoprotein cholesterol classes. The Framingham study. *Arteriosclerosis.* 1983;3(3):260-272.

175. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc.* 1992;40(9):922-935.

176. Lancu I, Olmer A. [The minimental state examination--an up-to-date review]. *Harefuah.* 2006;145(9):687-690, 701.

177. Fastenau PS, Denburg NL, Hufford BJ. Adult norms for the Rey-Osterrieth Complex Figure Test and for supplemental recognition and matching trials from the Extended Complex Figure Test. *Clin. Neuropsychol.* 1999;13(1):30-47.

178. Osterrieth PA. Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire. = Test of copying a complex figure; contribution to the study of perception and memory. *Arch. Psychol. (Geneve).* 1944;30:206-356.

179. Gallagher C, Burke T. Age, gender and IQ effects on the Rey-Osterrieth Complex Figure Test. *Br. J. Clin. Psychol.* 2007;46(1):35-45.

180. Shin MS, Park SY, Park SR, Seol SH, Kwon JS. Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. *Nat. Protoc.* 2006;1(2):892-899.

181. Ivnik RJ, Malec JF, Tangalos EG, Petersen RC, Kokmen E, Kurland LT. The Auditory-Verbal Learning Test (AVLT): Norms for ages 55 years and older. *Psychological Assessment: A Journal of Consulting and Clinical Psychology.* 1990;2(3):304-312.

182. Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique. (Les problems.). = The psychological examination in cases of traumatic encepholopathy. Problems. *Arch. Psychol. (Geneve).* 1941;28:215-285.

183. Schmidt M. *Rey Auditory Verbal Learning Test: A Handbook.* Los Angeles.1996.

184. Schmidt JP, Tombaugh TN, Faulkner P. Free-recall, cued-recall and recognition procedures with three verbal memory tests: Normative data from age 20 to 79. *Clinical Neuropsychologist (0920-1637).* 1992;6(2):185.

185. Howard DV. Category norms: a comparison of the Battig and Montague (1969) norms with the responses of adults between the ages of 20 and 80. *Journal of gerontology.* 1980;35(2):225-231.

186. Bezdicek O, Stepankova H, Motak L, et al. Czech version of Rey Auditory Verbal Learning test: normative data. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition.* 2014;21(6):693-721.

187. Schoenberg MR, Dawson KA, Duff K, Patton D, Scott JG, Adams RL. Test performance and classification statistics for the Rey Auditory Verbal Learning Test in selected clinical samples. *Arch. Clin. Neuropsychol.* 2006;21(7):693-703.

188. Vyhnalek M, Nikolai T, Andel R, et al. Neuropsychological correlates of hippocampal atrophy in memory testing in nondemented older adults. *J Alzheimers Dis.* 2014;42 Suppl 3:S81-90.

189. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology.* 1988;38(6):900-903.

190. Friedman NP, Miyake A, Young SE, Defries JC, Corley RP, Hewitt JK. Individual differences in executive functions are almost entirely genetic in origin. *J. Exp. Psychol. Gen.* 2008;137(2):201-225.

191. Wechsler D. *Wechsler Adult Intelligence Scale - Revised Manual. .* New York: Psychological Corporation; 1981.

192. van Uffelen JG, Hopman-Rock M, Chin APMJ, van Mechelen W. Protocol for Project FACT: a randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and psychosocial wellbeing in older adults with mild cognitive impairment [ISRCTN19227688]. *BMC Geriatr.* 2005;5:18.

193. Hoyer WJ, Stawski RS, Wasylyshyn C, Verhaeghen P. Adult age and digit symbol substitution performance: a meta-analysis. *Psychology and aging.* 2004;19(1):211-214.

194. Salthouse T. The processing-speed theory of adult age differences in cognition. *Psychol. Rev.* 1996;103(3):403-428.

195. Sumerall SW, Timmons PL, James AL, Ewing MJ, Oehlert ME. Expanded norms for the Controlled Oral Word Association Test. *Journal of clinical psychology.* 1997;53(5):517-521.

196. Benton A, Hamsher K. Multilingual aphasia examination (2nd ed.). . Iowa City, IA: AJA Associates; 1976.

197. Loonstra AS, Tarlow AR, Sellers AH. COWAT metanorms across age, education, and gender. *Applied neuropsychology.* 2001;8(3):161-166.

198. Wechsler D. Selection and description of tests. *The measurement of adult intelligence.* Baltimore: Williams & Wilkins Co; 1939:75-103.

199. Wechsler D. *Wechsler memory scale (WMS-III).* third ed. San Antonio; Toronto1997.

200. Ramsay MC, Reynolds CR. Separate digits tests: A brief history, a literature review, and a reemination of the factor structure of the Test of Memory and Learning (TOMAL). *Neuropsychol. Rev.* 1995;5(3):151-171.

201. National Longitudinal Survey of Youth Children and Young Adults. *National Longitudinal Surveys* 1979; https://www.nlsinfo.org/content/cohorts/nlsy79-children/topical-guide/assessments/wechsler-intelligence-scale-children. Accessed 6/25/2015, 2015.

202. Kaplan E, Goodglass H, Weintraub S. Boston Naming Test (Boston Diagnostic Aphasia Exam). Philadelphia, PA: Lea & Febiger; 1983.

203. Mack WJ, Freed DM, Williams BW, Henderson VW. Boston Naming Test: shortened versions for use in Alzheimer's disease. *Journal of gerontology.* 1992;47(3):P154-158.

204. Harry A, Crowe SF. Is the Boston Naming Test still fit for purpose? *Clin. Neuropsychol.* 2014;28(3):486-504.

205. Lahiri DK, Bye S, Nurnberger JI, Jr., Hodes ME, Crisp M. A non-organic and non-enzymatic extraction method gives higher yields of genomic DNA from whole-blood samples than do nine other methods tested. *J. Biochem. Biophys. Methods.* 1992;25(4):193-205.

206. Snowden MB, Atkins DC, Steinman LE, et al. Longitudinal association of dementia and depression. *Am J Geriatr Psychiatry.* 2014.

207. Jose PE. ModGraph-I: A programme to compute cell means for the graphical display of moderational analyses: The internet version, Version 3.0. . Victoria University of Wellington, Wellington, New Zealand.; 2013.

208. *G*Power © 1992-2014* [computer program]. Version 3.1.9.2. Germany1992.

209. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* 3 ed. New York: Academic Press; 1988.

210. Kilander L, Nyman H, Boberg M, Lithell H. Cognitive function, vascular risk factors and education. A cross-sectional study based on a cohort of 70-year-old men. *Journal of internal medicine.* 1997;242(4):313-321.

211. Perlmuter LC, Nathan DM, Goldfinger SH, Russo PA, Yates J, Larkin M. Triglyceride levels affect cognitive function in noninsulin-dependent diabetics. *J. Diabet. Complications.* 1988;2(4):210-213.

212. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am. J. Med.* 1977;62(5):707-714.

213. Singh-Manoux A, Gimeno D, Kivimaki M, Brunner E, Marmot MG. Low HDL cholesterol is a risk factor for deficit and decline in memory in midlife: the Whitehall II study. *Arterioscler. Thromb. Vasc. Biol.* 2008;28(8):1556-1562.

214. Ward MA, Bendlin BB, McLaren DG, et al. Low HDL cholesterol is associated with lower gray matter volume in cognitively healthy adults. *Front. Aging Neurosci.* 2010;2.

215. Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH. Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B,E(LDL) receptors in the brain. *J. Biol. Chem.* 1987;262(29):14352-14360.

216. Wang H, Eckel RH. What are lipoproteins doing in the brain? *Trends Endocrinol. Metab.* 2014;25(1):8-14.

217. Zhang J, Muldoon MF, McKeown RE. Serum cholesterol concentrations are associated with visuomotor speed in men: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Am. J. Clin. Nutr.* 2004;80(2):291-298.

218. VanderWeele TJ. On the distinction between interaction and effect modification. *Epidemiology.* 2009;20(6):863-871.

219. Henderson VW. Action of estrogens in the aging brain: Dementia and cognitive aging. *Biochimica et Biophysica Acta (BBA) - General Subjects.* 2010;1800(10):1077-1083.

220. Fogelman AM. The complexity of high-density lipoproteins. *Circulation.* 2010;122(19):1900-1901.

221. Vaisar T, Pennathur S, Green PS, et al. Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. *J. Clin. Invest.* 2007;117(3):746-756.

222. Nair DR, Nair A, Jain A. HDL Genetic Defects. *Curr. Pharm. Des.* 2014.

223. Johansen CT, Hegele RA. Genetic bases of hypertriglyceridemic phenotypes. *Curr. Opin. Lipidol.* 2011;22(4):247-253.

224. Andersen CJ, Fernandez ML. Dietary approaches to improving atheroprotective HDL functions. *Food & Function.* 2013;4(9):1304-1313.

225. Klop B, Wouter Jukema J, Rabelink TJ, Castro Cabezas M. A physician's guide for the management of hypertriglyceridemia: the etiology of hypertriglyceridemia determines treatment strategy. *Panminerva Med.* 2012;54(2):91-103.

226. Tak E, Kuiper R, Chorus A, Hopman-Rock M. Prevention of onset and progression of basic ADL disability by physical activity in community dwelling older adults: a meta-analysis. *Ageing Res Rev.* 2013;12(1):329-338.

227. Idland G, Pettersen R, Avlund K, Bergland A. Physical performance as long-term predictor of onset of activities of daily living (ADL) disability: a 9-year longitudinal study among community-dwelling older women. *Arch. Gerontol. Geriatr.* 2013;56(3):501-506.

228. den Ouden ME, Schuurmans MJ, Arts IE, van der Schouw YT. Physical performance characteristics related to disability in older persons: a systematic review. *Maturitas.* 2011;69(3):208-219.

229. Paterson DH, Warburton DE. Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. *The international journal of behavioral nutrition and physical activity.* 2010;7:38.

230. Seals DR, Melov S. Translational geroscience: emphasizing function to achieve optimal longevity. *Aging.* 2014;6(9):718-730.

231. Fries JF. Measuring and monitoring success in compressing morbidity. *Ann Intern Med.* 2003;139(5 Pt 2):455-459.

232. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. *Clin Geriatr Med.* 2009;25(4):563-577, vii.

233. Sjolund BM, Nordberg G, Wimo A, von Strauss E. Morbidity and physical functioning in old age: differences according to living area. *J Am Geriatr Soc.* 2010;58(10):1855-1862.

234. Reuben DB, Ix JH, Greendale GA, Seeman TE. The predictive value of combined hypoalbuminemia and hypocholesterolemia in high functioning community-dwelling older persons: MacArthur Studies of Successful Aging. *J Am Geriatr Soc.* 1999;47(4):402-406.

235. Huisman M, Poppelaars J, van der Horst M, et al. Cohort profile: the Longitudinal Aging Study Amsterdam. *Int. J. Epidemiol.* 2011;40(4):868-876.

236. Markides KS, Coreil J. The health of Hispanics in the southwestern United States: an epidemiologic paradox. *Public Health Rep.* 1986;101(3):253-265.

237. Medina-Inojosa J, Jean N, Cortes-Bergoderi M, Lopez-Jimenez F. The Hispanic paradox in cardiovascular disease and total mortality. *Prog. Cardiovasc. Dis.* 2014;57(3):286-292.

238. Argeseanu Cunningham S, Ruben JD, Narayan KM. Health of foreign-born people in the United States: a review. *Health Place.* 2008;14(4):623-635.

239. Daviglus ML, Talavera GA, Aviles-Santa ML, et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *Jama.* 2012;308(17):1775-1784.

240. Schargrodsky H, Hernandez-Hernandez R, Champagne BM, et al. CARMELA: assessment of cardiovascular risk in seven Latin American cities. *Am. J. Med.* 2008;121(1):58-65.

241. Dallo FJ, Booza J, Nguyen ND. Functional limitations and nativity status among older Arab, Asian, Black, Hispanic, and White Americans. *Journal of immigrant and minority health / Center for Minority Public Health.* 2013.

242. Carrasquillo O, Lantigua RA, Shea S. Differences in functional status of Hispanic versus non-Hispanic White elders: data from the Medical Expenditure Panel Survey. *Journal of Aging and Health.* 2000;12(3):342-361.

243. Liang J, Xu X, Bennett JM, Ye W, Quiñones AR. Ethnicity and changing functional health in middle and late life: A person-centered approach. *Journals of Gerontology: Series B: Psychological Sciences and Social Sciences.* 2010;65B(4):470-481.

244. Shetterly SM, Baxter J, Morgenstern NE, Grigsby J, Hamman RF. Higher instrumental activities of daily living disability in Hispanics compared with non-Hispanic whites in rural Colorado. The San Luis Valley Health and Aging Study. *Am J Epidemiol.* 1998;147(11):1019-1027.

245. Paz S, Spritzer K, Morales L, Hays R. Evaluation of the Patient-Reported Outcomes Information System (PROMIS) Spanish-language physical functioning items. *Qual. Life Res.* 2013;22(7):1819-1830.

246. Schur CL, Bernstein AB, Berk ML. The importance of distinguishing Hispanic subpopulations in the use of medical care. *Med Care.* 1987;25(7):627-641.

247. Hajat A, Lucas JB, Kington R. Health outcomes among Hispanic subgroups: data from the National Health Interview Survey, 1992-95. *Adv. Data.* 2000(310):1-14.

248. Lara M, Gamboa C, Kahramanian MI, Morales LS, Bautista DE. Acculturation and Latino health in the United States: a review of the literature and its sociopolitical context. *Annu. Rev. Public Health.* 2005;26:367-397.

249. *Table 6. Percent of the Projected Population by Race and Hispanic Origin for the United States: 2015 to 2060 (NP2012-T6)* U.S. Census Bureau, Population Division; December 2012 2012.

250. Palloni A, Pinto-Aguirre G, Pelaez M. Demographic and health conditions of ageing in Latin America and the Caribbean. *Int. J. Epidemiol.* 2002;31(4):762-771.

251. *I Informe estado de situación de la persona adulta mayor en Costa Rica.* San José, Costa Rica2008. ISBN 978-9968-9688-1-2.

252. Newman AB, Brach JS. Gender gap in longevity and disability in older persons. *Epidemiol. Rev.* 2001;23(2):343-350.

253. Okoro CA, Strine TW, Balluz LS, et al. Serious psychological distress among adults with and without disabilities. *International journal of public health.* 2009;54 Suppl 1:52-60.

254. Schiller JS, Lucas JW, Ward BW, Peregoy JA. *Summary health statistics for U.S. adults: National Health Interview Survey, 2010.* National Center for Health Statistics;2012.

255. Gorman BK, Read JG. Gender disparities in adult health: an examination of three measures of morbidity. *J. Health Soc. Behav.* 2006;47(2):95-110.

256. Guo X, Matousek M, Sundh V, Steen B. Motor performance in relation to age, anthropometric characteristics, and serum lipids in women. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2002;57(1):M37-44.

257. Zunzunegui MV, Alvarado BE, Beland F, Vissandjee B. Explaining health differences between men and women in later life: a cross-city comparison in Latin America and the Caribbean. *Soc. Sci. Med.* 2009;68(2):235-242.

258. Lee Y, Kim JH, Lee KJ, Han G, Kim JL. Association of cognitive status with functional limitation and disability in older adults. *Aging Clin. Exp. Res.* 2005;17(1):20-28.

259. McGough EL, Kelly VE, Logsdon RG, et al. Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed "up & go" test. *Phys. Ther.* 2011;91(8):1198-1207.

260. Rosero-Bixby L, Fernandez X, Dow W. CRELES: Costa Rican Longevity and Healthy Aging Study, 2005 (Costa Rica Estudio de Longevidad y Envejecimiento Saludable) Sampling and Methods (072406/Z/03/Z) WTUK, trans. Vol ICPSR26681-v2. ICPSR26681-v2 ed. Ann Arbor, MI: Inter-university Consortium for Political and Social Research; 2010.

261. Rosero-Bixby L, Fernández X, Dow W. CRELES-2: Costa Rican Longevity and Healthy Aging Study - Wave 2, 2006-2008 (Costa Rica Estudio de Longevidad y Envejecimiento Saludable, Ronda 2). /Z/03/Z) WTUK, trans. ICPSR31263-v1 ed. Ann Arbor, MI: Inter-university Consortium for Political and Social Research; 2013.

262. Rosero-Bixby L, Brenes G, Dow W. CRELES-3: Costa Rican Longevity and Healthy Aging Study - Wave 3, 2009 (Costa Rica Estudio de Longevidad y Envejecimiento Saludable, Ronda 3). Sampling methods. In: (ICPSR) I-UCfPaSR, ed. /Z/03/Z) WTUK, trans. ICPSR35250-v1 ed. Ann Arbor, MI: Inter-university Consortium for Political and Social Research 2015.

263. Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet.* 2015.

264. Hubert HB, Bloch DA, Oehlert JW, Fries JF. Lifestyle habits and compression of morbidity. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2002;57(6):M347-351.

265. Organization WH. *Towards a Common Language for Functioning, Disability and Health: ICF.* World Health Organization; 2002.

266. Young Y, Xiong K, Pruzek RM, Brant LJ. Examining heterogeneity of functional recovery among older adults with hip fractures. *J. Am. Med. Dir. Assoc.* 2010;11(2):132-139.

267. Demidenko E. *Mixed models : theory and applications with R.* Second ed: Hoboken: Wiley; 2013.

268. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry.* 2004;61(3):310-317.

269. Bauer DJ. Evaluating individual differences in psychological processes. *Curr. Dir. Psychol. Sci.* 2011;20(2):115-118.

270. Liu S, Rovine MJ, Molenaar P. Selecting a linear mixed model for longitudinal data: repeated measures analysis of variance, covariance pattern model, and growth curve approaches. *Psychol. Methods.* 2012;17(1):15-30.

271. Nezlek J. Using multilevel random coefficient modeling to analyze social interaction diary data *Journal of Social and Personal Relationships.* 2003;20:437-469.

272. Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *Hypertension.* 2015;65(6):1372-1407.

273. Schafer HH, De Villiers JN, Sudano I, et al. Recommendations for the treatment of hypertension in the elderly and very elderly--a scotoma within international guidelines. *Swiss Med. Wkly.* 2012;142:w13574.

274. Raudenbush S, Bryk A. *Hierarchical linear models: Applications and data analysis methods. .* Thousand Oaks, CA: Sage Publications; 2002.

275. Al Snih S, Markides KS, Ray L, Ostir GV, Goodwin JS. Handgrip strength and mortality in older Mexican Americans. *J Am Geriatr Soc.* 2002;50(7):1250-1256.

276. Botoseneanu A, Bennett JM, Nyquist L, et al. Cardiometabolic Risk, Socio-Psychological Factors, and Trajectory of Grip Strength Among Older Japanese Adults. *Journal of Aging and Health.* 2015;27(7):1123-1146.

277. Rantanen T, Masaki K, Foley D, Izmirlian G, White L, Guralnik JM. Grip strength changes over 27 yr in Japanese-American men. *Journal of applied physiology (Bethesda, Md. : 1985).* 1998;85(6):2047-2053.

278. Sayer AA, Syddall HE, Dennison EM, et al. Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. *QJM.* 2007;100(11):707-713.

279. Sanders JL, Ding V, Arnold AM, et al. Do changes in circulating biomarkers track with each other and with functional changes in older adults? *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2014;69(2):174-181.

280. Bingenheimer JB, Raudenbush SW. Statistical and substantive inferences in public health: issues in the application of multilevel models. *Annu. Rev. Public Health.* 2004;25:53-77.

281. *Life Expectancy Gains and Public Programs for the Elderly in Latin America and the Caribbean.* Washington, DC: Population Reference Bureau; April 2014 2014.

282. Buettner D. *The Blue Zones: Lessons for Living Longer From the People Who've Lived the Longest.* Washington, D.C.: National Geographic Society; 2010.

283. Rosero-Bixby L, Dow WH, Rehkopf DH. The Nicoya region of Costa Rica: a high longevity island for elderly males. *Vienna yearbook of population research / Vienna Institute of Demography, Austrian Academy of Sciences.* 2013;11:109-136.

284. Gamba P, Testa G, Gargiulo S, Staurenghi E, Poli G, Leonarduzzi G. Oxidized cholesterol as the driving force behind the development of Alzheimer's disease. *Front. Aging Neurosci.* 2015;7:119.

285. Stewart R, White LR, Xue QL, Launer LJ. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. *Archives of neurology.* 2007;64(1):103-107.

286. Rosero-Bixby L, Dow WH. Surprising SES Gradients in mortality, health, and biomarkers in a Latin American population of adults. *The journals of gerontology. Series B, Psychological sciences and social sciences.* 2009;64(1):105-117.

287. Rehkopf DH, Dow WH, Rosero-Bixby L. Differences in the association of cardiovascular risk factors with education: a comparison of Costa Rica (CRELES) and the USA (NHANES). *Journal of epidemiology and community health.* 2010;64(9):821-828.

288. Roberts H, Denison H, Martin H, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing.* 2011;40(4):423-429.

289. Rosero-Bixby L, Dow WH. Predicting mortality with biomarkers: a population-based prospective cohort study for elderly Costa Ricans. *Population health metrics.* 2012;10(1):11.

290. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc.* 2007;55(5):780-791.

291. Havranek EP, Mujahid MS, Barr DA, et al. Social Determinants of Risk and Outcomes for Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation.* 2015;132(9):873-898.

292. Samson S, Mundkur L, Kakkar VV. Immune response to lipoproteins in atherosclerosis. *Cholesterol.* 2012;2012:571846.

293. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *The New England journal of medicine.* 2005;352(16):1685-1695.

294. Hottman DA, Chernick D, Cheng S, Wang Z, Li L. HDL and cognition in neurodegenerative disorders. *Neurobiol. Dis.* 2014;72, Part A:22-36.

APPENDIX

Appendix A: Letters

Appendix A1: Approval of IRB Exemption

USF
UNIVERSITY OF
SOUTH FLORIDA

RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799
(813) 974-5638 • FAX (813) 974-7091

5/15/2015

Marianne Chanti-Ketterl,
School of Aging Studies
4202 E. Fowler Avenue, MHC 1300
Tampa, FL 33620

RE: **NOT Human Research Activities Determination**
IRB#: Pro00022315
Title: Lipoproteins and Health Outcomes: Cognitive and Physical Function in Older Adults
Dear Dr. Chanti-Ketterl:

The Institutional Review Board (IRB) has reviewed the information you provided regarding the above referenced project and has determined the activities do not meet the definition of human subjects research. Therefore, IRB approval is not required. If, in the future, you change this activity such that it becomes human subjects research, IRB approval will be required. If you wish to obtain a determination about whether the activity, with the proposed changes, will be human subjects research, please contact the IRB for further guidance.

All research activities, regardless of the level of IRB oversight, must be conducted in a manner that is consistent with the ethical principles of your profession and the ethical guidelines for the protection of human subjects. As principal investigator, it is your responsibility to ensure subjects' rights and welfare are protected during the execution of this project

Also, please note that there may be requirements under the HIPAA Privacy Rule that apply to the information/data you will use in your activities. For further information about any existing HIPAA requirements for this project, please contact a HIPAA Program administrator at 813-974-5638.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

V Jorgensen MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board

Appendix A2: Approval by Cambridge Press

USF

Marianne Chanti-Ketterl <mchantik@mail.usf.edu>

RE: Permission to re-use material
1 message

Adam Hirschberg <ahirschberg@cambridge.org> Thu, May 28, 2015 at 4:00 PM
To: Marianne Chanti Ketterl <mchantik@mail.usf.edu>

Dear Ms. Chanti -Ketterl,

Cambridge journal authors are allowed to reprint their journal article as their dissertation provided the journal article is acknowledged in the new work.

Regards,

Adam Hirschberg
Senior Permissions Associate
Cambridge University Press
32 Avenue of the Americas
New York, NY 10013-2473

tel.: 212-337-5088 (direct)
tel.: 212-924-3900 (general)
fax: 212-691-3239 (general)
email: ahirschberg@cambridge.org
web: www.cambridge.org/us

From: Marianne Chanti Ketterl [mailto:mchantik@mail.usf.edu]
Sent: Monday, May 25, 2015 11:35 AM
To: manderson@cambridge.org
Subject: Permission to re-use material

Hello Mr. Anderson.

My name is Marianne Chanti-Ketterl, I'm a doctoral candidate in the School of Aging Studies at the University of South Florida. I have an article published in the Journal of International Psychogeriatrics titled "Cholesterol and cognitive performance among community volunteers from the Czech Republic", doi: http://dx.doi.org/10.1017/S1041610215000320 **I am the first author of the paper. Here is the exact reference:**

Chanti-Ketterl, M., Andel, R., Lerch, O., Laczo, J., & Hort, J. (2015). Cholesterol and cognitive performance among community volunteers from the Czech Republic. *Int Psychogeriatr*, 1-9. doi: 10.1017/s1041610215000320

Part of my dissertation for the PhD degree in Aging Studies includes some sections that were part of this published manuscript and I would like to ask for permission to include these sections. The methods I am using in the dissertation are different from the article published. The dissertation includes only adults over the age of 60 vs. over 40 as published in the article, plus additional correlations and moderation analysis are included in the dissertation that are not on the manuscript published.

Please let me know what are the steps I need to follow or the language you required me to specifically use in my dissertation if granted permission.

Thank you ahead of time for your time and assistance in this matter.

Sincerely,

Marianne Chanti-Ketterl, MD, MSPH
Instructor / Doctoral Candidate
School of Aging Studies
University of South Florida
Tampa, FL