Evaluation of Plasma Lipoprotein Profiles in a Mediterranean Diet Intervention

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DISSERTATION

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Psychology
in the Graduate College of the
University of Illinois at Chicago, 2020
Chicago, Illinois

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DEDICATION

"*You will have many acquaintances, loves, and friends my dear,*
but it'll be your family when it most counts who will be there when it's the most important."
–Mary Karstens, PhD
5/25/1991

To my father, James Robert Karstens.
I dedicate this work, and all of my honorable pursuits in this life to you.

To my mother, Mary Karstens.
Thank you for your sacrifices, your guidance, and for always showing up to battle.

To my siblings, Joe, Adam, Maria, and Sarah.
Thank you for loving me at my worst and teasing me at my best.
You are a constant reminder of the goodness in this world.

ACKNOWLEDGEMENTS

Thank you to the LaDu lab for adopting me into the world of basic science. None of this work would be possible without the army of undergraduates, research assistants, fellow graduate students, postdocs, and of course, Dr. Mary Jo LaDu. My life and work were forever changed when you agreed to mentor me for my dissertation and the T32 Fellowship. I am especially grateful to Ana, Yaseen, Kai, Sandra, Bing, Juan, Cat, Deebika, and Naomi. Thank you to Dr. Scott Langenecker and his lab for adopting me first, and always supporting me in my endeavors. MJ and Scott, as individuals and as a team you have been such incredible models of professionalism and advocacy. I hope to carry on your level of dedication to my own mentees.

Thank you to the entire BRIDGE Trial team. Working on this project from its infancy has been an incredible opportunity. I learned so much from the talented team of PIs, staff, and students, including my committee members Dr. Marian Fitzgibbon and Dr. Lisa Tussing-Humphreys. Lisa, thank you for lending your expertise and guidance through two doctoral milestones on the Mediterranean diet. I am especially grateful to the energy and brilliance of Andrew, Nefertiti, Mona, Roxanne, Leilah, and Liga. Finally, to the BRIDGE Trial participants. Thank you for your commitment, patience, and life lessons.

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LIST OF ABBREVIATIONS OR NOMENCLATURE

AD	Alzheimer's disease
Aβ	amyloid β
apoB	apolipoprotein B
apoE	Apolipoprotein E
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BBB	Blood brain barrier
BMI	Body Mass Index
BRIDGE	Bridging Research in Diet and CoGnition
CSF	Cerebrospinal fluid
DHA	Docosahexaenoic acid
DXA	Dual energy x-ray absorptiometry
FPLC	Fast Protein Lipid Chromotography
FAD	Familial Alzheimer's disease
HDL	High density lipoprotein
LDL	Low density lipoprotein
LDLR	Low density lipoprotein receptor
LXR	Liver X receptor
MCI	Mild cognitive impairment
MedDiet	Mediterranean Diet
PET	Positron Emission Topography
pVIQ	Predicted verbal IQ
RCI	Reliable Change Index
RCT	Randomized controlled trials
SEC	Size exclusion chromatography
TAG	Triacylglycerols
VAT	Visceral adipose tissue
VLDL	Very low density lipoproteins

SUMMARY

Alzheimer's disease (AD) is the most common neurodegenerative disorder in older adults with no cure and few, very modest palliative treatments [1, 2]. Nonpharmacological interventions that target *modifiable risk factors* such as obesity, diet, sedentary lifestyle, and downstream metabolic correlates (e.g., dyslipidemia) are increasingly being investigated [3, 4]. African Americans are disproportionately at risk for both AD and the aforementioned modifiable risk factors [5]. From a public health perspective, targeted prevention is key to reducing the global impact of AD. Dietary interventions, (e.g., the Mediterranean diet; MedDiet) show promise as a method of modifying risk and delaying cognitive decline [6]. Thus, there is a need for more randomized controlled trials (RCT) to understand whether individuals at risk for AD will benefit from dietary interventions like the MedDiet. The greatest genetic risk for sporadic AD lies in *APOE4* carriers [7, 8]. In female carriers, *APOE4* risk is substantially greater than male carriers [9-12]. Obesity, poor diet, and commonly comorbid dyslipidemia exacerbate this risk [13]. Though exact mechanisms underlying the *APOE4* genotype and female sex risk is unknown, targeting modifiable risk in these groups may still prove beneficial in preventing or delaying symptom onset. We used a precision medicine approach to study a potential AD biomarker and clinical intervention through a model of risk in a sample of female obese older adults that is predominately African American. The plasma lipoprotein profile is the ideal biomarker that has specificity for universal and modifiable AD risk. The current study examines the plasma lipoprotein profile as an *APOE*-dependent biomarker in the context of an RCT of the MedDiet.

I. CONCEPTUAL FRAMEWORK AND RELATED LITERATURE

Alzheimer's Disease (AD) is the most common form of dementia affecting nearly 10% of the population over 65 [1, 14]. *Universal biological variables* (UBV; e.g., *APOE* genotype, sex) and *modifiable risk factors* (e.g., diet, chronic metabolic conditions) for AD are well established [15-18]. While age is the greatest risk factor for sporadic AD, the greatest genetic risk factor is the ε4 variant of *APOE.* Importantly, compared to males, female *APOE4* carriers have a greater lifetime risk for developing AD and an increased rate of cognitive decline [9-12]. Chronic metabolic conditions caused by poor diet and other genetic/environmental determinants have a compounding AD risk, both alone and in combination with *APOE* genotype and sex [13, 19, 20]. In the absence of a disease-modifying therapeutic, lifestyle interventions may be essential to reducing the global impact of AD. This work has largely focused on homogeneous White populations, though ethnic minority groups are disproportionately affected. African Americans are twice as likely to develop AD [21]. Therefore, the complex associations between UBVs and modifiable risk factors in ethnic minorities is needed. The association between adherence to healthy diet (e.g., the MedDiet) and brain health (i.e., cognition, reduced dementia risk) is well-established [22]. Various metabolic pathways are implicated in this relationship, including lipid transport [23]. However, randomized controlled trials (RCT) are needed to determine whether the MedDiet can directly target AD pathogenesis in at-risk individuals, particularly populations at disproportionate risk. The current study leverages data from an RCT of the MedDiet conducted in obese, predominately African American, older females to determine shifts in the plasma lipoprotein profile with a MedDiet intervention.

A. AD pathogenesis, diagnosis, and biomarkers

AD is a multifactorial neurodegenerative disorder characterized by amyloid plaques, neurofibrillary tangles, and neuroinflammation [24]. AD pathology initially emerges in the medial temporal lobe (e.g., entorhinal cortex, hippocampal formation) and progresses to other cortical areas (e.g.,

posterior cingulate, prefrontal cortex) [25]. The causative autosomal mutations in familial AD (FAD; 2-3% of all AD cases) lead to enzymatic overproduction of the amyloid-beta peptide (Aβ). Aβ42, the highly charged 42 amino acid allele of the peptide, forms benign amyloid plaques or neurotoxic oligomeric Aβ [26-30]. Typical cognitive sequelae in AD includes progressive learning and memory decline followed by marked deficits in executive functioning, attention, language, and visuospatial ability [31-33]. Amyloid deposition can precede the clinical syndrome by decades or can exist without cognitive decline [34].

As there are no definitive prognostic or diagnostic AD biomarkers, clinical diagnosis can only be confirmed at autopsy. *In vivo,* behavioral and biological evidence (e.g., cognitive testing, positron emission topography imaging; PET), cerebrospinal fluid (CSF) biomarkers) are incorporated to assume a level of diagnostic confidence [35-37]. Clinical and research heuristics are continuously refined for earlier and more reliable detection of AD. Preclinical AD, Prodromal AD, mild cognitive impairment (e.g., amnestic), and the AD spectrum developed by the National Institutes on Aging-Alzheimer's Association (NIA-AA criteria) are used to study the disease course and identify at-risk candidates for clinical trials [37-40]. Multivariate risk models including cognition, comprehensive biomarkers and genetics are more robust predictors of MCI or AD conversion [41]. Ideally, a minimally invasive and inexpensive blood-based biomarker would extend this approach of early identification and comprehensive diagnosis to clinical settings. To date, blood-based biomarkers have been similarly limited specificity and early prognostic ability (e.g., neurofilament light, 24-hydroxycholesterol, Aβ42/Aβ40) [42].

The NIA-AA nomenclature is an important step in acknowledging the staging of AD as a biological entity involving amyloid and tau pathology. Amyloid plaques and neurofibrillary tangles continue to take center stage in the failing AD drug development pipeline [2]. Challenges to detecting short-term meaningful change or stability in cognitive data and/or PET imaging is a limiting factor. Drivers of the functional decline in AD are likely multifactorial and/or altered by key demographic or environmental factors. In clinical trials, biomarkers must be physiologically relevant to the specific

treatment target(s) and AD pathogenesis. For example, PET imaging of amyloid may not be sensitive enough to detect the effect of drugs targeting apoE structure/function and the downstream effects on amyloid/tau deposition may be a more appropriate downstream indicator after long term follow up. Precision models of risk will be directive in identifying biomarkers and intervention targets that *precede* and *predict* the onset of cognitive impairment. As outlined below, our group posits that disrupted lipid transport contributes to the pathogenesis of AD through impaired clearance of Aβ that is 1) moderated by the major genetic and modifiable risk factors for AD and 2) warrants further examination as a biomarker and treatment target.

1. Precision medicine framework: UBVs and modifiable risk

Precision medicine is a personalized translational science approach, incorporating the effects of biological and social factors on health and disease. The goal is to individualize detection, prevention, and treatment for clinical implementation. The major UBVs and modifiable risk factors presented in this work provide one model of precision medicine for AD, though there are many relevant models proposed in the literature. The etiology of AD is multifactorial with genetic, epigenetic, and environmental drivers of disease progression [43]. Therefore, a universal biomarker or a panacea for AD is unlikely.

UBV and modifiable risk factors hold a number of shared AD pathogenic mechanisms including inflammation, oxidative stress, blood brain barrier, gut microbiota, and others. These shared mechanisms are dynamic and do not occur in a vacuum, however, this review primarily focuses on lipid transport and lipoprotein remodeling. The plasma lipoprotein profile is a minimally invasive biomarker may be useful for tracking relative risk and treatment response to specific populations where lipid transport is a major catalyst of AD, a multifactorial disorder. Importantly, this biomarker reflects a shared mechanism that involves UBVs and modifiable risk factors that are central to AD risk. This may be particularly relevant to populations with disproportionate risk for cardiovascular/metabolic diseases. As an early and necessary

mechanism of aberrant amyloid accumulation, lipid transport is an important target of prevention, particularly for individuals who carry specific risk related to genetics or their lifestyle/medical history.

2. UBVs: age, *APOE4,* and female sex

Age is the greatest risk factor for sporadic AD [14]. The greatest genetic risk factor for AD is *APOE4,* increasing risk 5- to 15-fold compared to the common *APOE3*, while the rare *APOE2* reduces risk [7]. *APOE*, encoding apolipoprotein E (apoE), gives rise to three naturally occurring isoforms, ε2, ε3, and ε4, that differ by one or two amino acid residues. *APOE4* carriers have an earlier onset of amyloid deposition and clinical syndrome, and a more progressive decline (i.e., preclinical, prodromal, MCI and mild AD) [44-46]. African Americans have greater e2 and e4 allelic frequencies (i.e., e2/2, e2/3, e2/4, e3/4, e4/4) relative to the homogenous White populations that are used to determine *APOE* relative risk. As a result, *APOE4* risk is often categorized dichotomously (*APOE4* carrier vs. noncarrier). Similarly, distinct patterns of allelic frequencies have been observed amongst regions and ethnic groups across the world [47, 48]. In the US specifically, *APOE4* analyzed dichotomously may over- or underestimate risk in ethnically and genetically heterogenous Black populations (i.e., African American, Afro-Caribbean, mixed-race). While beyond the scope of this review, the frequency of understudied genotypes (e.g., e2/e4), and other results of admixture (e.g., promoter length, *APOE* gene cluster variations) may further complicate estimations based on a socially constructed, though highly salient variable. While the limited studies are mixed, there are a number of studies to suggest that there is not a significant difference in *APOE* risk for AD or cognitive decline.

Females are at greater risk of AD, making up 2/3rd of all AD cases [14]. However, marked sex differences in clinical/pathological manifestation (e.g., onset/progression, verbal memory, neuropathology) may lead to delayed diagnosis in females [49-54]. Importantly, compared to males, female *APOE4* carriers have a greater lifetime risk for developing AD, earlier onset (shifted 5 years ε4 heterozygotes, 10 years in ε4 homozygotes), and accelerated clinicopathological progression [9-12, 49,

55-59]. The evidence for the synergistic effect of *APOE4* and female sex ranges from cognitively intact individuals with subjective complaints to precision transgenic AD mouse models [17, 60, 61]. Nevertheless, this relationship is not fully understood and often neglected in AD research.

3. Modifiable risk factors: diet, obesity, and dyslipidemia

At mid-life, chronic metabolic conditions like obesity increase the risk for cognitive decline and dementia [62-65]. Population attributable risk estimates suggest that a 20% reduction of modifiable risk is to reduce the number of AD cases by over 16% in 2050 [66]. Behavioral health trends in the United States do not favor this outcome, with 9.3% of adults meeting recommended daily vegetable intake and 44.8% of middle-aged adults in the United States classified as obese [67, 68]. Obesity is the result of discordant energy intake vs. expenditure; characterized by excess adipose tissue and a body mass index (BMI) ≥ 30. Obesity, poor diet, and other commonly comorbid chronic metabolic conditions (e.g., diabetes, dyslipidemia, hypertension) share a number of pathological mechanisms (e.g., insulin resistance, inflammation) with AD [69]. Obesity leads to altered lipid homeostasis, inflammation, insulin resistance, oxidative stress, and gut microbiota dysbiosis [70, 71]. Diet is both a causal and maintaining factor of obesity. The prevalence of metabolic syndrome and its components is on the rise for African American women. Importantly, African Americans on average have less atherogenic lipid panels (i.e., less triglycerides, higher HDL) compared to Caucasians, and these components are less prognostic or paradoxical for cardiovascular outcomes [72, 73]. Similarly, the pathways and relevant biomarkers in AD may vary by population due to the complex effect of UBVs and modifiable risk on metabolic functioning. Importantly, autopsy studies in women and in African American populations show that mixed vascular and AD pathology is more common [50, 74].

4. Modifiable risk in female *APOE4* carriers: Multiplicative risk and prevention

The relationship between age, *APOE4* genotype, female sex, and modifiable risk factors on AD is critical, but not well understood. Estrogen and apoE appear central to the convergence of risk factors at

mid-life. Females have increased risk for unhealthy weight gain/obesity, dyslipidemia, and associated inflammation post-menopause, particularly those with poor dietary habits (e.g., high in red meat and refined cereal) [75-84] Importantly, estrogen regulates adipose distribution. Postmenopause, adipose tissue storage shifts from gluteo-femoral to more androgenic and visceral [75]. Females may specifically be more susceptible to weight gain with low quality high fat foods [85, 86]. *APOE4* carriers are at greater risk of developing hyperlipidemia and obesity with poor diet [87, 88]. In turn, a number of epidemiological studies show an exacerbated effect of modifiable risk factors (e.g., high caloric diet/saturated fat intake, obesity, physical inactivity, smoking) on AD-related outcomes in *APOE4* carriers [13, 19, 89, 90]. For example, in a large cohort of postmenopausal females, *APOE4* carriers with poor metabolic profiles exhibited worse cognition across multiple domains [91].

A combination of genetic, epigenetic, and environmental factors have been implicated in the increased risk of AD in females, and estrogen depletion from menopause appears to be the primary catalyst. Though exact mechanisms are unknown, numerous hypotheses have been proposed (e.g., bioenergetics, hypometabolic alterations) and tested experimentally with animal models and in studies of natural or induced menopause [77, 92-94] [95]. This literature, in its infancy, has identified unique and shared pathways of apoE and estrogen (e.g., upregulation of apoE via estrogen receptors)[96]. Following amyloidosis, there is evidence of an sex driven effect on tau pathology as well [56, 97]. While still elusive, these many mechanisms are important targets to consider for developing interventions [98].

B. Peripheral versus CNS lipid transport

1. ApoE in the CNS

ApoE is the protein component of plasma lipoproteins and the main apolipoprotein expressed in the brain [99]. Surface apoE provides structural stability to lipoproteins and serves as a cofactor for enzymatic reactions and a ligand for lipoprotein receptors (e.g., LDL receptor; LDLR, liver X receptor; LXR) [100]. CNS lipoproteins facilitate intracellular transport of lipid/protein particles, including the clearance of Aβ across the BBB or into CSF. CNS apoE is secreted primarily by astrocytes as nascent

particles [101]. ApoE4 is less abundant in both the CNS and periphery compared to apoe3 and apoE2 for different reasons. There are no isotope differences in apoE expression [102-104]. We hypothesize that decreased levels of apoE4 in the brain contribute to the pathogenesis of AD as follows. Compared to the dense, lipid-rich apoE3, apoE4 is lipid-poor, discoidal, and less structurally stable [101]. As a result, apoE4 is more susceptible to degradation by proteases, clearance into CSF, or plaque binding. In turn, there is less apoE4 to form a complex with the neurotoxic oligomeric forms of Aβ [28, 105, 106]. Thus, apoE4 lipidation may be key to delaying the onset of amyloidosis.

2. ApoE in the periphery

In parallel with the CNS, peripheral apoE4 levels are lower (apoE4 < apoE3 < apoE2), and are associated with a higher risk of dementia [107, 108]. Peripheral apoE expression and lipoprotein synthesis occur primarily in the liver. Interestingly, elevated plasma apoE has been associated with an increased risk of ischemic heart disease in men [109]. There is normally no communication between CNS and peripheral lipoproteins, as confirmed by liver transplantation studies[110]. However, both CNS and peripheral apolipoproteins facilitate transportation of lipids/proteins across the blood brain barrier (BBB)[111]. An estimated 60% of variability in plasma cholesterol levels is attributable to genetics, with *APOE* specifically accounting for 14% of this genetic variability [112].

Unlike CNS lipoproteins, the conformation of peripheral lipoproteins is more diverse. Plasma lipoproteins are classified by density and size (e.g., chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), high density lipoproteins (HDL-2, HDL-3). ApoE isoforms have specific lipoprotein affinities: apoE4 with chylomicron/VLDL particles, apoE2 with LDL particles, apoE3 with HDL particles [113, 114]. Preferential binding of apoE4 with larger lipoproteins results in more efficient clearance of remnant particles to LDL (reviewed later). Downregulation of hepatic LDL receptors results in a dyslipidemic plasma lipoprotein profile with higher LDL and lower apoE4, and greater total cholesterol (see Table I) [115]. If relevant to CNS functioning, *APOE* dependent lipid transport in plasma

would be a useful method of tracking apoE (e.g., lipidation) targets in clinical trials [116]. ApoE is a multifunctional and abundant protein, therefore, therapeutic manipulation of apoE has been prone to adverse side effects [117]. Lifestyle interventions targeting lipid transport have potential as an alternative or augmentative approach to modify AD risk [118].

Table I. Peripheral Lipid and Proteins Vary by *APOE* Genotype

APOE2	*APOE3*	*APOE4*
Lowest cholesterol	Intermediate cholesterol	Highest cholesterol
apoE2 preferentially binds to LDL	similar LDL affinity as apoE4 apoE3 preferentially binds to HDL	apoE4 preferentially binds to VLDL/Chylomicrons
<u>Lower plasma LDL</u> • Less efficient clearance of remnant particles by LDL receptor (LDLR) • Hepatic LDLR up-regulated as a result of slowed clearance • Slowed conversion of VLDL to LDL	Intermediate LDL	<u>Higher plasma LDL</u> • More efficient clearance of remnant particles on larger lipoproteins • Hepatic LDLR downregulated
Elevated plasma apoE	Intermediate plasma apoE	Lower plasma apoE

C. Plasma lipoproteins versus plasma lipoprotein profiles

The -*omics* era has popularized techniques like mass spectrometry to link patterns of lipid and protein species to disease. Along with the standard lipid panel, these lipidomic approaches lack physiological relevance to AD. In theory, longitudinal lipidomics could be informative to identify target biomarkers. However, these less targeted approaches lack reliability with repeat analysis. The plasma lipoprotein profile is the signature of peripheral lipid transport that can track lipoprotein remodeling over time. Size exclusion chromatography (SEC) is highly reproducible and has been optimized for analyzing intact lipoproteins from small plasma samples. SEC is commonly used as a gentle separation method for

mechanistic biomarkers in cardiovascular research (e.g., lipoprotein remodeling, lipid peroxidation, cholesterol efflux) [119, 120]. Plasma lipoprotein profiles are generated via fast liquid protein chromatography (FPLC; see Figure I). FPLC elutes lipoproteins from largest to smallest

Figure I. Illustration of a typical plasma lipoprotein profile.

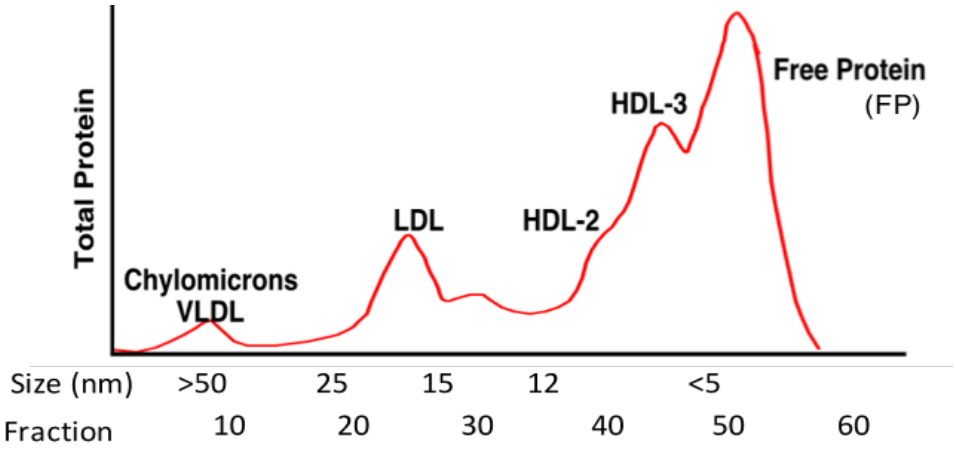


Figure I. Typical human plasma lipoprotein profile through size exclusion chromatography. Plasma can be separated into constitutive lipoprotein classes (Chylomicrons/VLDL, LDL, HDL) and non-lipidated free protein. A normolipidemic shift is indicated by increased total protein in the right side of the profile (i.e., greater higher density, smaller lipoproteins) and decreased total protein on the left side of the profile (i.e., less lower density, large lipoproteins).

(chylomicrons/VLDL, LDL, HDL-2, HDL-3, and free proteins) and resulting fractions can be further analyzed for lipid/protein content (e.g., cholesterol). For example, subtle shifts detect changes in the composition and number of lipoproteins including observable dyslipidemic shifts (e.g., increased VLDL or LDL) and eulipidemic shifts (e.g., decreased triglycerides/LDL cholesterol). Plasma lipoprotein profiles are age-, *APOE*-, and sex-dependent and are influenced by the majority of modifiable risk factors [121, 122]. Determining the *APOE*-dependent signature plasma lipoprotein profile of obese female older adults will help define how lipid transport is altered with AD risk. The plasma lipoprotein profile is ideal for use in clinical trials targeting a number of shared AD/cardiovascular mechanisms including a dietary lifestyle intervention.

1. Modifiable risk and peripheral lipid transport

Diet has direct and downstream effects on excess adipose storage and dyslipidemia as follows: lipid components of lipoproteins include cholesterol and phospholipids, comprising 5% of dietary lipids, and triacylglycerols (TAG) comprising 95% of dietary fat. Cholesterol and phospholipids provide structural stability to lipoprotein membranes that contain hydrophilic cholesterol esters and TAG. Cholesterol derived endogenously and exogenously (e.g., meat, eggs, dairy) is a key precursor to steroids and bile acid. TAG are consumed directly from animal-based fats or from the conversion of carbohydrates to glucose. Other fatty acids can only be obtained exogenously through specific dietary sources such as docosahexaenoic acid (22:6 n-3; DHA) found in fish and shellfish. Chylomicron transports dietary fat to non-hepatic tissue (e.g., TAG to adipose). Without adequate energy expenditure, excess TAGs can accumulate into unhealthy body fat. Other lipoproteins transport endogenous lipids processed hepatically including those transported by chylomicron remnants. TAG depleted chylomicrons remnants are converted to VLDL. VLDL undergoes a similar process of TAG depletion that is regulated in part by apoE. Remnant VLDL particles are converted to cholesterol rich LDL. LDL and HDL play dynamic roles in cholesterol transport. LDL and HDL both bind to LDL receptors via membrane bound apolipoproteins (apoB-100, apoE). LDL transports cholesterol to peripheral tissues (via apoB-100 and apoE) with LDL receptors. Excess cholesterol in LDL can become displaced and become atherogenic. HDL facilitates reverse transport of cholesterol from tissue/lipoproteins to the liver (via apoA-1, apoE). In the liver, cholesterol is stored temporarily or undergoes hydrolysis to be excreted as bile salts. Weight-loss alters lipid metabolism through a number of complex mechanisms (e.g., intermittent fasting, exercise, diet) related to energy expenditure, digestion, gene expression, and other signaling (e.g., adipose tissue) that is beyond the scope of this review [123-125]. It is notable that for African American females, insulin sensitivity plays a major role on the effect of adipose tissue and nutrient intake on lipid metabolism [126, 127]. Importantly, in obese females, there is evidence that aerobic exercise and weight-loss decrease triglycerides and HDL cholesterol[128, 129].

The structural and functional capacities of peripheral lipoproteins, simplified above, are heterogenous and complex [130]. Distilling these dynamic processes to a single measurement is overly simplistic. The HDL/LDL ratio is widely known as a marker of cardiovascular risk, with HDL being considered the "good" lipoprotein. As a stand-alone biomarker, HDL/LDL has limited predictive power for cardiovascular events and AD-related risk [131]. As mentioned above, this is particularly true in African American populations. Size, structure, and function of HDL particles are more predictive of atheroprotective and anti-inflammatory processes [119]. Similarly, while BMI is widely used to study obesity, visceral fat surrounding the vital organs is a better proxy of morbidity and health risk [63, 132-134]. In relation to AD risk, oversimplified interpretation of biomarkers is not uncommon. For example, repeated findings of low/decreased body weight and nutrient deficiencies during stages of dementia/AD negated literature described above. It is now accepted that these results reflect reverse causality. Decreased nutrient intake and subsequent weight loss are prodromal symptoms that may precede a diagnosis by 2 to 8 years [64, 135, 136]. Moreover, significant weight loss in advanced age may stress an underlying pathogenic process [137]. Investigations into the progression and intervention of modifiable risk must precede significant cognitive symptoms until an optimal window of prevention is identified.

D. *APOE* effects on the plasma lipoprotein profile

Consider the interaction of *APOE* genotype and fatty acid consumption relevant to the synergistic nutrients in the MedDiet. *APOE* genotype alters the lipoprotein profile in a response to dietary interventions to improve the quality of fat intake (e.g., increased polyunsaturated fatty acids) [138, 139]. However, evidence for seafood and long-chain omega 3 fatty acids to reduce risk of cognitive decline and AD in *APOE4* carriers is conflicting [140-142] DHA is considered highly beneficial for brain health and has recently been studied as a modulator of oAβ [143-145]. Membrane bound DHA improves membrane fluidity and acts as a ligand for retinoid X receptor. Importantly, DHA relies on apoE to cross the BBB, a process that is less efficiently carried out by apoE4. Certain dietary nutrients support DHA as precursors

or cofactors for DHA membrane synthesis or antioxidant, whereas trans fatty acids compete with DHA for desaturation enzymes. Antioxidants and reduction of "bad" fats may be particularly relevant to *APOE4* carriers [146]. These translational findings highlight the potential of synergistic dietary approaches. Precision medicine is the necessary next frontier for discovering viable AD biomarkers and treatments[147, 148].

It is well-established that cardiovascular disease and metabolic risk factors manifest differently based on sex and race/ethnicity [72, 149, 150]}. Mixed findings regarding the interactions of specific *APOE* genotypes, sex, and modifiable risk on metabolic function and AD-related outcomes in humans and transgenic mouse models cannot be ignored [151-153]. Unsurprisingly, the exacerbated *APOE*-dependent dyslipidemic shifts (e.g., hypercholesterolemia, hypertriglyceridemia) in lipoprotein profiles of obese older adults is not uniform[154]. The question is not whether obesity confers greater *APOE*-dependent risk, but rather, what *APOE*- and sex-dependent mechanisms are exacerbated by specific modifiable risk factors and to what degree are these mechanisms pathogenic? There is an opportunity to identify the most relevant *APOE*- and sex-dependent biomarkers and prognostic thresholds. This literature further illustrates the need to adopt precision medicine approaches to understand how risk factors interact at a systems level.

E. The plasma lipoprotein profile as an AD biomarker in lifestyle interventions

Healthy lifestyle factors are associated with cognitive reserve and account for ~20% variance in cognitive performance for older adults [155]. However, long-term health behaviors do not equate to late life intervention. Lowering circulating cholesterol through diet is difficult and relies on a balanced reduction of "bad" fats (e.g., saturated fats) and carbohydrates with the supplementation of "good" fats (e.g., polyunsaturated fatty acids) [156]. The most effective way to reduce fat mass is through a combination of diet and energy expenditure [157]. Lifestyle interventions that lead to significant weight loss (greater than 5% body weight) have a normolipidemic effect on the plasma lipids [158]. Weight-loss

and healthy diets like the MedDiet have the potential to mitigate the aforementioned modifiable risk pathways through purported metabolic, antioxidant, and anti-inflammatory effects [23, 65, 159, 160].

The MedDiet is composed of fruits, vegetables, whole grains, olive oil, fish, nuts, legumes, moderate amounts of red wine, and limited red/processed meat and dairy products [161]. Numerous RCTs have provided support for the efficacy of the MedDiet on obesity reduction and normolipidemic profile shifts [162-170]. It is now widely accepted that long-term adherence to the MedDiet and similar dietary patterns (e.g., MIND diet, Nordic diet) are associated with beneficial physical and cognitive health outcomes [171-173]. Select studies have examined outcomes specifically relevant to AD including learning/memory, hippocampal volume, and PET amyloid [174-178]. RCTs are needed to delineate whether the MedDiet is a viable intervention in diverse middle to older age populations.

A recent meta-analysis examining the MedDiet as an intervention across health outcomes found, at best, mixed evidence for improving cardiometabolic factors including LDL cholesterol following RCTs [179]. Findings from the limited number of RCTs of the MedDiet to improve cognition are also mixed [177], however, a number of methodological and baseline RCT papers have been recently published [180-182]. The benefit of a robust multi-nutrient diet is challenged by the ability to provide strong empirical interventions and assessments of a comprehensive dietary pattern. The heterogeneity of intervention protocols and additive components (e.g., hypocaloric, food supplements) limits conclusions. Of note, studies with more rigorous designs (e.g., study length/intensity, dietician developed materials, in-person lessons/consulations) elicit beneficial results [183, 184]. Strong study designs are needed to identify and optimize interventions for the target population. Reliable measures of dietary adherence, metabolic change, and suspected drivers of AD pathogenesis in MedDiet RCTs are needed. However, work is needed to establish the plasma lipoprotein profile as a potential biomarker within a dietary intervention. The plasma lipoprotein profile is suitable for determining individual level changes in lipid transport, providing a personalized approach in the context of complex UBVs and modifiable risk.

F. Study Aims

The current study examines the plasma lipoprotein profile as a mechanistic biomarker in a MedDiet intervention for obese older adults, the Bridging Research in Diet and CoGnition (BRIDGE) trial. We leveraged pre-post intervention blood plasma from females in 2 iterations of an 8-month RCT including MedDiet alone (MedDiet-A) vs. MedDiet+weight loss (MedDiet-WL) vs. usual diet (Control). Broadly, we hypothesize that individualized analytical approaches will distinguish changes in the plasma lipoprotein profiles that are not well-captured using gross measures of total lipid/proteins in plasma. Aim 1. Determine patterns of plasma lipoprotein remodeling in a MedDiet intervention. *We hypothesize that a MedDiet intervention alone and with a hypocaloric weight-loss component will result in a normolipidemic shift in plasma lipoprotein profiles. We predict that the greatest shift in cholesterol will be in the chylomicron/VLDL fractions. We hypothesize that individual level analyses will reflect robust changes and treatment adherence.* Aim 2. Establish *APOE* genotype signature plasma lipoprotein profile in obese female African American older adults including the distribution of cholesterol. Examine *APOE* effects on intervention response in a subsample of participants. *We hypothesize that the signature plasma lipoprotein profile will reflect atypical APOE-dependent dyslipidemic shifts in this population* (Table I)*. We hypothesize that patterns of APOE dependent shifts will be observed in the profiles following a MedDiet intervention.*

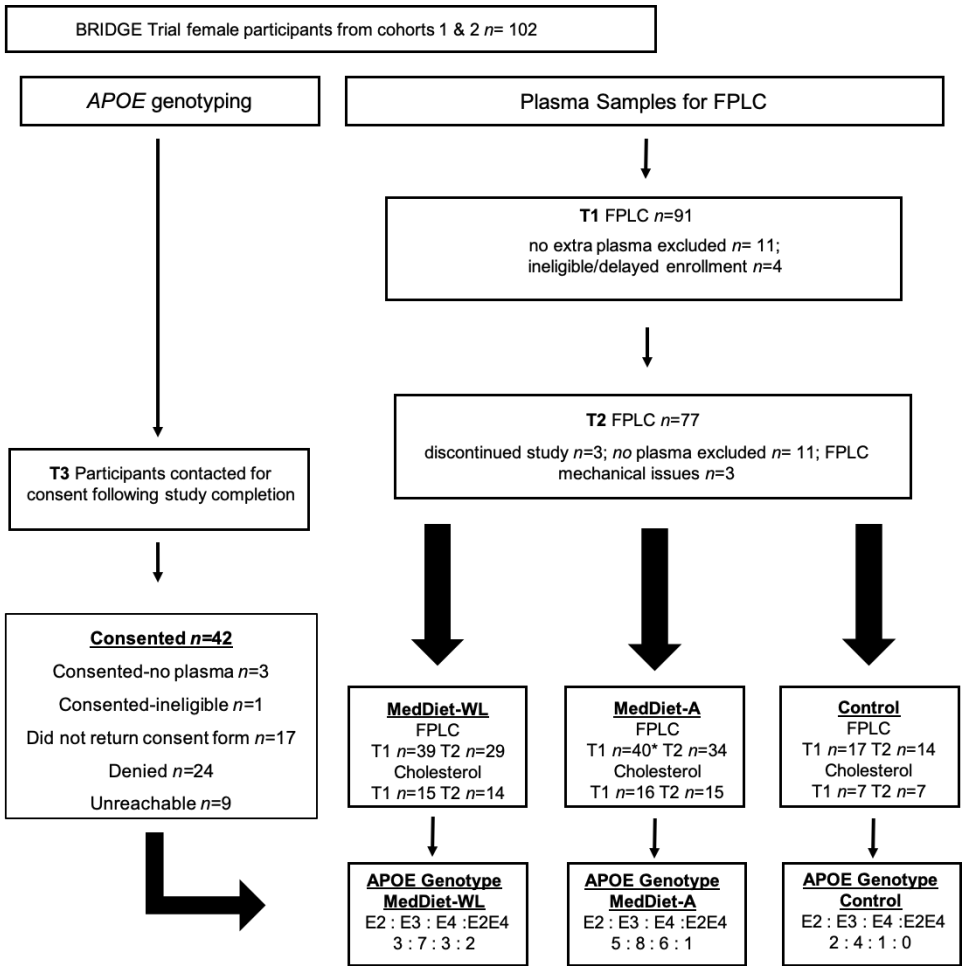
II. METHODS

A. Participants

The proposed study includes participants from the BRIDGE trial, a lifestyle intervention focused on improving cognition in obese older adults through diet and weight-loss conducted in Chicago, IL. This study was conducted at the University of Illinois, Chicago (UIC) and approved by the UIC and Rush University Medical Center Institutional Review Boards and conducted in accordance with the Declaration of Helsinki of 1975 as revised in 1983. The BRIDGE trial recruited English-speaking, predominately ethnic minority, participants. Participants were recruited for the BRIDGE trial through a research registry, community outreach (e.g., advertisements, fliers, listserv), and word of mouth. All participants provided written informed consent.

The current study leveraged data from the first 2 iterations of the study conducted on Chicago's Southside. Due to the limited power to look at sex differences in the full cohort, the proposed study recruited from the female participants only (*n*=102). Participant biospecimens from baseline and post-intervention assessments were used for the current study if 1) participants gave prior consent to use of stored biospecimen samples and 2) sufficient plasma was available for use (i.e., not designated for other analyses). 14-month follow-up data was not included. FPLC analysis was ongoing with the BRIDGE trial.

Figure II. Study procedures and sample recruitment flowchart



A subsample was recruited following the full completion of the BRIDGE trial for *APOE* genotyping at participants' final 14-month assessment study visit or over the phone. Participants provided written consent in person or via mail (See Figure II for enrollment flowchart).

1. The BRIDGE Trial

The BRIDGE trial is a three-arm 8-month randomized control trial of the MedDiet in obese (BMI 30-50 kg/m^2), English-speaking, nondemented older adults (≥55) who were predominately African American. Participants were initially screened over the phone and again in person for inclusion/exclusion criteria. Exclusionary criteria included the following: renal disease, autoimmune disorders, immunodeficiency, severe pulmonary disease, bariatric surgery, uncontrolled diabetes (hemoglobin A1c ≥ 9.0% at screening blood draw), neurological disorder (e.g., dementia, epilepsy) or traumatic injury, and psychiatric disorder. Participants were excluded if they received cancer treatment within 12 months of recruitment, prescribed Coumadin, reported drinking alcohol in excess (> 2 alcoholic drinks daily), weight greater than 450 lbs, were currently dieting or in a formal weight-loss program, anticipated receiving bariatric surgery, adhered too closely to the MedDiet (assessed via screener), or received neuropsychological testing in the 12 months prior to enrollment (i.e., research or clinical evaluations). Upon enrollment, participants were included if they were cognitively normal or in the MCI range (score ≥19 on the Montreal Cognitive Assessment; MoCA) [185].

At baseline (T1), participants underwent a dietary assessment, neuropsychological protocol, fasting blood draw, psychosocial questionnaires, dual x-ray absorptiometry scan, walk test, 7-day accelerometer reading, and optional stool sample collection. The neuropsychological assessment included the Wechsler Test of Adult Reading as a proxy of IQ and reserve (i.e., premorbid functioning and educational attainment; pVIQ) [186]. The post-intervention (T2) and 14-month follow-up assessments were identical. Participants were randomized using a stratified blocked sequence in SAS to the MedDiet-A, MedDiet-WL or Control group following the T1 assessments based on sex, age (55-69 or ≥ 70 years) and cognitive function (MoCA scores – 19-26 and 27-30). During the 8-month intervention, in-person group intervention sessions were held weekly through month 6 and bi-weekly thereafter. Participants in MedDiet-A receive 60-minute group sessions and MedDiet-WL receive 60-minute group sessions in

addition to a 30-minute supervised exercise. To summarize, the group intervention sessions emphasize lifestyle changes (e.g., through group activities such as cooking MedDiet recipes) to adhere to the MedDiet and MedDiet-WL additionally emphasized weight-loss through exercise and caloric restriction. MedDiet-WL and MedDiet-A participants were provided almonds, olive oil, and up to $10 per week for MedDiet congruent foods/groceries. See Tussing-Humphrey and colleagues' methodology paper for the full BRIDGE Trial study protocol including content of the intervention group sessions [187].

B. Procedures

Procedures and recruitment for the current study protocol are outlined in Figures II and III.

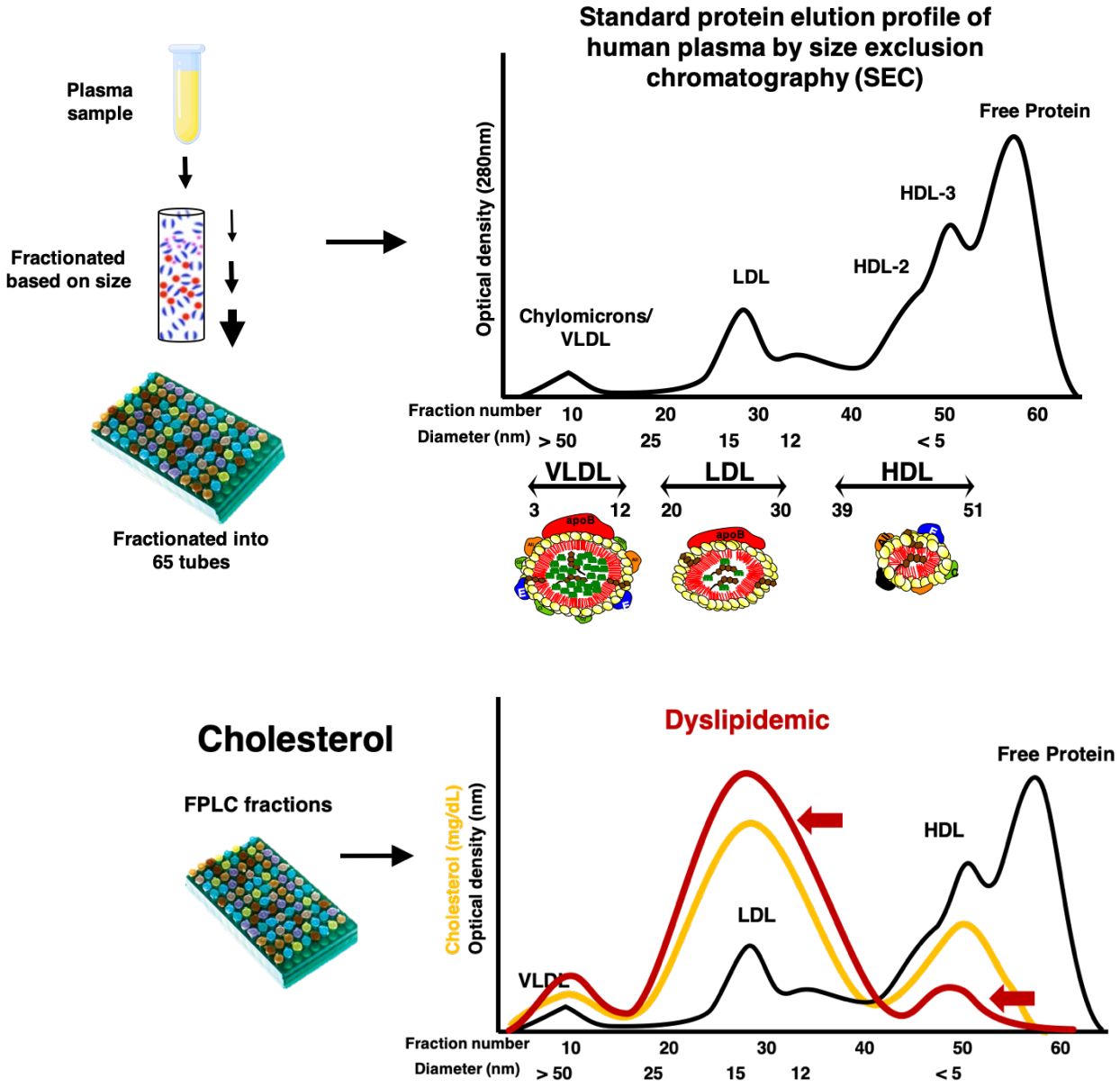
1. Plasma Collection and Storage

Fasting blood draws (≥10 hours from last meal) were completed by trained research personnel via venipuncture. Blood was immediately centrifuged at 4 degrees centigrade 3,000 rpm for 10 min. Plasma samples were transferred on dry ice and stored in a -80°C freezer until analysis. Analysis for all samples occurred <12 months after freezing.

2. Size Exclusion Chromatography

Plasma samples were defrosted on ice and subsequently centrifuged for 15 minutes at 1.5 rcl. Plasma (250 μL) was fractionated by size-exclusion chromatography, FPLC with two Superose 6 GL6/300 columns in tandem in 0.02 M sodium phosphate, 0.05 M NaCl, 0.03% EDTA, and 0.02% sodium azide, pH 7.2. Sixty-five fractions of 400 μL are collected at a flow rate of 0.4 mL/min with a void volume of 12 mL (NGC™ 10 Chromatography System, Bio-Rad Laboratories Inc). The lipid/protein content in FPLC is highly correlated with whole plasma measurement (r^2 = .99), is reproducible and maintains conformation with 73-101% detection of lipid/protein particles after plasma freezing at -80°C for over 12 months [188].

Figure III. Plasma lipoprotein profile protocol and assay



3. Assays

Cholesterol concentrations were quantified in every 3rd FPLC fraction starting with the 3rd fraction and interpolated. Interpolation procedure takes the raw values from the wells to determine mg/dL cholesterol based on standard wells that underwent the same analysis from their respective kits. Cholesterol was measured using cholesterol assays (Thermo Fisher Scientific). Area under the curve (AUC) of FPLC and fraction concentrations were calculated using integration (Prism version 8.3.1; Graphpad Software LLC). For simplicity, Chylomicron/VLDL fractions will be referred to as VLDL in the methods and results sections.

4. *APOE* Genotyping

APOE genotyping was based on allele-specific polymerase chain reaction (PCR) methodology adapted to real-time PCR using a TaqMan probe [189]. 2 single nucleotide polymorphisms in the 112th (rs429358) and 158th (rs7412) amino acids of *APOE* identified each allele (ε2, ε3, ε4). *APOE* genotype was defined as E2 (e2/2, e2/3), E3 (e3/3), and E4 (e3/4, e4/4). Genotyping was conducted by the UIC Genome Research Core. Participants with e2/4 (E2E4) alleles were not included in baseline *APOE* statistical analyses. E2E4 profiles are illustrated in Figure IV.

5. Dietary assessment

The Harvard Food Frequency Questionnaire (FFQ) is a semi-quantitative questionnaire (frequency and serving size of 131 foods) that was administered by trained research personnel as a structured dietary intake assessment with standardized food models [190]. The MedDiet score was developed by Panagiotakos et al. [191] and then adapted for use in US populations [192]. Self-reported weekly-portion consumption of MedDiet adherent and nonadherent foods were calculated. MedDiet adherent foods (i.e., unrefined grains, fruits, vegetables, potatoes, fish, legumes, and nuts) were scored using the following scale: 0 = never, 1 = rare, 2 = frequent, 3 = very frequent, 4 = weekly, and 5 = daily consumption. This scale was reversed (e.g., 5 = never, 4 = rare, etc.) for 3 nonadherent MedDiet foods (i.e., red and processed meat, poultry, full-fat dairy). Alcohol consumption was scored to reflect high MedDiet

adherence for moderate daily alcohol consumption. MedDiet scores range from 0 to 55, with greater MedDiet adherence reflected in higher scores.

6. Body composition/Anthropomorphic measures

Weight was measured in duplicate, averaged, and rounded to the nearest .1 kg using a digital scale. Dual energy x-ray absorptiometry (DXA; General Electric Lunar iDXA machine; GE Healthcare, US) was used to calculate visceral adiposity (VAT) and %total body fat (%body fat). Weight was measured in duplicate, averaged, and rounded to the nearest .1 kg using a digital scale. Body mass index was calculated using the standard formula: $BMI = \frac{weight(kg)}{height(m)^2}$

III. Statistical Analyses

1. Data accuracy

Missing data due to sampling limitations and procedural errors (e.g., participants lost to follow-up, *APOE* subsample, lost data from FPLC malfunction) led to inconsistent sample sizes across analyses. Specifics are detailed in Figure II. We addressed missing data in a number of ways that are detailed below. Intervention group differences in participant characteristics (e.g., age, BMI) were assessed for each varied sample. We applied analyses capable of performing powerful repeated measures analyses in small samples. Mixed models specifically were performed without deleting cases with missing data. Specific instances of missing or extreme data were handled through careful data manipulation for select samples. Flow void disruption during FPLC runs were corrected for by removing corresponding time-based optical density data points (n=4); fraction collection was not affected. Scores were imputed based on a regression model of the 4 preceding fractions for 1 participant sample FPLC run that ended prematurely. Extreme outliers (1 fraction adjusted, n = 2) +/- 4 SD outside of the interquartile range were adjusted with winsorization to maintain our sample size while mitigating the potential influence of outliers.

2. Analyses

Group differences (MedDiet-A, MedDiet-WL and Control; *APOE* genotypes) in participant demographic and health characteristics were examined using Chi-square analyses for nominal variables and ANOVAs for continuous variables. Correlations within the MedDiet-WL and MedDiet-A groups between percent of classes attended and measures of change in diet and weight/fat as a proxy for intervention dose-response for follow-up analyses. See Tables II and III for characteristics of the baseline/intervention and Table IV for the *APOE* subsample. Analyses were conducted using Prism version 8.3.1 (Graphpad Software LLC), SPSS version 24 (IBM), and SAS 3.8 (SAS Institute Inc., Cary, NC). AUCs were calculated using the integral function in Prism v. 8. Lipoprotein classes were defined by the following peaks: VLDL (peaks 3-12), LDL (peaks 20-30), and HDL (peaks 39-51). Repeated or random effects, mixed models were

applied for baseline and intervention analyses as these models are suitable for nested/grouped repeated measures with high covariance across subjects and time in small samples [193]. All models used a Kenward Rogers adjustment for degrees of freedom. All statistical analyses controlled for age and BMI. Additional covariates are listed in text.

1. **Aim 1**

Multilevel mixed models determined the effects of the MedDiet intervention on T2 peak fraction concentrations (total protein, cholesterol) within lipoprotein classes. Similar multilevel mixed models were run for T2 fractions while controlling for T1 fraction concentrations. The covariance structure of the repeated effects was compound symmetric. To determine significant person-level intervention response, reliable change indices (RCI) were calculated (individual peaks) to determine significant individual T1 to T2 changes and to graphically represent dispersion amongst the groups. RCI was calculated using the Christensen and Mendoza formula with significance set at z =+/-1.96 for 95% confidence [194]. Control group concentrations from T1 (*X*) and T2 (*Y*) were used to calculate the standard error of the difference for all participants.

$$RCI = \frac{(X-Y)}{SE_{Mdiff}\sqrt{S_X^2 + S_Y^2 - 2S_x S_Y r_{XY}}}$$

To determine whether shifts were detectable at the level of total lipoprotein class lipids/proteins, ANCOVAs and RCIs examined the effect of intervention group on change scores of lipid/protein concentration AUCs (ΔAUC = T2 – T1) within lipoprotein classes (VLDL, LDL, HDL).

Table II. Participants Characteristics by Intervention Group: Baseline sample

	MedDiet-WL (n = 35)	MedDiet-A (n = 40)	Control (n = 17)
Age, *M*(SD)	64.8(5.0)	66.2(6.2)	67.1(6.5)
Racial/ethnic minority, *n*, %	35, 100%	39, 100%	16, 94%
Education, *n*, %			
< high school	1, 2.9%	0, 0.0%	0, 0.0%
high school or GED	3, 8.6%	0, 0.0%	0, 0.0%
some college or Associates	9, 25.7%	18, 45.0%	8, 47.1%
college graduate	12, 34.3%	4, 10.0%	4, 23.5%
graduate or professional	10, 28.6%	17, 42.5%	5, 29.4%
pVIQ, *M*(SD)	95.4(8.5)	92.5(8.7)	97.4(10.0)
MoCA, *M*(SD)	25.3(2.7)	24.9(2.4)	25.0(2.9)
BMI, *M*(SD)	37.4(4.2)	36.5(4.4)	35.9(3.9)
Cholesterol Medications, *n*, %	8, 22.9%	6, 15.0%	3, 17.6%

Note: BMI: Body mass index; pVIQ: predicted verbal intelligence quotient; MoCA: Montreal Cognitive Assessment. Baseline analyses include participants with any T1 data available.

Sensitivity analyses and case study: Additional ANCOVAs were conducted to determine whether individuals who responded to the primary intervention targets (i.e., improved diet adherence, body composition changes) showed more beneficial shifts in their plasma lipoprotein profiles. We determined our groups (High vs. Low Responders) by coding whether there was a significant or greater than the median response in at least 3 metrics of MedDiet adherence changes (ΔMedDiet), weight loss (Δweight), and body composition (visceral adiposity, %body fat; ΔVAT, Δ%fat). We first coded groups regardless of MedDiet intervention dichotomously including

Table III. Participants Characteristics by Intervention Group: Intervention sample

	MedDiet-WL (*n* = 32)	MedDiet-A (*n* = 37)	Control (*n* = 16)
Age, *M*(SD)	65.1(4.9)	66.6(6.2)	67.5(6.5)
Racial/ethnic minority, *n*, %	29, 100%	34, 100%	13, 93%
Education, *n*, %			
< high school	1, 3.1%	1, 2.7%	0, 0.0%
high school or GED	3, 9.4%	0, 0.0%	0, 0.0%
some college or Associates	9, 28.1%	16, 43.2%	8, 50.0%
college graduate	10, 31.3%	4, 10.8%	3, 18.8%
graduate or professional	9, 28.1%	16, 43.2%	5, 31.3%
pVIQ, *M*(SD)	94.6(9.0)	93.5(7.7)	96.5(10.3)
MoCA, *M*(SD)	25.4(2.8)	25.0(2.4)	24.7(2.8)
BMI, *M*(SD)	37.2(4.4)	36.5(4.5)	36.2(3.8)
Cholesterol Medication, *n*, %	7, 21.9%	6, 16.2%	3, 18.7%

Note: BMI: Body mass index; pVIQ: predicted verbal intelligence quotient; MoCA: Montreal cognitive assessment. Intervention sample includes all participants with any T2 data available, i.e., not including individuals lost to follow-up or without sufficient T2 plasma.

MedDiet High vs. Low (median split increase MedDiet scores), significant losers (≥5% body weight loss) vs. non-losers, and body composition High vs. Low (median split decrease in VAT grams, VAT cm^3 or %body fat). Plotted plasma lipoprotein profiles of High Responders and Low Responders were used to determine post-hoc analyses (see Figure IV. Significant peak differences were then analyzed to determine whether dietary and/or body composition drove profile shifts using dichotomous groups. Bonferroni corrections were applied to post-hoc analyses within each lipoprotein class. Insufficient data was available for sensitivity analyses with cholesterol concentrations, however this data was further interpreted via exemplar cases. Case examples are illustrated in detail to demonstrate the utility of the plasma lipoprotein profile to reliably detect individual differences.

2. Aim 2

Baseline plasma lipoprotein profiles were plotted graphically to illustrate the mean total group profile and by *APOE* genotypes (Figures IV and V). Significant differences are noted in corresponding figures based on the following analyses. Multilevel mixed models controlling for age and BMI determined fraction concentration (protein, cholesterol) differences within lipoprotein classes (fraction peaks) by *APOE* genotype. The PROC MIXED procedure was used to test the effects of "time" or fraction (level 1), *APOE* genotype (level 2), and participant IDs (level 3). The same covariance structures were used as the procedures in Aim 1. This approach limited multiple comparisons to interpret consistent data-driven patterns vs. isolated significant

results.

IV. Results

Tables II–IV show participant characteristics for baseline and intervention data. No other group differences were observed across intervention groups or *APOE* genotype (*p*'s>.05). The percentage of intervention classes attended by MedDiet-WL and MedDiet-A was significantly correlated with ΔMedDiet [$r(66)=.308$, $p = .01$], Δfat% [$r(65)=-0.36$, $p = .003$], but not ΔVAT [$r(62)=-0.05$, $p = .68$, *ns*] or Δweight [$r(66)=-0.10$, $p = .41$, *ns*].

A. Aim 1. MedDiet Intervention

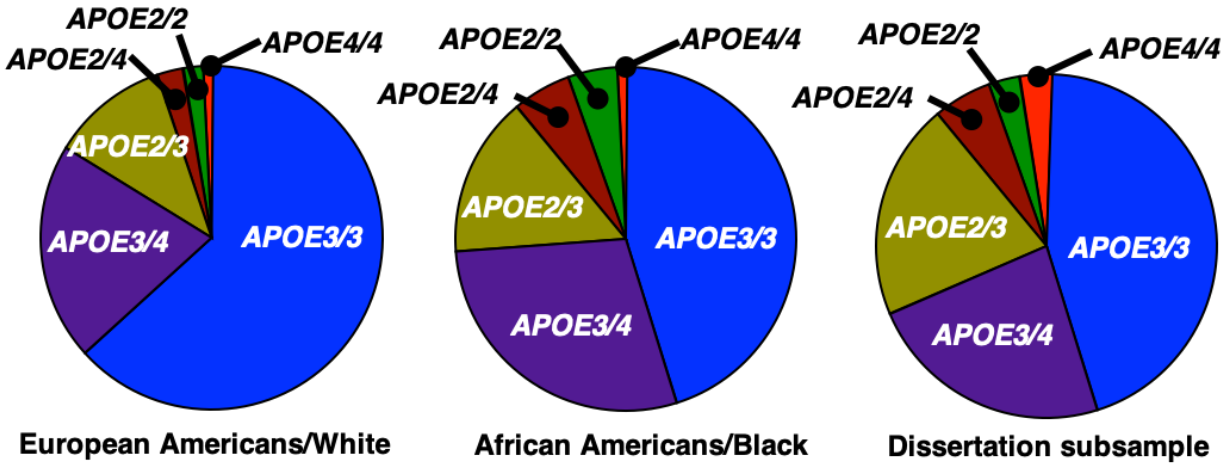
T1 and T2 overlaid plasma lipoprotein profiles and lipoprotein class ΔAUCs are plotted by group in Figures V. Mixed models revealed significant and marginal intervention*time interaction effects while adjusting for T1 respective concentrations, age, and BMI: T2 VLDL cholesterol concentration [Fraction 9 (MedDiet-A>Control), *b*=1.53, *SE*=.86, *p*=.08, *ns*]; T2 LDL protein concentration [Fraction 30 (MedDiet-A<MedDiet-WL), *b*= -0.014, *SE*=.007, *p*=.06, *ns*]; T2 HDL [Fraction 46 (MedDiet-WL < Controls), *b*= -0.04, *SE*=.02, *p*=.06, *ns*; (MedDiet-WL < MedDiet-A), *b*= -0.03, *SE*=.02, *p*=.08, *ns*]; T2 HDL [Fraction 47 (MedDiet-WL < Controls), *b*= -0.05, *SE*=.02, *p*=.02; (MedDiet-WL < MedDiet-A), *b*= -0.04, *SE*=.02, *p*=.01]; T2 HDL Fraction 48 (MedDiet-WL < Controls) *b*=-.05, *SE*=.02, *p*=.02; (MedDiet-WL < MedDiet-A), *b*= -0.06, *SE*=.02, *p*=.01]. RCIs identified heterogenous significant (protein/lipid increase $z \geq 1.96$; protein/lipid decrease $z \leq -1.96$) plasma lipoprotein profile shifts amongst a number of participants from MedDiet-WL and MedDiet-A, that was more evident at the peak level (Figures VI-VII). ANCOVAs revealed no significant effects of the MedDiet intervention on ΔAUC lipoprotein class protein/lipid concentrations (see Table V). The dyslipidemic and eulipidemic shifts are evident in exemplar profiles in Figure VIII.

Table IV. Participants Characteristics in *APOE* Genotype Subsample

	APOE2 e2/2 + e2/3 (*n*=10)	*APOE3* e3/3 (*n*=19)	*APOE4* e3/4 + e4/4 (*n*=10)	*APOE2/4* e2e4 (*n*=3)
Age, *M*(SD)	66.6(8.3)	63.6(4.1)	63.4(7.1)	64.0(8.9)
Racial/ethnic minority, *n*, %	10, 100%	19, 100%	10, 100%	3, 100%
Education, *n*, %				
< high school	0, 0.0%	1, 0.05%	0, 0.0%	0, 0.0%
high school or GED	1, 10%	1, 0.05%	1, 10%	0, 0.0%
some college or associates	2, 20%	5, 26.3%	4, 40%	1, 33%
college graduate	4, 40%	7, 36.8%	2, 20%	1, 33%
graduate or professional	3, 30%	5, 26.3%	3, 30%	1, 33%
pVIQ, *M*(SD)	96.7(5.1)	93.1(7.5)	97.6(10.8)	94.7(9.1)
MoCA, *M*(SD)	24.8(2.6)	24.5(2.6)	24.1(2.6)	28(1.7)
BMI, *M*(SD)	36.68(5.0)	38.0(5.7)	35.4(3.7)	36.8(2.3)
Cholesterol Medication, *n*, %	0, 0.0%	4, 21.1%	2, 20.0%	0, 0.0%

Note: e2: e2/e2 and e2/e3 carriers, e3: e3/e3 carriers, e4: e3/e4 and e4/e4 carriers, e2e4: e2/e4 carriers; BMI: Body mass index; MoCA: Montreal cognitive assessment; pVIQ: predicted verbal intelligence quotient. Statistical comparisons were made amongst E2, E3, E4 as E2E4 were not included in *APOE* specific analyses.

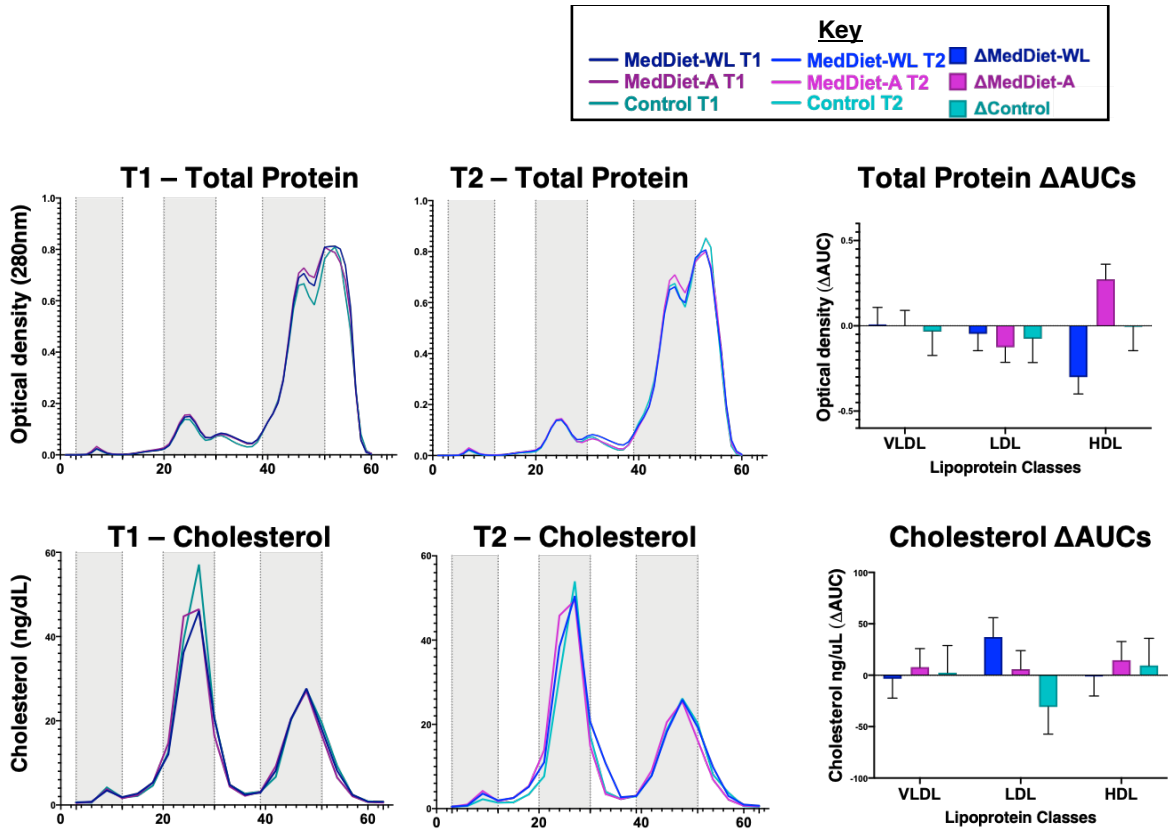
Figure IV. Population vs. BRIDGE Trial Subsample *APOE* Genotype Frequencies



APOE genotype	European Americans/White	African Americans/Black	Dissertation subsample
APOE3/3	63.4%	45.2%	45.2% (*n*=19)
APOE3/4	21.4%	28.6%	19% (*n*=8)
APOE2/3	10.2%	15.1%	21.4% (*n*=9)
APOE2/4	2.4%	5.7%	7.14% (*n*=3)
APOE4/4	2.4%	4.5%	5.7% (*n*=2)
APOE2/2	0.2%	0.7%	2.4% (*n*=1)

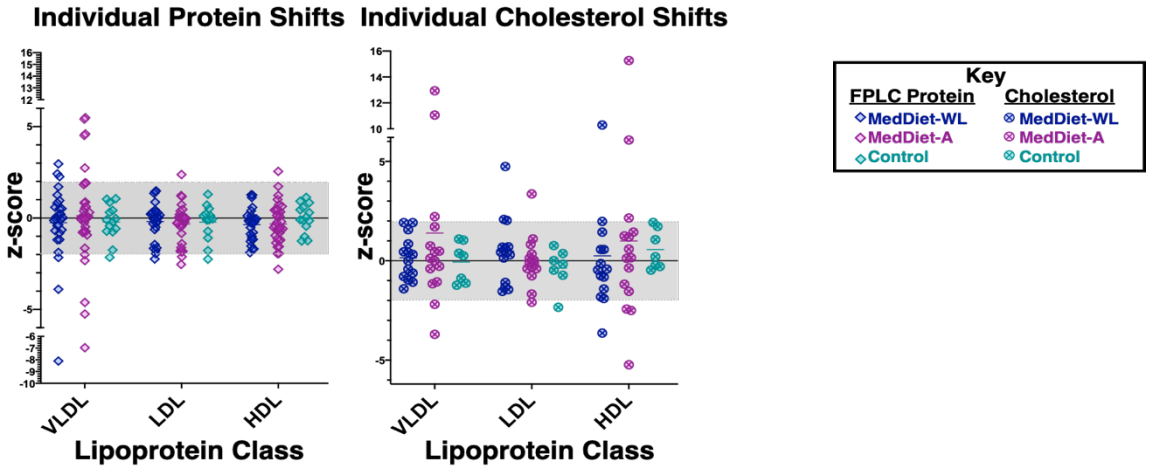
T1 and T2 plasma lipoprotein profiles of High and Low Responders are plotted in Figure IX. ANCOVAs revealed that High Responders had significantly decreased protein concentrations compared to Low Responders in VLDL peaks [see Figure IX; Fraction 6 $F(1, 58)= 8.86$, $p=.004$; Fraction 7 $F(1, 57)= 14.30$, $p<.001$; Fraction 8 $F(1, 58)= 10.47$, $p=.002$; Fraction 7 $F(1, 57)= 5.20$, $p=.02$, *ns*]. All but Fraction 9 survived Bonferroni correction ($p < .0125$). ANCOVAs controlling for baseline age and BMI revealed the same pattern of significant effects of median split ΔVAT (Fraction 7 $F(1, 57)= 4.71$, $p=.03$) median split Δ%fat (Fraction 6 $F(1, 57)= 4.79$, $p=.03$; Fraction 7 $F(1, 57)= 4.86$, $p=.03$; Fraction 8 $F(1, 57)= 3.90$, $p=.05$) and significant weight loss on shifts (Fraction 7 $F(1, 57)= 5.62$, $p=.02$), but not ΔMedDiet (nonsignificant data not shown, p's > .05).

Figure V. T1 vs T2 Intervention Group Plasma Lipoprotein Profiles



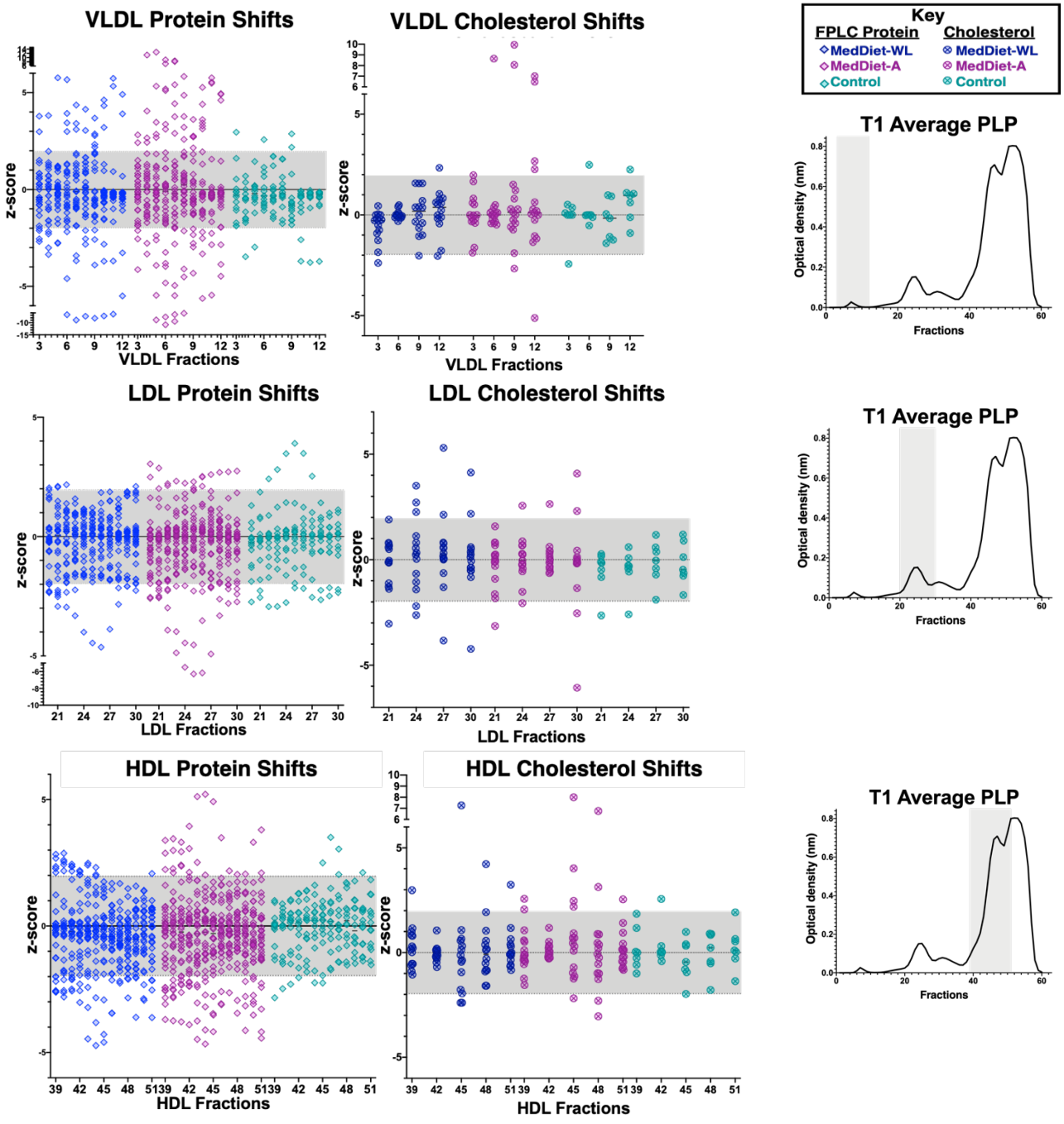
Note: AUC: Area under the curve; HDL: High density lipoprotein; LDL: low density lipoprotein; T1: baseline assessment; T2: post-intervention assessment; VLDL: very low density lipoprotein

Figure VI. Lipoprotein Class AUC RCIs by Intervention Group



Note: AUC: Area under the curve; HDL: High density lipoprotein; LDL: low density lipoprotein; T1: baseline assessment; T2: post-intervention assessment; VLDL: very low density lipoprotein.

Figure VII Lipoprotein Class Peak RCIs by Intervention Group



Note: Average PLP: Plasma lipoprotein profile made rendering of all participant baseline profiles with VLDL, LDL, or HDL peaks shaded gray; HDL: High density lipoprotein; LDL: low density lipoprotein; RCI: Reliable change index; T1: baseline assessment; VLDL: very low density lipoprotein. Significant reliable change indices ($z \geq 1.96$ & $z \leq -1.96$) are represented outside of the shaded areas on the graphs.

Table V. Intervention Group Effects on ΔAUCs

		ΔAUC Protein		
Lipoprotein class	df	*F*	η^2	*p*
VLDL	(4, 72)	.246	.007	.78
LDL	(4, 72)	.307	.008	.74
HDL	(4, 72)	.506	.01	.61
Lipoprotein class		ΔAUC Cholesterol		
VLDL	(4, 31)	1.208	.07	.31
LDL	(4, 31)	.664	.04	.52
HDL	(4, 31)	.359	.02	.70

Note: AUC: Area under the curve; HDL: High density lipoprotein; LDL: low density lipoprotein; MedDiet: Mediterranean diet; VLDL: very low density lipoprotein. ANCOVAs controlled for age and T1 BMI.

Figure VIII. Individual Eulipidemic vs. Dyslipidemic Plasma Lipoprotein Profile Shifts

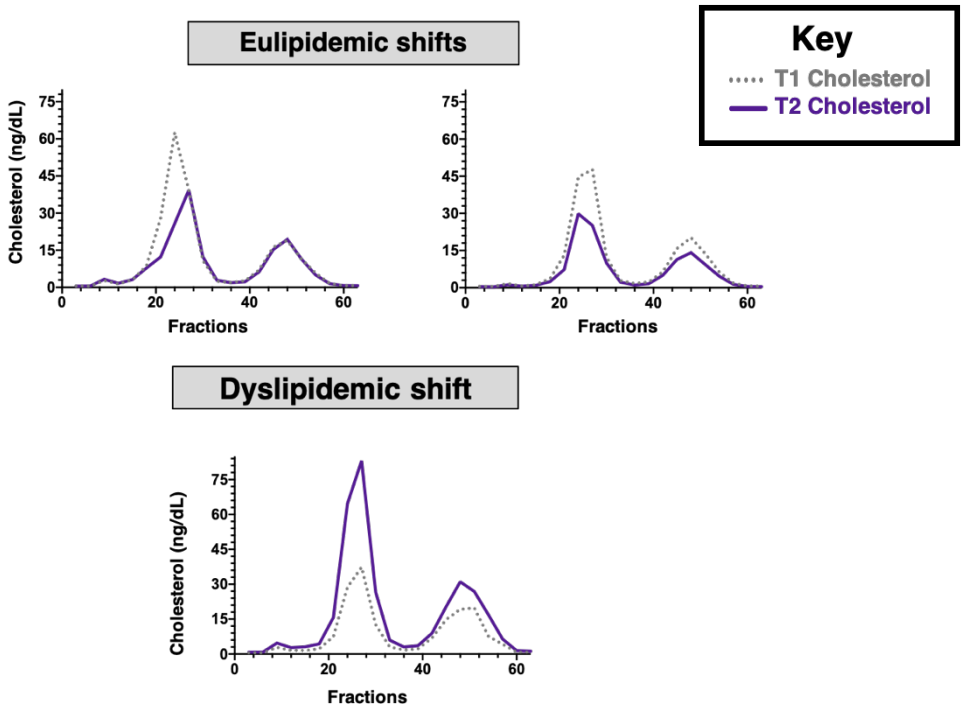
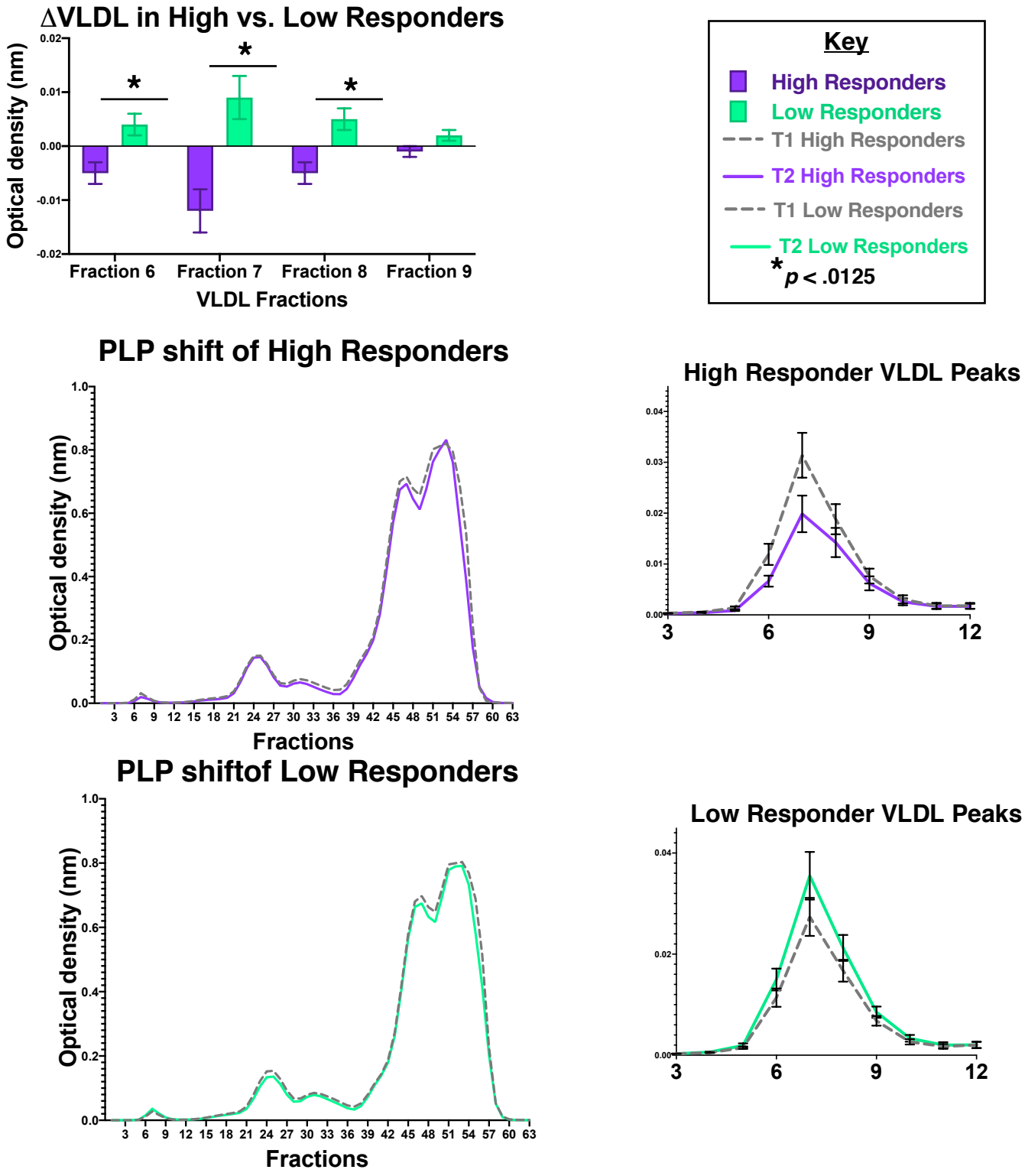


Figure IX. MedDiet Intervention High Responders vs. Low Responders Plasma Lipoprotein Profile Shifts

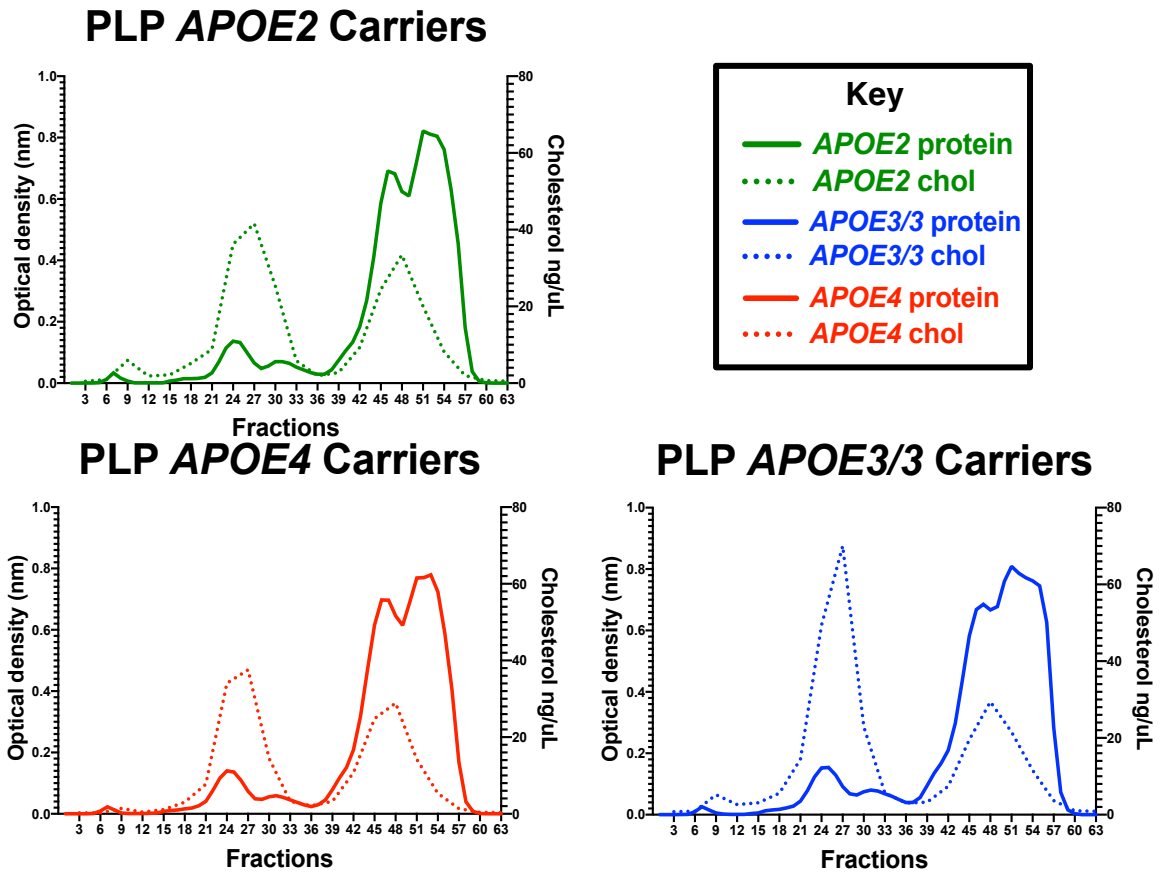


Note: HDL: High density lipoprotein; LDL: low density lipoprotein; PLP: Plasma lipoprotein Profile; T1: baseline assessment; T2: post-intervention assessment; VLDL: very low density lipoprotein.

B. Aim 2. *APOE* subsample

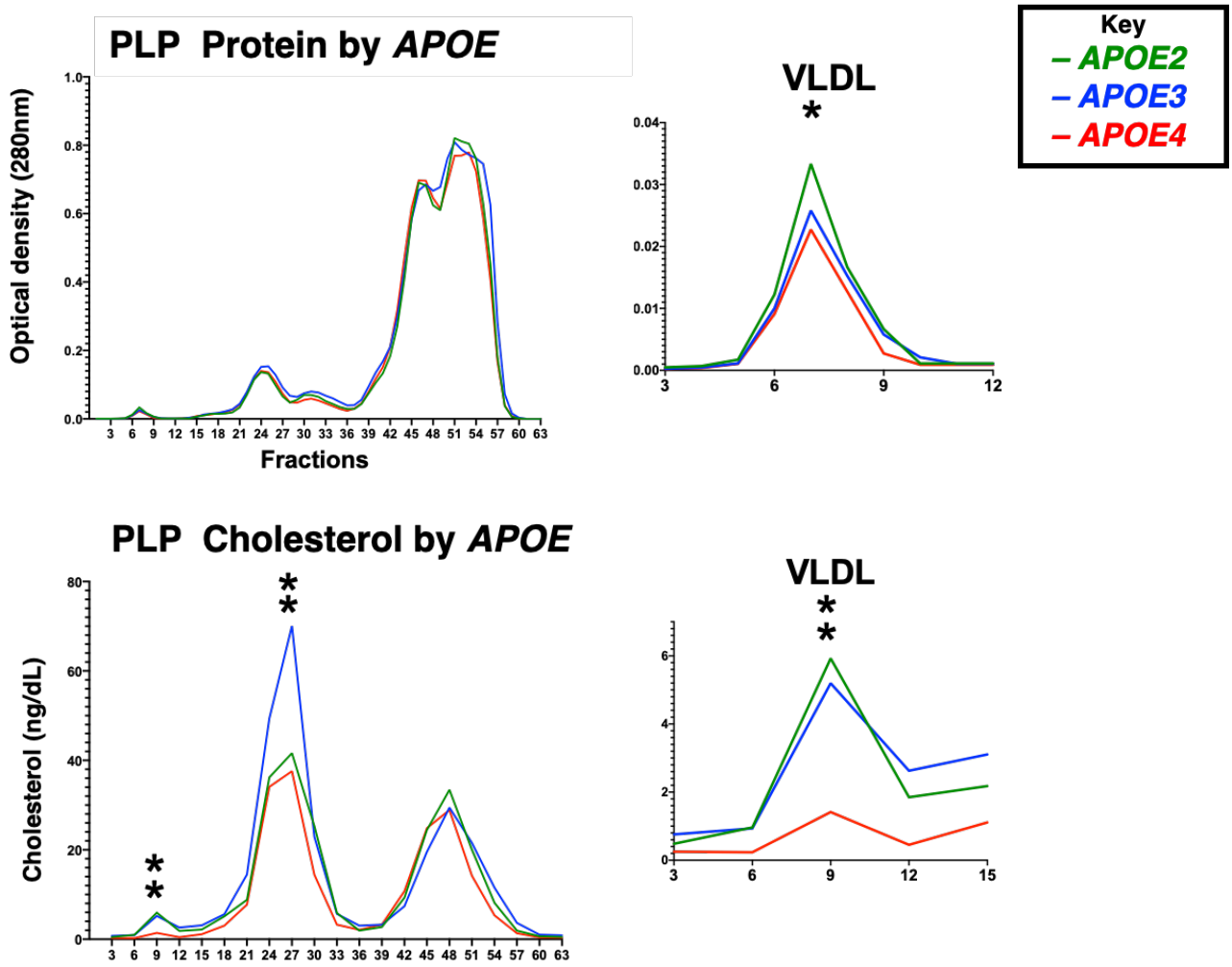
APOE signature plasma lipoprotein profiles are illustrated in Figures X. Fully adjusted mixed models examining peak concentrations within lipoprotein classes revealed significant *APOE**time interactions for VLDL peaks: Protein (E2 > E4; Fraction 7), *b*=0.013, *SE*=.005, *p*=.008; cholesterol (E2 > E4; Fraction 9) *b*=4.28, *SE*=1.66, *p*=.03; cholesterol (E3 > E4; Fraction 9) *b*=3.28, *SE*=1.39, *p*=.02; (E2 > E4; Fraction 9) *b*=4.28, *SE*=1.66, *p*=.01. LDL peaks: cholesterol (E3 > E4; Fraction 27), *b*=29.91, *SE*=11.27, *p*=.009; cholesterol (E3 > E2; Fraction 27), *b*= 27.98, *SE*=11.98, *p*=.02. See Figure XI.

Figure X. APOE Signature Plasma Lipoprotein Profiles



Note: APOE2: e2/2 carriers and e2/3 carriers; *APOE3:* e3/3 carriers; *APOE4:* e3/4 carriers and e4/4 carriers; chol: cholesterol; HDL: High density lipoprotein; LDL: low density lipoprotein; PLP: Plasma lipoprotein Profile; T1: baseline assessment; T2: post-intervention assessment; VLDL: very low density lipoprotein.

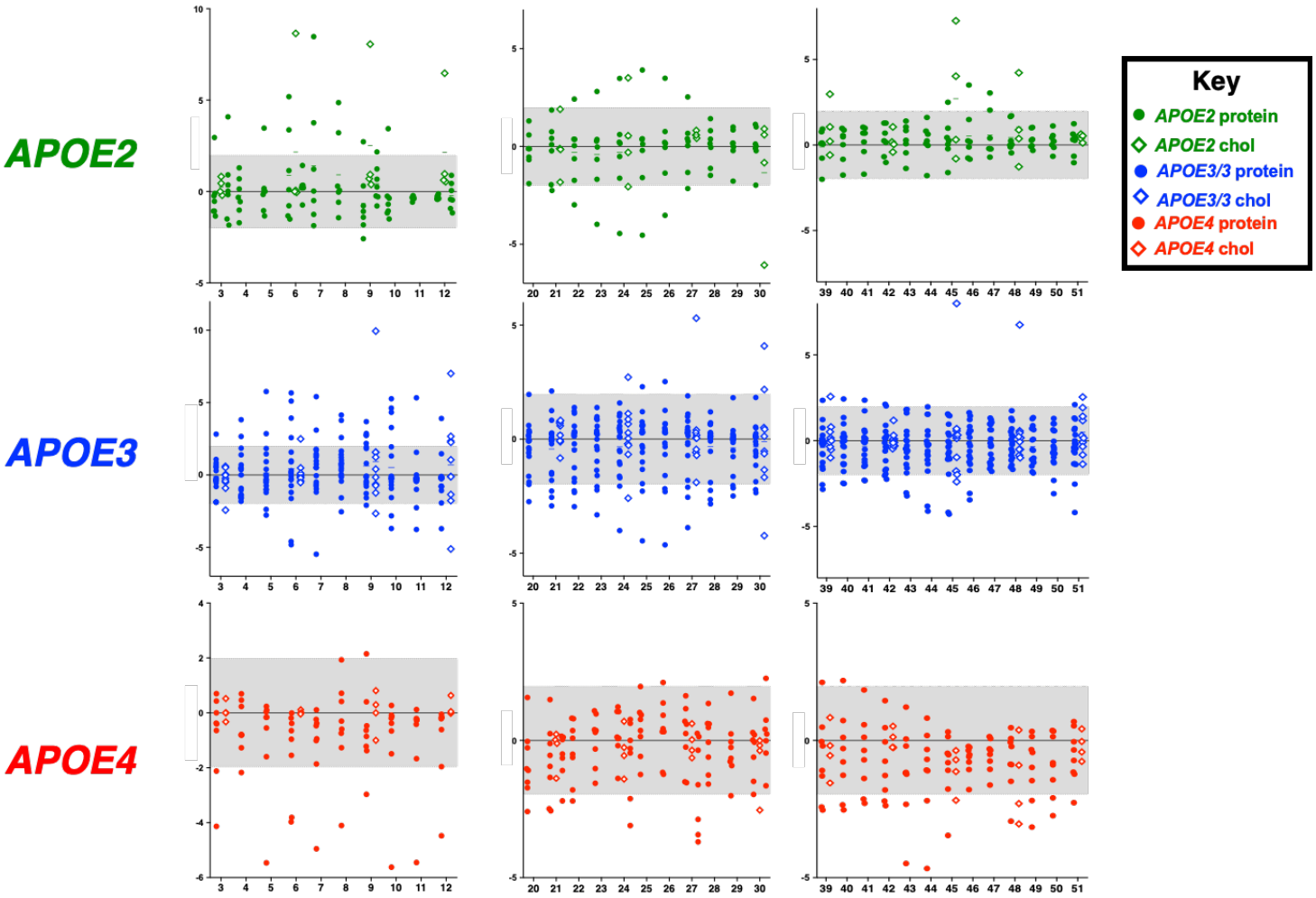
Figure XI. *APOE* dyslipidemic effects in VLDL protein/cholesterol and LDL cholesterol



Note: APOE2: APOE e2/2 carriers and e2/3 carriers; *APOE3: APOE* e3/3 carriers; *APOE4: APOE* e3/4 carriers and e4/4 carriers; HDL: High density lipoprotein; LDL: low density lipoprotein; PLP: Plasma lipoprotein Profile; T1: baseline assessment; T2: post-intervention assessment; VLDL: very low density lipoprotein.

RCIs plotted across groups revealed genotype specific patterns of responses, predominately in VLDL fractions (See Figure XII). *APOE2* RCIs generally revealed significant increases in protein/cholesterol, with a number of extreme values in VLDL fractions, and very limited significant peak changes in HDL. *APOE3* results were bidirectional, with changes in indicated across lipoprotein classes, and greater shifts in lower density lipoprotein peaks. *APOE4* showed significant decreases across lipoprotein classes, and very few increases in protein content that was just above the significant cut-point ($z \geq 1.96$).

Figure XII. Reliable Change Indices of Lipoprotein Class AUCs in *APOE* Subsample



Note: APOE2: e2/2 carriers and e2/3 carriers; *APOE3:* e3/3 carriers; *APOE4:* e3/4 carriers and e4/4 carriers; HDL: High density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein. Significant reliable change indices ($z \geq 1.96$ & $z \leq -1.96$) are represented outside of the shaded areas on the graphs.

V. Discussion

A. Key Results

The current study the plasma lipoprotein profile as an *APOE* dependent biomarker in a MedDiet RCT. This study is the first, to our knowledge, to use SEC as a personalized biomarker of intervention response, and to address the potential of this biomarker in a sample of obese female older adults that were predominately ethnic minorities (i.e., African American or mixed race). First, we demonstrated MedDiet intervention effects on the plasma lipoprotein profiles, with results primarily driven by changes in body composition. We then determined the *APOE*-dependent signature profiles and shifts. Finally, case exemplars were given to further illustrate the utility of the plasma lipoprotein profile as a biomarker.

B. Mediterranean Diet Intervention

Linear mixed models revealed significant shifts in VLDL, LDL, and HDL fractions in relation to either the MedDiet-A or MedDiet-WL groups. Across various analytical approaches, VLDL exhibited the most consistent shifts. This is consistent with our hypotheses as chylomicrons/VLDL are the exogenous lipid transporting lipoproteins involved in fat distribution and are most responsive to decreased adiposity/aerobic exercise [128, 129]. Sensitivity analyses indicated that those from either MedDiet arm with improvement on at least 2 measures of efficacy (i.e., diet, total fat, visceral fat, weight) had greater decreases in peak VLDL fractions. This was driven by individuals with above the median decreases in visceral fat and percent total body fat, and individuals with significant weight loss (>5% baseline reduction). There were also shifts in LDL (nearest Lp(a) fractions) and HDL-3, that could denote specific cardiovascular benefit. Individuals in the standard MedDiet-A group and in the hypocaloric MedDiet-WL group showed significant, but heterogeneous shifts in the plasma lipoprotein profiles.

While group level differences were captured in models that account for individual differences, AUCs did not capture this. were not captured by AUCs that may provide a gross comparison to a lipid panel. As hypothesized, plasma lipoprotein profile shifts were not uniform. The RCIs revealed a variety

of significant interindividual patterns. Importantly, the RCIs calculated for participants at individual fractions indicate that while the most frequent and robust shifts occurred in VLDL, numerous participants showed changes in LDL and HDL fractions. Shifting endogenous lipids carried by LDL and HDL is more difficult, but was notable in some individuals in our sample. Identifying the fractions and components that are more specific markers of disease progression is the next step in establishing the utility of the plasma lipoprotein profile as a biomarker of lipoprotein remodeling for AD and other disorders. *APOE* is part of a larger gene cluster that determines the lipoprotein profile, and confers risk/resilience for AD in African Americans [195-197]. Personalized biomarkers are needed given the complexity and degree of genetic and modifiable factors involved in peripheral lipid transport.

Overall the trial showed a clear dose-response pattern of efficacy, as increased MedDiet scores and decreased body fat percentage were correlated with intervention attendance. Thus, both the behavioral intervention, and the obesity targets promote eulipidemic shifts on the plasma lipoprotein profile. Median split MedDiet scores within the intervention groups were not associated with shifts in VLDL fractions. This may be due in part to the heterogeneity of the MedDiet, or that some dietary supplements were standardized across groups (i.e., almonds, olive oil). Further, the specific nuances of dietary changes within the intervention groups may be more notable in lipids (e.g., cholesterol, triglycerides), and not enough cholesterol data was available for the sensitivity analyses. A number of factors such as adequate fiber, nutrient density, food quality, and maintaining poor lifestyle habits (e.g., trans fatty acid intake, sedentary behavior) could further drive these differences [88, 198-201]. For example, it is likely that some individuals increased consumption of fruits without balanced decrease in sugar/carbohydrates. Certain foods/beverages are ubiquitously high in sugar though disguised as being healthy (e.g., through vegetable/fruit base, marketing) such as tomato-based sauces or protein bars [202, 203]. Alternatively, the reliability of this measure could be skewed by factors that would not influence the body composition measures including biased reporting related to psychological reasons (e.g., consistency

or desirability) or as it related to accuracy (e.g., mild cognitive impairment). Future work will further analyze food components that may be better proxies of the dietary changes implicated in the profiles.

C. APOE signature profiles

APOE signature profiles in predominately African American females with compounding modifiable risk were largely consistent with our hypotheses. Specifically, the lower chylomicron/VLDL lipoproteins observed in the E4 carriers is consistent with the high apoE4 affinity for this lipoprotein class and LDL receptors. While e2 homozygotes have the lowest AD risk, a poor diet puts them at increased risk for cardiovascular disease and type III hyperlipoproteinemia as a consequence of low LDL affinity [204, 205]. The dyslipidemic signature in E3 carriers (greater chylomicron/VLDL protein and chylomicron/VLDL/LDL cholesterol concentrations) is intriguing, and not consistent with our hypotheses or prior work in African American populations [206]. This does not appear to be an artifact of lipid reducing medications (see Table IV). However, there may be complex interactions with obesity and other medical conditions (e.g., diabetes, cancer history) in our sample of post-menopausal females that drive this signature. More work is needed to develop comprehensive plasma lipoprotein profiles in well-matched samples that consider the interplay of relevant genetic, medical, and lifestyle factors. Our personalized approach using RCIs show preliminary evidence for an *APOE* specific response to diet. The control group was predominately e3/3 carriers and the majority of e3/4 and e4/4 carriers were in the intervention groups (see Figure 3). For this same reason, we were unable to examine how *APOE* moderated treatment response at the group level. A number of studies have identified preferential, limited, or adverse treatment response in *APOE4* females [207-210]. Randomization with equal distributions of *APOE* genotypes for group stratification in future studies is needed to understand the implications for dietary intervention. Broadly, there is evidence that diet has a beneficial effect on brain health outcomes

regardless of genotype. However, future work has the potential identify ways to tailor diet as a method of prevention or treatment augmentation [211].

In relation to the cardiovascular literature, thresholds for lipoprotein synthesis may exist in an isoform-specific manner. Thus, a lipoprotein profile of an E4 carrier with relatively less LDL cholesterol may still confer risk for AD. It may be difficult to disentangle these effects on AD via cognitive outcomes in humans, as a number of factors may be directly or indirectly involved (e.g., insulin resistance, white matter disease). In EFAD mice fed a Western diet, E3FADs exhibited greater weight gain and metabolic disturbance with some worsened behavioral outcomes, whereas E4FADs showed advanced AD pathology overall [212]. Similar findings have been shown in other FAD/APOE transgenic models [213, 214]. Of course, transgenic AD mouse models have their own limitations for addressing this question [60, 215]. Continued translational work is needed to determine to what degree modifiable factors (e.g., obesity, Western diet) exhibit *APOE*-dependent risk thresholds for driving pathogenic burden. *APOE* directly affects treatment response for other modifiable risk factors and related drug therapies [216, 217].The plasma lipoprotein profile is an ideal marker for defining the specific risk-dependent changes in peripheral lipid transport and dietary intervention.

Our formal *APOE* analyses did not include the E2/E4 group due to the small sample (n=3),. Select studies have examined the duality of the elusive e2/4 phenotype. In the National Alzheimer's Coordinating Center collaborative multisite cohort (AD cohort n=11,871; 2.5% e2/4 carriers), the risk of incident AD via clinical diagnosis is increased in e2/4 (HR=1.74) compared to e3/e3 [218]. In a sample of French-Canadian older adults with cardiometabolic risk in which e2/4 is more prevalent, e2/4s exhibit similar intermediate effects on lipoprotein profiles with notable patterns of: total TAG/hypertriglyceridemia e2/2 > e2/4 > e3/3, VLDL TAG/cholesterol e2/2 > e2/4 = e4/4, and LDL cholesterol e2/2 < e2/4 = e4/4. See Villenueve et al., 2015 for more comprehensive results [154]. This study used ultra-centrifugation and did not stratify by sex. While rare in general US population, studying e2/4 heterozygotes is important for understanding competitive dynamics between different isoforms that

could, in theory, be leveraged in developing *APOE* therapeutics. Further, e2/4 is more prevalent in a number of populations (e.g., nearly 6% in African Americans) [219]. In sum, the plasma lipoprotein profiles of obese female older adults have unique *APOE*-dependent signatures. Comparisons of the plasma lipoprotein profiles with other age-matched relevant groups (non-obese or metabolically healthy obese, normal weight obese, males) will be valuable to conceptualize these results. More work is warranted to understand the interplay of chronic modifiable risk (i.e., poor diet, obesity) and universal biological risk (i.e., sex, *APOE*) on peripheral lipid transport that has not been captured by the recent influx of metabolomics studies. Biomarker validation studies will further define parameters of risk in the profiles for AD and related pathology (e.g., small vessel disease) in this population [220] [221].

D. Limitations

There are notable limitations to this study. The nature of the funding and recruitment of this add-on study led to a smaller and unequally distributed sample with *APOE* genotypes and inconsistent samples for group-level intervention analyses. There was also loss to follow-up in the BRIDGE Trial's 2nd iteration that limited the sample size available for intervention analyses. Risk factors (e.g., diabetes, breast cancer history) that weaken blood vessels were common in this population. Difficulty with venipuncture and blood draw quantity reduced the available plasma samples for this add-on study. However, the personalized biomarker approach lent itself to examination of small and even individual samples. While lifestyle interventions have the potential for more robust multi-target outcomes, there is overt heterogeneity introduced by behavioral methods. While participants received supplemental food items, controlling participant's complete dietary intake in the context of a large study is not feasible. However, the study was designed and implemented by a diverse research team that has experience working with racial/ethnic minorities in research and clinical settings. Specific aspects of the lifestyle intervention likely increased participation and adherence to nonpharmacological interventions in this population (e.g., social support from a group setting/interventionists) [222]. Overall, our study benefited from the rigorous methodology, overall sample size, length, intensity, and quality of the BRIDGE Trial intervention [187].

Importantly, our use of every 3rd fraction to assay cholesterol limited this aspect of the plasma lipoprotein profiles, and may have substantially limited the power to observe robust cholesterol shifts. While this approach allowed us to use the cholesterol kits on more participant samples, additional fraction analysis is needed. Future work may include more comprehensive lipid/protein analysis (e.g., phospholipids, DHA, apoB, oxidation) in individuals with variable risk for AD.

While the MedDiet-A group was intended to maintain their weight and caloric intake, numerous individuals in our subsample lost significant (>5% of baseline) weight (n = 11) or lost body fat above the combined MedDiet-A/MedDiet-WL group median (%body fat n = 14; VAT n = 19). It is possible that the emphasis on learning and implementing dietary changes alone was more palpable then the added pressure to decrease calories and increase physical activity.

A notable strength of The Bridge Trial is the targeted recruitment of individuals in communities that are disproportionately affected by modifiable AD risk. In addition to limiting scientific progress, the failure of science and medicine to acknowledge human diversity has led to public health disparities for women and racial/ethnicity minorities [74, 223]. In the US, urban minority-predominant communities are underserved in medicine and underrepresented in the medical literature [224, 225]. In addition, sex differences in cardiovascular disease plays a role in the sex disparity in the mixed dementia (AD + vascular disease) in females [226]. Ultimately, numerous biomarkers will likely be incorporated to appreciate various risk factors and population-specific thresholds that acknowledge diversity. Once target dietary foods are identified, a number of cultural, psychological, and socioeconomic factors must be taken into consideration for successfully implementing sustainable interventions at the community level [227].

E. Conclusion

Our results provide early support for plasma lipoprotein profiles as an *APOE*-dependent biomarker. Further work is warranted to validate plasma lipoprotein profiles as a surrogate biomarker. RCTs employing precision medicine approaches are necessary to determine if risk modification is viable

in older at-risk populations. Our findings demonstrate that lipoprotein remodeling occurs in a heterogenous patterns in response to multi-nutrient diets. Though preliminary, *APOE* specific patterns of response were observed in many individuals. Importantly, this work highlights the potential of the plasma lipoprotein profile to capture target engagement and eulipidemic shifts that may go undetected using standard lipid panels or -omics methods. Further validation of the profiles will require a more in-depth understanding of the plasma lipoprotein profile and complex genetic and modifiable risk. Ultimately, characterization of signature profiles in relation to clinical outcomes (e.g., cognition) will establish whether the plasma lipoprotein profile is a surrogate AD biomarker.

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VII. VITA

AIMEE JAMES KARSTENS, MA

CLINICAL PSYCHOLOGY DOCTORAL CANDIDATE

http://karsten29.wixsite.com/aimeekarstens

EDUCATION

University of Illinois, Chicago — In progress
PhD. Clinical Psychology — Chicago, IL

University of Illinois, Chicago — May, 2016
M.A. Clinical Psychology — Chicago, IL

Tulane University — May, 2013
B.S. Psychology, Cum Laude — New Orleans, LA

POSTDOCTORAL FELLOWSHIP

Mayo Clinic, Rochester — Start date September 2020
Clinical Neuropsychology

CLINICAL INTERNSHIP

Brown University Alpert School of Medicine — July 2019 – Present
Track: Neuropsychology — Providence, RI

8-month Neuropsychology Assessment Rotation: Providence Veterans Affairs Medical Center Supervisors: Steve Correia, PhD ABPP-CN, Megan Spencer, PhD ABPP-CN, Don Labbe, PhD ABPP-CN
Outpatient and inpatient neuropsychological evaluations for veterans with neurodevelopmental, psychiatric, medical, and neurological conditions.

4-month Psychiatric Neuropsychology Rotation: Butler Hospital
Supervisors: Karen Holler, Ph.D., Athene Lee, Ph.D., Nicole McLaughlin, Ph.D.
Neuropsychological assessments in a private psychiatric hospital serving children to geriatric inpatients, and neuropsychological evaluations in multidisciplinary outpatient clinics including the Memory and Aging Program, Hydrocephalus clinic and Movement Disorders clinic.

12-month Primary Care Behavioral Health Rotation: Kent Hospital Family Care Clinic
Supervisor: Stephanie Czech, PhD
Brief behavioral health assessments and interventions in an integrated community-based primary care setting.

12-month Research Rotation: Rhode Island Hospital
Principal Investigator/Mentor: Geoffrey Tremont, PhD ABPP-CN

Ongoing projects emphasize the interaction of genetic and modifiable risk on cognitive aging and diagnostic criteria for mild cognitive impairment and dementia.

DOCTORAL MILESTONES

Dissertation: The Mediterranean Diet as an intervention to improve cognition in female obese older adults: *APOE* genotype as a moderator and plasma lipoprotein profiles as a mechanism of response.
Proposal Defended September 2018

Preliminary Examination: The Mediterranean Diet and early markers of dementia. *Defended October 2017*

Master's Thesis: The Separate and Interactive Associations of Trauma and Depression on Cognition in Urban Dwelling Adults. *Defended February 2016*

RESEARCH FUNDING

Brown University Predoctoral Seed Money Research Gran	September 2019
American Psychological Foundation Benton Meier Scholarship	August 2019
Provost Graduate Research Award	November 2018
Alzheimer's Disease and Related Dementias T32 AG057468, *Fellow*	September 2018
Provost Deiss Award	April 2018

HONORS AND AWARDS

3 Minute Thesis Competition Finalist	March 2019
Alzheimer's Disease and Related Dementias T32 AG057468, *Associate*	October 2017
International College of Psychoneuropharmacology Conference Junior Investigator Award	October 2016
University of Illinois Department of Psychology Travel Award	2015; 2016; 2017; 2018; 2019

FORMER RESEARCH POSITIONS

T32 Fellow/Research Assistant May 2017-June 2019
University of Illinois, Chicago LaDu Neurodegeneration Research Lab Chicago, IL
Principal Investigator/Mentor: Mary Jo LaDu, PhD

Research Assistant June 2016-October 2018
University of Illinois, Chicago Institute for Health Rehabilitation and Policy Chicago, IL
Principal Investigators: Marian Fitzgibbon, PhD, Melissa Lamar, PhD, & Lisa Tussing-Humphreys, PhD, RD

Research Assistant May 2017-August 2018
University of Illinois, Chicago Department of Psychiatry, Cognitive Neuroscience Center Chicago, IL
Principle Investigator/Mentor: Scott Langenecker, PhD

Research Assistant July 2017-August 2018
Northwestern University & Institute for Therapy Through the Arts Chicago, IL

Principle Investigator: Borna Bonakdarpour, MD

Research Assistant August 2014-November 2016
University of Illinois, Chicago Department of Psychiatry, VITALS Laboratory Chicago, IL
Principle Investigator/Mentor: Melissa Lamar, PhD

Research Assistant June 2013-August 2014
Northwestern University Cognitive Neurology and Alzheimer's Disease Center Chicago, IL
Principle Investigators: Emily Rogalski, PhD & Sandra Weintraub, PhD

Research Assistant August 2011-May 2013
Tulane University, Molix Social Psychology Lab New Orleans, LA
Principle Investigator: Lisa Molix, PhD

FORMER CLINICAL PRACTICA

Advanced Neuropsychology Practicum July 2018 – July 2019
University of Chicago Medical Center Department of Psychiatry and Behavioral Neuroscience Chicago, IL
Supervisors: Maureen Lacy, PhD ABPP-CN, Joseph Fink, PhD ABPP-CN

Advanced Neuropsychology Practicum July 2017 – June 2018
University of Illinois, Chicago Department of Psychiatry and Neuropsychiatric Institute Chicago, IL
Supervisors: Neil Pliskin, PhD ABPP-CN, Woojin Song, PhD ABPP-CN, Jason Soble, PhD ABPP-CN

Psychotherapy and Assessment Practicum August 2015 - June 2017
University of Illinois Office of Applied Psychological Services Chicago, IL
Supervisors: Jenna Rowen, PhD, Nancy Dassoff, PhD,
Gloria Balague, PhD, Bibiana Adames, PhD, Neil Pliskin, PhD ABPP-CN,
& Amanda Lorenz, PhD

Psychometrician January 2012 - May 2012
Touro Hospital/Private Practice New Orleans, LA
Supervisor: Richard J. Wakeman, PhD

PUBLICATIONS

Bessette, K.L., **Karstens, A.J.**, Crane, N.A., Peters, A.T., Stange, J.P., Elverman, K.H., Morimoto, S.S., Weisenbach, S.L. & Langenecker, S.A. (2020). A Lifespan Model of Interference Resolution and Inhibitory Control: Risk for Depression and Changes with Illness Progression. *Neuropsychology Review*. https://doi.org/10.1007/s11065-019-09424-5

#Balu, D., **#Karstens, A.J.,** Loukena, E., Maldonado Weng, J., Valencia-Olvera, A.C., LaDu, M.J. (2019). The role of *APOE* in transgenic mouse models of Alzheimer's disease. *Neuroscience Letters*, 707(10) DOI: 10.1016/j.neulet.2019.134285 **#both authors contributed equally**

Boots, E., Zhan, L., Dion, C., **Karstens, A. J.,** Pevens, J., Ajilore, O., Lamar, M. (2019). Cardiovascular disease risk factors, tract-based structural connectomics, and cognition in older adults. *NeuroImage*, 196, 152-160 DOI: 10.1016/j.neuroimage.2019.04.024

Karstens, A. J., Tussing-Humphreys, L., Zhan, L., Rajendran, N., Cohen, J., Dion, C., Zhou, J. X. Lamar, M. (2019). Associations of the Mediterranean Diet with cognitive and neuroimaging phenotypes of dementia in non-demented older adults. American Journal of Clinical Nutrition, 109(1), 361–368. ahttps://doi.org/10.1093/ajcn/nqy275

Deldonno, S. R., **Karstens, A. J.,** Cerny, B., Kling, L. R., Jenkins, L. M., Stange, J. P., Nusslock, R., Shankman, S., & Langenecker, S. A. (2019). The Titrated Monetary Incentive Delay Test: Convergent and divergent validity in an RDoC sample. *Journal of Clinical and Experimental Neuropsychology, 41*(5), 512-529. DOI: 10.1080/13803395.2019.1585519

Karstens, A. J., Korzun, I., Avery, E. T., Kassel, M. T., Keelan, R., Kales, H., Abercrombie, H., Eisenlohr-Moul, T., Langenecker, S. A., & Weisenbach, S. (2018). Examining HPA-axis functioning as a mediator of the relationship between depression and cognition across the adult lifespan. DOI: 10.1080/13825585.2018.1495309

Karstens, A. J., Ajilore, O., Rubin, L. H., Yang, S., Zhang, A., Leow, A., Kumar, A. & Lamar, M. (2017). Separate and interactive associations of trauma and depression on brain structure in urban dwelling adults. *International Journal of Geriatric Psychiatry Special Issue.* DOI: 10.1002/gps.4755

Karstens, A. J., Rubin, L. H., Shankman, S. A., Ajilore, O., Libon, D., Kumar, A. & Lamar, M. (2017). Investigating the separate and interactive associations of trauma and depression on cognition in urban dwelling adults. *Journal of Psychiatric Research.* 89, 6-13 DOI: 10.1016/j.jpsychires.2017.01.008

PUBLICATIONS UNDER REVIEW

Bessette, K. L., **Karstens, A. J.,** Crane, N. A., Peters, A., Stange, J. P., Morimoto, S. S., Weisenbach, S., & Langenecker, S. A. A lifespan model of interference resolution and inhibitory control: Risk for depression and changes with illness progression.

CONFERENCE SYMPOSIA

Karstens, A. J., Korzun, I., Avery, E. T., Kassel, M. T., Keelan, R., Kales, H., Abercrombie, H., Eisenlohr-Moul, T., Langenecker, S. A., & Weisenbach, S. (2017, October). *Examining HPA-axis functioning as a mediator of the relationship between depression and cognition across the adult lifespan.* Panel presentation at the International College of Psychoneuropharmacology Conference.

Karstens, A. J., Ajilore, O., Kumar, A. & Lamar, M. (2017, August). *Trauma Exposure through Natural Disasters: Using Neuropsychological and Neurological Implications to Inform Intervention*. American Psychological Association Annual Meeting.

Karstens, A. J., Ajilore, O., Libon, D. J., Charlton, R., Kumar, A. & Lamar, M. (2017, February & March). *Adapting Boston Process Approach algorithms used in dementia research to a normal aging population.* Panel presentation at the International Neuropsychological Society 45th Annual Meeting & data blitz at the University of Illinois, Chicago Cross-program Conference.

Karstens, A., Ajilore, O., Kumar, A. & Lamar, M. (2016, October). *The separate and interactive associations of urban trauma and depression on cognition and brain structure: Implications for assessing depression and dementia in older adults.* Panel presentation at the International

College of Psychoneuropharmacology Conference; Seminar presentation at University of Illinois, Chicago Neuroscience Seminar Series.

INVITED COLLOQUIA

Karstens A. J., Valencia-Olvera, A. C., Coronel, S., Panchapakesan, K., Xiang, B., Saleh, Y., Tussing-Humphreys, L., Fitzgibbon, M., LaDu, M. J. (2019, March). The plasma lipoprotein profile as a prognostic marker of cognition in older adults: Preliminary data from a dietary intervention. GH Miller Symposium.

Karstens, A. J. (2019, March). Evaluation of Plasma Lipoprotein Profiles in a Dietary Intervention to Improve Cognition: Methodology and Preliminary Data. University of Illinois, Chicago Neuroscience Graduate Research Symposium.

Karstens, A. J. (2019, March). Preventing Alzheimer's Disease with a Healthy Diet. University of Illinois, Chicago 3 Minute Thesis Competition, Finalist.

Karstens, A. J. (2019, February). Fahr's Disease. University of Chicago Neuropsychology Series invited seminar.

Karstens, A. J. (2018, October). White matter tracts. University of Chicago Neuropsychology Series invited seminar.

Karstens, A. J., & Kinney, K. (2018, October). Medical comorbidities: Considerations in clinical intake, intervention, and assessment. University of Illinois, Chicago invited seminar.

Kang, M. & **Karstens, A. J.** (2018, February). *Axonal transport defects and dying-back neuropathy in neurodegenerative diseases*. University of Illinois, Chicago invited symposium and clinical case conference.

Karstens, A., & Kinney, K. (2018, February). Huntington's Disease. University of Illinois, Chicago invited seminar.

Karstens, A. J. (2017, March). *The Mediterranean Diet and early markers of dementia*. Invited talk at the University of Illinois, Chicago's Association for Neuropsychological Student Training event.

Karstens, A., Ajilore, O., Kumar, A. & Lamar, M. (2016, September). *The separate and interactive associations of urban trauma and depression on cognition and brain structure* Invited seminar at the University of Illinois, Chicago Neuroscience Seminar Series.

POSTER PRESENTATIONS

*****acted as mentor to the student presenter***

Karstens, A. J., Coronel, S., Panchapakesan, K., Saleh, Y., Xiang, B.,Valencia-Olvera, A. C., LaDu, M. J. The potential of plasma lipoprotein profiles as a cognitive biomarker in a dietary intervention for obese females. Poster presented at Society for Neuroscience. Chicago, IL. October 2019.

******Xiang, B., Coronel, S., Panchapakesan, K., Saleh, Y., Valencia-Olvera, A. C., LaDu, M. J., **Karstens, A. J.** The plasma lipoprotein profile in a novel transgenic mouse model is modulated by

Alzheimer's disease (AD) risk factors: Potential as an AD biomarker. Poster presented at Society for Neuroscience. Chicago, IL. October 2019.

Karstens, A. J., Hospelhorn, E., Wolfe, J. C., Ziemba, A., Morson, E., Wise, P., Crown, R., Rook, J., Bonakdarpour, B. Prosocial and neuropsychiatric benefits of a music intervention for people with dementia and their caregivers. Poster presented at Mesulam Center for Cognitive Neurology and Alzheimer's Disease Alzheimer Day Conference. Chicago, IL. April 2019.

Karstens, A. J., Coronel, S., Xiang, B., Panchapakesan, K., Saleh, Y., Valencia-Olvera, A. C., LaDu, M. J. Evaluation of plasma lipoprotein profiles in a dietary intervention to improve cognition: Methodology and preliminary data. Poster presented at the UIC LIN Symposium. Chicago, IL. April 2019.

Xiang, B., Panchapakesan, K., Saleh, Y., Coronel, S., Faulk, N., Maldonado Weng, J., York, J., Valencia-Olvera, A. C., LaDu, M. J., **Karstens, A. J. Effects of age, *APOE* genotype, and sex on the plasma lipoprotein profile of the EFAD mouse. Poster presented at the Chicago Society for Neuroscience conference. Chicago, IL. April 2019.

Panchapakesan, K., Saleh, Y., Xiang, B., Coronel, S., Faulk, N., Maldonado Weng, J., York, J., Valencia-Olvera, A. C., LaDu, M. J., **Karstens, A. J. Effects of age, *APOE* genotype, and sex on the plasma lipoprotein profile of the EFAD mouse. Poster presented at the Experimental Biology conference. Orlando, FL. April 2019.

Coronel, S., Xang, B., Panchapakesan, K., Saleh, Y., Valencia-Olvera, A. C., **Karstens, A. J., LaDu, M. J. Cognitive improvements induced by the Mediterranean Diet is reflected by changes in the plasma lipoprotein profile: Potential biomarker for Alzheimer's disease. Poster presented at the Latin@s Gaining Access to Networks for Advancement in Science Conference. Chicago, IL. March 2019.

Karstens, A.J., Hospelhorn, E., Wolfe, J., Ziemba, A., Morson, E., Demaster, R., Wise, P., Crown, R., Rook, J., Bonakdarpour, B. Music intervention for people with dementia using a dyadic approach: Clinical experience to shape a clinical trial. Poster presented at the Alzheimer's Association International Conference. Chicago, IL. July 2018.

Boots E.A., Zhan L., Dion C., **Karstens A.J.**, Cohen J., Lamar M. Tract-based structural connectomics influences on stroke risk and cognition in cognitively-normal older adults. Poster presented at the Alzheimer's Association International Conference. Chicago, IL. July 2018.

Karstens, A. J., Eisenlohr-Moul, T., Caveney, A. F., Kassel, M. T., Rao, J., Giordani, B., Weisenbach, S., Pliskin, N., & Langenecker, S. A. (2018, May) Convergent validity and reliability of the Michigan Spatial Relations Task: A visuospatial five-trial learning test. Poster presented at the Midwest Neuropsychology Group.

Eihentale, L., **Karstens, A. J., Peters, A., Bessette, K., Kling, L., Skerrett, K., Passarotti, A., & Langenecker, S. A. (2018, May). *Relationship between subjective complaints and objective measures of executive functioning in remitted mood disorders.* Poster Session Presentation at the Midwest Neuropsychology Group, Ypsilanti, MI.

Dion, C., Boots, E., Zhan, L., **Karstens, A. J.**, Cohen, J., Ajilore, O., Maki, P.M., Marquez, D.X. & Lamar, M. *Considering physical activity and sex differences as they relate to verbal learning, memory, and hippocampal subfields in older adults.* 46th Annual Meeting of the International Neuropsychological Society. Washington, D.C. February 2018.

Boots, E. A., Dion, C., Rajendran, N., **Karstens, A. J.**, Cohen, J., Ajilore, O., Lamar, M.. *Preclinical Profiles of Memory Versus Executive Function Weakness as Related to Cognition, Stroke Risk, and White Matter Integrity in Older Adults.* 46th Annual Meeting of the International Neuropsychological Society. Washington, D.C. February 2018.

Karstens, A. J., Ajilore, O., Shankman, S., Yang, S., Zhang, A., Leow, A., Kumar, A. & Lamar, M. (2016, September & 2017, February). *Brain-behavior profiles distinguishing psychological resilience from depression after trauma in an urban dwelling sample of adults: the possible role of rumination.* Poster session presented at University of Illinois, Chicago's Psychiatry Department Research Extravaganza & the International Neuropsychological Society 45th Annual Meeting.

Dion, C., **Karstens**, **A. J.,** Zhan, L., Cohen, J., Boots, E., Ajilore, O., Leow, A., Marquez, D. X., & Lamar, M. (2016, September & 2017, February). *Associations of sedentary behavior and physical activity with learning, memory and hippocampal volume in a diverse sample of older adults.* Poster session presented at University of Illinois, Chicago's Psychiatry Department Research Extravaganza & the International Neuropsychological Society 45th Annual Meeting.

Karstens, A. J., Cohen, J., Ajilore, O., Rubin, L., Shankman, S., Kumar, A. & Lamar, M. (2015, September; 2016, February & April). *The separate and interactive effects of trauma and depression on cognition in urban dwelling adults.* Poster session presented at University of Illinois, Chicago's Psychiatry Department Research Extravaganza, 44th Annual Meeting of the International Neuropsychological Society, and University of Illinois, Chicago's Student Research Forum.

Romo, K., **Karstens, A. J.,** Cohen, J., Dion, C., Leon, A., Maki, P. M. & Lamar, M. (2016, April). *Sex-related differences in verbal learning and memory and the role of bilingualism.* Poster session presented at University of Illinois, Chicago's Student Research Forum.

Gonzales, M., Ajilore, O., Cohen, J., Charlton, R. C., Sieg, E., **Karstens, A. J.**, Yang, S., Zhang, A., Kumar, A., & Lamar, M. (2015, September; 2016, February). *Divergent influences of cardiovascular risk factors on cognition, grey, and white matter morphology.* Poster session presented at University of Illinois, Chicago's Psychiatry Department Research Extravaganza. Paper session presented at 44th Annual Meeting of the International Neuropsychological Society.

Cohen, J., Gonzales, M., **Karstens, A. J.**, Romo, K., Janecek, J., & Lamar, M. (2015, September; 2016, February). *The oblique effect: applying ophthalmological and physiological principles of visuospatial processing to cognitive aging and vascular health.* Poster session presented at University of Illinois, Chicago's Psychiatry Department Research Extravaganza, and 44th Annual Meeting of the International Neuropsychological Society.

Karstens, A. J., Whitney, K., Cook, A., Weintraub, S., Mesulam M. M., & Rogalski, E. (2014, May). *Vascular risk factors in cognitively healthy aging: A preliminary medical history report of SuperAgers.* Poster session presented at Northwestern University's Alzheimer's Disease Day Conference, Chicago, IL.

Whitney, K., Rezutek, A., Gefen, T., Martersteck, A., **Karstens, A. J.,** Guela, C., Weintraub, S., Mesulam M. M., & Rogalski, E. (2014, May). *Correlates of active engagement in life in the elderly: a study of cognitive SuperAgers.* Poster session presented at Northwestern University's Alzheimer's Disease Day Conference, Chicago, IL.

LEADERSHIP AND COMMITTEE MEMBERSHIP

Brown University Resident Diversity Committee*, Neuropsychology Representative*
Association of Neuropsychological Student Training, *University of Illinois Group Founder & Former Representative* *https://uicanst.wixsite.com/anst*
Society for Clinical Neuropsychology/Division 40, *Program Committee*
Graduate Women in Science, National & Chicago Chapter, *Grant Review Committee*
Psi Chi, Tulane University Chapter, *Former Vice President*

PROFESSIONAL MEMBERSHIPS

American Psychological Association
    Society for Clinical Neuropsychology/Division
    Association of Neuropsychological Student Training
International Neuropsychological Society
Society for Neuroscience
International College for Geriatric Psychoneuropharmacology
Graduate Women in Science, National & Chicago Chapter
University of Illinois, Chicago Cross-Program Mentorship Program
University of Illinois, Chicago Clinical Psychology Peer Mentorship Program

TEACHING EXPERIENCE

Teaching Assistant and Guest Lecturer August 2015 – May 2017
University of Illinois, Chicago Chicago, IL
Courses: Abnormal Psychology, Psychological Assessment, Clinical Psychology Lab, Psychological Interventions, Social Psychology, Research Methods

MENTORSHIP

Mentee Awards

Sandra Coronel L@S GANAS Fellow	Fall 2019-Present
Bingtao Xiang, Chicago Society for Neuroscience Undergraduate 2nd Place Poster Presentation	April 2019
Kailash Panchapakesan, Honors College Travel Grant	Spring 2019
Sandra Coronel, Honors College Undergraduate Research Award	Spring 2019
Bingtao Xiang, Honors College Undergraduate Research Award	Spring 2019
Kailash Panchapakesan, Honors College Undergraduate Research Award	Spring 2019

CERTIFICATIONS AND SKILLS

Relevant skills and training courses: Human Neuroanatomy; Blood-born Pathogens Certification; Magnetic Resonance Imaging Technician and Preprocessing, Dual-energy X-ray absorptiometry, Graph-theory based structural connectomics workshop

Computer program proficiencies: Prism, Epic software, Microsoft Office programs; Pecolsus Online Sign-up System; Prism; Qualtrics; SAS statistical software packages, Sona Systems; SPSS statistical software packages, Titanium software