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The effects of physical function and genetics on cognition and blood biomarkers in individuals at-risk for Alzheimer's disease and related dementias

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The effects of physical function and genetics on cognition and blood biomarkers in individuals at-risk for Alzheimer's disease and related dementias

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Health, Sport, and Exercise Science

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Contents

Abstract

Alzheimer's disease and related dementia (ADRD) rates are expected to triple by the year 2050. Early detection and specific mitigation efforts are warranted to blunt the alarming rate. Physical function (PF) declines with age, but higher physical function is associated with better cognitive functioning in middle-to- older age individuals. Moreover, greater physical activity (PA) is associated with better global cognition; however, Apoliporotein *e4* carriers may not gain the same benefits with exercise. Additionally, plasma phosphorylated tau 217 (p-tau217) has been identified as a novel diagnostic ADRD biomarker which needs further research to examine associations with risk factors. Therefore, the aims of this investigation were (1) Understand if higher physical function clusters produce better cognitive outcomes and blood biomarker profiles compared to lower functioning clusters among at-risk individuals, (2) Evaluate the ApoE gene's mitigating effect on physical activity and blood biomarkers, (3) Examine the associations between risk factors and p-tau217. Participants (n=216;73.1% female; 45-75years) enrolled in the study and completed a DXA scan, venous blood draw, RBANS, handgrip, sit-to-stand power with tendo, dual-task (4-meter and 10-meter), 6-minute walk distance test, nine behavioral risk surveys, and 6 digital cognitive tests. A hierarchal cluster analysis was utilized to identify PF cluster for participants, a one-way ANCOVA was used to assess differences in cognition among clusters. A 2x2 factorial ANCOVA to examine interactions between PA and genetics. A multiple linear regression was used to evaluate risk factors (independent variables) on p-tau217 (dependent variable). Cluster 1 (C1; n =29) was characterized with the highest strength, power, faster dual-task walking time, and higher aerobic capacity, Cluster 3 (C3; n =113) had the lowest values among PF variables, Cluster 2 (C3; n = 74) was in-between C1 and C3. C1 had significantly higher global cognitive, visuospatial scores, digital executive functioning and associative learning compared to C2 ($p < 0.05$). C3 and C1 had significantly higher values on

line orientation task and figure recall than C2 ($p < 0.05$). Moreover, physically active ApoE carriers had lower body mass index scores compared to physically inactive carriers where the opposite was seen among non-carriers ($p < 0.05$). Lastly, the regression model accounted for 84% of the variance for p-tau217 ($p = .01$), SF-12 accounted for 9% of that model as the only significant predictor ($p < 0.05$). The results from this current study demonstrate that individuals with higher physical functioning output among clustered variables have higher global cognitive scores than individuals with lower physical functioning output, lower BMI scores were found among physically active ApoE carriers, and quality of life may be directly linked to ptau217. Examining physical functioning variables together may be a valuable tool when assessing cognitive decline among at-risk individuals. However, larger sample sizes and longitudinal data is needed to substantiate these claims.

Chapter 1: Introduction

The rates of Alzheimer's disease (AD) and dementia are steadily rising with the aging population increasing. As of 2018, approximately 5.7 million Americans were diagnosed with AD with an additional person being diagnosed every 65 seconds (Alzheimer's Association, 2018). Furthermore, AD is the sixth leading cause of death and responsible for more than 80,000 deaths annually in the United States (US) (Alzheimer's Association, 2015). The rise in rates of AD coupled with the increasing number of older adults is a major contributor to increased long-term healthcare costs in the US. As a result, early detection and tracking brain health in the aging population is important more now than ever. The earlier brain health decline is detected, the more likely clinicians can implement programs to improve modifiable risk factors. One modifiable risk factor is exercise. The improvement and maintenance of aerobic fitness in an at-risk population may be able to offset declines in brain health scores (memory and processing), increase cerebral blood flow, and maintenance of brain volume (Bugg & Head, 2011; Kirk-Sanchez & McGough, 2013). Moreover, muscular fitness has been shown to improve brain function through the upregulation of BDNF through induced IGF-1 levels; higher muscular fitness is associated with higher processing speed and executive function (Herold et al., 2019; Törpel et al., 2018). The combination of these two components of physical fitness may tell a greater story about an individual's cognitive function than one component. However, genetics play a role in cognitive decline; specifically, Apolipoprotein E (ApoE), possibly hindering some of the benefits from exercise.

ApoE main role is the regulation of cholesterol and synthesis and distribution which helps synaptic function maintenance(Huebbe et al., 2007). There are three different forms of ApoE (e2, e3, e4), the Apo e4 isoform is a non-modifiable risk factor of Alzheimer's and related

dementia (ADRD) (Huebbe et al., 2007; Prince, 2018). A person who inherits one ApoE *ε4* alleles has 3x the likelihood of developing AD compared to inheriting an ApoE3 allele (Holtzman et al., 2012). Inheriting two ApoE ε4 alleles increases the risk of developing ADRD by eight to twelve-fold (Holtzman et al., 2012; Loy et al., 2014; Michaelson, 2014). Currently, equivocal evidence exists that shows exercise may overcome the ApoE ε4 genetic risk of Alzheimer's and some literature contradicts those claims (Colovati et al., 2021; Stringa et al., 2020). While there is no consensus whether exercise can overcome the genetic risk, there is plenty of literature that shows the overwhelming cognitive benefits.

While providing exercise as an intervention is a useful method to curb cognitive decline, better techniques to capture early cognitive decline are needed. Most common methods are standard cognitive batteries which detect mild cognitive impairment and dementia after the onset (Alzheimer's Association, 2019). Moreover, MRIs, PET scans, cerebral spinal fluid taps are an expensive and invasive techniques examining cognitive decline. Recently, venous blood draws examining phosphrolyated tau 217 (p-tau217) have been just as strong as common other biomarkers such as CSF beta amyloid and neurofilament light, and has shown higher accuracy than p-tau181 (a valid CSF marker) (Mattsson-Carlgren et al., 2020; Palmqvist et al., 2020, 2021). More research is needed to examine what risk factors are correlated with this marker to help practitioners target certain health issues in curbing cognitive decline in early interventions.

While interventions increasing physical activity and exercise have improved cognitive outcomes in high-risk individuals; it remains to be seen whether high physical function at baseline, despite multiple risk factors, produce better cognitive domain scores in high-risk individuals. Physical function decline later in life is linked to cognitive decline; but physical function variables clustered together has not been examined. Understanding whether physical

function clusters can delineate cognitive ability among clusters before noticeable decline may provide health care professionals time and cost-efficient method of evaluating cognition. Moreover, ApoE ε4 cognitive decline risk on high-risk individuals with higher physical activity remains equivocal. It is important to identify whether physical activity can mitigate specific genetic risk. Lastly, human plasma p-tau217 has been identified as an accurate novel diagnostic marker of ADRD. However, associations with behavioral and metabolic risk factors have not been examined among at-risk individuals. Therefore, the purposes of this investigation: (1a). Understand if higher physical function clusters produce better cognitive outcomes among high-risk, (1b) Examine if higher physical function clusters effect blood biomarker profiles among at-risk individuals, (2) Evaluate the ApoE gene's mitigating effect on physical activity and blood biomarkers, (3) Examine the associations between risk factors and p-tau217. **Hypothesis 1.** I predict individuals in higher physical function clusters will have better cognitive scores (memory, learning, language, attention). Also, greater plasma neuroprotective marker levels, and less cholesterol blood levels when compared to individuals in the lowest physical function cluster. **Hypotheses 2**. ApoE ε4 carriers will have lower cognitive outcomes in every physical activity and exhibit higher neurodegenerative blood levels than non-ApoE ε4 carriers. **Hypothesis 3.** Metabolic risk factors and subjective cognitive decline will be associated with greater likelihood of high p-tau217 plasma concentration.

Chapter 2: Literature Review

Impact

Alzheimer's disease (AD) is a developing public health concern in the United States (Alzheimer's, 2015; Alzheimer's Association, 2019; Prince, 2018). As of 2020, approximately 6 million Americans were diagnosed with Alzheimer's disease or related dementia (ADRD) (Alzheimer's Association, 2019). A new diagnosis occurs every 65 seconds, resulting in 1 million new diagnoses each year potentially tripling AD diagnoses by 2050 (Alzheimer's, 2015). While average diagnosis of AD occurs at 70 years of age, cognitive decline associated with AD begins 20-30 years before the onset (Rajan et al., 2015; Wilson et al., 2011). Moreover, AD is the seventh leading cause of death in the US, and accounts for 121,000 deaths annually (Alzheimer's Association, 2019). Since 2000, deaths from heart disease have decreased 14%, while deaths form AD have increased by 89%. Moreover, AD kills more seniors than breast cancer and prostate cancer combined, with 1 in 3 seniors dying from Alzheimer's disease and related dementias ("2020 Alzheimer's Disease Facts and Figures," 2020).

Diseases leading to dementia

Table 1. *Diseases and dementia*

Disease	Pathology	Prevalence	Symptoms
Alzheimer's Disease (AD)	-Beta-amyloid (plaques) outside of neurons in the brain -protein tau (tangles) inside neurons neurodegeneration -inflammation in brain and plasma, -reduced glucose metabolism (Alzheimer's Association, 2019)	60-80% of cases (Alzheimer's Association, 2019).	Memory deficits: names, recent events or conversations -apathy or depression early in symptomology Later symptoms: -diminished communication skills -disorientation -confusion -poor judgement -behavioral changes -difficulty speaking, swallowing, walking
Cebrovascular disease and vascular dementia (Brenowitz et al., 2017; Kapasi et al., 2017)	-blood vessel blockage -damage to areas of brain tissue or bleeding in brain -mixed pathology with AD is common	8-10% of cases	-Impaired judgement or ability to make decisions, plan or organize -detiortating cognitive and motor function
Lewybody disease	Abnormal aggregations of protein α-synuclein in neurons (develops in cortex leading to	5-10% of cases	-sleep disturbances -well-formed visual hallucinations or visuospatial impairment -slowness in gait or imbalances

	dementia with Lewy Bodies) (Alzheimer's Association, 2019)		
Frontotemporal lobar degeneration	-Significant atrophy in frontal and temporal lobe -upper layers of cortex usually are soft, spongy, and display abnormal tau pathology or transactive response DNA-binding protein	<10% of cases but 60% of cases are diagnosed in those 45-60 years of age (Alzheimer's Association, 2019; Prince, 2018)	-Personality behavior and comprehending decrements early in disease -Loss of memory later in disease
Parkinson's Disease	α-synuclein aggregates in substantia nigra -aggregates lead to degeneration in neurons that specifically produce dopamine (Cherubini & Wade-Martins, 2018; Stojkovska et al., 2018)		-uncontrollable shaking -motor impairment
Mixed Pathology	-Mixture of diseases leading to mixed pathology dementia	-multiple studies indicate 50% of AD dementia cases presented multiple pathologies -community based studies found >50% of dementia cases were MD (Brenowitz et al., 2017; De Reuck et al., 2018; James, 2012; Kapasi et al., 2017)	-Mixture of symptoms

Discrepancy in treatment leading to prevention measures

Currently, the FDA has approved several drug combinations to relieve cognitive symptoms of AD, but not permitted any drugs to slow the rate of cognitive decline in individuals at risk for AD. There is no current cure for AD, but delaying the onset of diagnoses by one year could diminish future pervasiveness by 11% and reduce health care costs by $219 billion annually in adults 70 and older (Zissimopoulos et al., 2014). Additionally, early detection of AD can save an estimated $7.9 trillion in medial expenditures, with an estimated $7.0 trillion saved under a partial early diagnosis projection (Prince, 2018). Early detection for individuals at risk

for cognitive decline is valuable, allowing for earlier intervention and treatment planning, both of which can reduce the costs connected with ADRD. The National Institute of Aging-Alzheimer's Association (NIA-AA) and international working group (IWG) proposes three stages of AD, the first being asymptomatic at-risk individuals (**high-risk**) exhibiting biomarker evidence for AD (Prince, 2018). Since the most ideal time to curb cognitive decline is before noticeable deficits are detected, high-risk individuals should be targeted for multi-domain interventions. One aspect of multi-domain interventions is physical activity. Higher physical activity volumes are associated with greater maintenance in different cognitive domains (Barnes et al., 2003; Barnes, 2015; Cassilhas et al., 2012; Chang et al., 2012).

Physical Activity and Exercise

There is mounting evidence that higher cardiovascular fitness may attenuate cognitive decline. Aging adults may benefit cognitively from higher cardiovascular fitness through the increase of cerebral blood flow, as well as structural and functional neuroprotection which could possibly delay the rate of cognitive decline (Colcombe et al., 2006; Cotman et al., 2007; Kramer & Erickson, 2007; van Praag et al., 1999). Rodent studies demonstrated that increasing CRF may stimulate nerve cell growth. This suggests increased CRF provides a neuronal buffer protecting against neurodegeneration associated with age (Barnes et al., 2003). Moreover, intervention studies evaluating cognitive functioning and CRF were conducted over multiple years and used similar cognitive batteries to evaluate cognition. These cognitive tests usually display a learning effect if taken more than once which may skew results in a longitudinal study design.

While examining cardiovascular fitness, it may be useful separating older adults by physical activity levels. A recent meta-analysis found that individuals who are more physically active in midlife and late life have lower risk for global cognitive decline (Kirk-Sanchez & McGough,

2013). While examining individual sex differences, there is a consensus among lower CRF levels and poor cognitive health. A longitudinal investigation in men identified participants who walked <1 mile per day had a 1.7-1.8 fold increased risk for developing ADRD compared to men who walked >2 miles per day (Kirk-Sanchez & McGough, 2013). Moreover, women in the Nurses' Health study, who walked 90 minutes per week demonstrated higher global cognitive scores than women who walked less than 40 minutes per week (Hagan et al., 2016). Additionally, lower CRF levels may be attributed to brain atrophy which is noticed in individuals with dementia. Bugg and Head (2011) found that both low exercisers (0.63 ± 7.4 MET) and high exercisers (7.8 ± 3.9 MET) displayed brain atrophy in several areas of the brain related to age (Bugg & Head, 2011). But in subcortical regions, including the medial temporal lobe, age was correlated with brain volume in the low exercise group but not the high exercise group. Higher exercise volume may moderate the amount of atrophy in the medial temporal lobe, which is associated with memory and executive function.

Recently, muscular fitness has been shown to improve brain structure and enhance certain domains of cognition. Increasing muscular fitness, via resistance training, induces significant functional brain modifications such as decreased white matter atrophy, smaller white matter lesion volumes, and increased cortical thickness (Herold et al., 2019; Törpel et al., 2018). Increased Insulin-like Growth Factor 1 (IGF-1), the mediator of these changes, is associated with neurogenesis, vascular density, glucose utilization, and synaptic health and memory formation (Herold et al., 2019; Lichtenwalner et al., 2001; Sonntag et al., 2000; Törpel et al., 2018). Previous studies suggest that IGF-1 augments synaptic plasticity and neuronal survival enhancing cognitive performance (Cotman & Berchtold, 2002; Vaynman et al., 2006; adlard, perreau, cotman, 2005). Moreover, IGF-1 has exhibited the ability to prevent the loss of brain

tissue and increase concentrations of brain derived neurotropic factor (BDNF) (Cotman & Berchtold, 2002). BDNF, found in the central nervous system, mechanistically works in areas associated with cognitive functioning such as the prefrontal cortex, striatum, hippocampus, cortex, septum neurons, cerebellum, and motor neurons. These changes in brain structure have been linked with improvements in processing speed and executive function (Chang et al., 2012).

Muscular strength declines with age which may influence cognition. Aging is a constant process in which functional, structural, and hemodynamic changes decrease an individual's capability to adapt to specific environments, which may induce the onset of pathological processes, with muscle mass and strength diminishing (Cassilhas et al., 2007; Roubenoff, 2000). Increases in muscle mass and strength is known to decrease risk for various chronic diseases while also decreasing anxiety and depression in the aging population. Recently, an 8-year investigation including 14,000 individuals over the age of 50 examined handgrip strength (McGrath et al., 2019). Researchers found a 5-kilogram decrease in handgrip strength was associated with 10% greater odds of cognitive impairment. The loss of muscle mass in the aging population leads to a weaker grip, but it also may be due to the brain's ability to direct needed movement. Required neural and motor functions needed for the grip strength examination could be compromised when cognitive decline begins (McGrath et al., 2019). Moreover, reduced handgrip strength has been associated with lower scores in executive function, attention, working memory, language, semantic fluency, and overall cognition in among non-demented older individuals (Buchman, Boyle, et al., 2007; Buchman, Wilson, et al., 2007; Guerrero-Berroa et al., 2014; Rand & Eng, 2011). Recent investigations have found that reduced handgrip strength at baseline has a high correlation with developing MCI and higher handgrip strength at baseline may be protective for cognitive function, functional status, mobility, and mortality in adults 60

and older (Boyle et al., 2010; Rijk et al., 2016). The handgrip test is a global indicator of muscular strength that is cost-effective and an easily accessible method to identify cognitive decline, in addition to other validated measures, promoting timely interventions.

Moreover, assessing muscular power in older adults provides a beneficial aspect to evaluating cognitive decline. While muscular strength is a valuable approach to examining cognition, muscular power could be more beneficial. Muscular power is a combination of movement velocity and strength of a particular muscle group. More precisely, lower-extremity muscular power shows a positive relationship with cognitive outcomes (Cherup et al., 2018; Gray et al., 2021; Petrella, 2004). Also, interventions aimed to augment muscular power demonstrated higher executive function scores (Yoon et al., 2017). Moreover, among older adults, muscular power is more highly associated with cognition compared to muscular strength (Casas-Herrero et al., 2013; Petrella, 2004), signifying that the velocity of lower-extremity movement is the most vital facet in the muscular power equation. Additionally, previous research suggests reductions in neural conduction velocity may contribute to these changes in muscular power by reducing the ability to move quickly (Palve & Palve, 2018). Testing muscular power provides a unique method of identifying cognitive impairment due to the incorporation of velocity providing insight on neural conduction. Higher baseline muscular power production may prevent further abnormal cognitive decline compared to lower power production. However, the beneficial effects of physical activity and exercise on the brain may be mitigated by genetics from person to person.

Apolipoprotein E (ApoE)

ApoE plays an essential role in circulating and central nervous system lipoproteins metabolism. Majority of production occurs in the brain by astrocytes and to a lesser extent by microglia and neurons (Huebbe et al., 2007). The key role of ApoE regulation of cholesterol and

synthesis and distribution which helps synaptic function maintenance. Three isoforms of ApoE exist (apoE2, apoE3, ApoE ε4), the ApoE ε4 isoform is a strong non-modifiable risk factor for developing AD (Alzheimer's Association, 2019; Huebbe et al., 2007; Prince, 2018). An individual inheriting one of the ApoE ε4 alleles has three times the risk of developing AD compared to an individual who has one ApoE3 allele (Holtzman et al., 2012). Individuals who inherit two ApoE ε4 alleles have an eight to twelve-fold risk of being diagnosed with AD (Holtzman et al., 2012; Loy et al., 2014; Michaelson, 2014). Individuals with the *e4* form are more likely to develop AD at a younger age than those with *e2* or *e3* forms of the ApoE gene (Spinney, n.d.). A study examining 26 AD centers in the US, found 65% of patients with AD had at least one copy of the ApoE ε4 gene. Therefore, it is important to evaluate genetic components in conjunction with physical activity of high-risk populations. While physical activity creates beneficial cognitive outcomes for aging individuals, ApoE ε4 gene could mitigate positive changes from physical activity and augment cognitive decline

APOE, Physical Activity, and related biomarkers

Physical activity and exercise are modifiable risk factors for cognitive decline but there is inconclusive evidence if ApoE mediates the potential positive effect of greater physical activity rates in individuals who inherit the e4 allele (Colovati et al., 2021; Stringa et al., 2020). A prior study demonstrated that physically active people who were ApoEe4 carriers showed stable cognitive functioning and protection against hippocampal atrophy during an 18-month follow up period compared to physically inactive carriers (Smith et al., 2016). These findings suggest that greater physical activity levels offer protection against neurodegeneration in ApoE ε4 carriers. In a recent investigation examining participants older than 65 years (362 carriers and 747 non-carriers), results identified multi-domain interventions were beneficial for cognitive function, even in patients that were carriers (Solomon et al., 2018). Moreover, another study examining

1,438 individuals over 6.5 years found that exercise was able to mitigate dementia risk in ApoE ε4 carriers compared to older adults that were physically inactive (Shih et al., 2018). These investigations demonstrate physical activity and exercise benefit ApoE ε4 carrier's cognitive functioning and structural maintenance of the brain.

However, several studies have failed to detect any effect of physical exercise on individuals carrying the ApoE ε4 allele (Stringa et al., 2020). One investigation found the likelihood of developing dementia was not significantly different between ApoE ε4 carriers who exercise and individuals who do not (Fenesi et al., 2017). Moreover, another study identified that exercise training did not modify the executive functioning in patients who were carriers (Stern et al., 2019). Additionally, studies have shown ApoE ε4 carriers have lower plasma concentration of Brain Derived Neurotropic Factor (BDNF), and exercise training did not improve the levels of this neurotropic factor (Allard et al., 2017). These studies suggest that exercise does not mitigate dementia risk, has no effect on executive function, nor neuroprotective blood markers in ApoE ε4 carriers.

Plasma Phosphophorlated-tau 217 (p-tau217)

Tau is a hallmark pathology in AD and associated with a buildup of senile aβ plaques. Plasma phosphophoralated-tau217 (p-tau217) has been identified as a potential diagnostic marker for AD (Mattsson-Carlgren et al., 2020; Palmqvist et al., 2020, 2021). Elevated p-tau217 has demonstrated a significant relationship with higher brain aβ levels measured by position emission tomography (Palmqvist et al., 2020). The same investigation found plasma p-tau217 was elevated among AD patients compared to other patients with tau pathologies and control patients, with a significantly higher diagnostic accuracy than p-tau181 (current gold standard marker); and similar diagnostic accuracy as neurofilament light chain and MRI-based biomarkers. Furthermore, a

longitudinal investigation found elevated plasma p-tau217 in preclinical populations leads to cognitive decline over time (Mattsson-Carlgren et al., 2020). While p-tau217 shows high accuracy in predicting cognitive decline, systemic and behavioral factors that contribute to this biomarker remain scarce. Age, poor diet, obesity, hypertension, diabetes, depression, anxiety, stress, poor social and cognitive ability, and low physical activity levels all contribute to cognitive decline. The level of impact that systemic and behavioral factors on plasma p-tau217 levels and the resulting effect on cognitive decline are unknown.

Metabolic and Systemic Factors

Metabolic and behavioral risk factors have a role in cardiovascular health and cognitive health (Alzheimer's Association, 2019; Baumgart, 2015; Cunningham, 2015). Multiple investigations show age, mid-life obesity, diabetes, and hypertension as strong indicators of cognitive decline (Beydoun et al., 2008; Biessels et al., 2006; Kivipelto & Solomon, 2006; Kloppenborg et al., 2008; Loef & Walach, 2013; Lu et al., 2009; McGuinness et al., 2009; Power et al., 2011; Profenno et al., 2010; Yang & Song, 2013); while high cholesterol has produced mixed results, and no association with vascular dementia (Anstey & Low, 2008; Kivipelto & Solomon, 2006). Recent evidence suggest statins medications used to lower cholesterol may reduce dementia (Beri et al., 2009; McGuinness et al., 2009; Muangpaisan et al., 2010); however, evidence is inconsistent that statins may lower dementia risk (Ligthart et al., 2010; McGuinness et al., 2016; Richardson et al., 2013). But, metabolic risk (obesity, high blood pressure, and insulin resistance) are consistently associated with chronic inflammation and higher risk of dementia (alberti et al., 2006; Farooqui et al., 2011; Nation et al., 2015; St-Onge et al., 2009; van Himbergen et al., 2012).

Several investigations and systemic reviews have shown that mid-life obesity has a strong association with cognitive decline and an increased risk of dementia (Beydoun et al., 2008; Kloppenborg et al., 2008; Lee et al., 2010; Loef & Walach, 2013; McGuinness et al., 2016).

However, with age, being overweight and possibly obese is correlated with a reduced risk of ADRD (Fitzpatrick et al., 2009; Luchsinger et al., 2007). Moreover, a recent large retrospective investigation found being underweight had an elevated risk of dementia and lower risk for individuals overweight at mid-life (Qizilbash et al., 2015). The protective effects of higher BMI on dementia could be due to low late-life blood pressure, high-later life cholesterol levels, higher leptin levels, age related changes in metabolism, less likelihood of fragility, increased intake of vitamin E and vitamin D (Emmerzaal et al., 2014; Qizilbash et al., 2015).

Multiple studies have shown a strong relationship between mid-life high blood pressure and cognitive decline but an inconsistent relationship between hypertension and dementia (Power et al., 2011; Sharp et al., 2011). Individuals who have a longer duration of hypertension mid-life have a greater likelihood of significant cognitive decline. Hypertension is associated with white matter lesion and impairment of cerebral circulation often leading to ischemic injury (Abell et al., 2018). RCTs suggest treating hypertension may reduce cognitive decline risk (Chang-Quan et al., 2011). Additionally later-life hypertension may be neuroprotective similar to obesity, more research is needed to understand the longitudinal relationship between cognition and hypertension (Corrada et al., 2017).

Strong evidence persists of diabetes and poor cognitive performance, and a higher risk for dementia for individuals with diabetes (Biessels et al., 2006; Kloppenborg et al., 2008; Lu et al., 2009; Profenno et al., 2010). Further evidence shows diabetics with MCI were more likely to develop ADRD than non-diabetics with MCI (Cooper et al., 2015). Moreover, recent investigations have shown that diabetes effects dementia risk through other biological/genetic pathways related to diabetes in addition to vascular pathways (De Felice & Ferreira, 2014; Yang & Song, 2013). A recent pathway discovered is through the BDNF Val66met, diabetics carrying

the Val polyporhism usually display lower cognitive output than Met carriers (Zhen et al., 2018). In older adults, metabolic risk factors are correlated with measurable brain tissue deficits in the temporal and frontal lobes, the cingulate gyrus, hippocampus and basal ganglia which are areas most affect by AD related atrophy (Baumgart, 2015).

Moreover, meta-analyses and systematic reviews showed current smoking, traumatic brain injuries, depression diagnoses, and lack of sleep also increase risk for cognitive decline (Chang et al., 2013; Diniz et al., 2013; Ju et al., 2014; Lye & Shores, 2000; Rusanen et al., 2011; Sabia et al., 2012; Wilson et al., 2014; Yaffe, 2012; Yaffe et al., n.d.). Individuals with a history of depression have a higher likelihood of a dementia diagnoses; while depressive symptoms are independently associated with poor cognitive performance (Diniz et al., 2013; Yaffe, 2012)(cite). It is not well understood if depression may augment an individual's risk or be an early marker of brain changes correlated with ADRD. Moreover, multiple investigations have displayed that lack of sleep is associated with cognitive decline (Potvin et al., 2012; Yaffe et al., 2011). Recently, investigations have shown that tau markers are correlated with a poor sleeping habits compared to beta-amyloid (Barthélemy et al., 2020).

Conversely, higher education, higher physical activity, socializing, and cognitive engagement have reduced risk of cognitive decline (Blondell et al., 2014; Fratiglioni et al., 2004; Sabia et al., 2012; Sofi et al., 2011; Stern, 2012). First, more years of formal education or higher literacy rate has been shown to reduce dementia risk compared to fewer years of education (Jefferson et al., 2011; Meng & D'Arcy, 2012). Moreover, socializing has shown protective factor against abnormal cognitive decline and ADRD (Fratiglioni et al., 2004; Sutin et al., 2020). Some forms of socializing include joining clubs and engaging in volunteer work; having larger social networks and history of social contact are correlated with higher cognitive functioning and reduced

risk for poor cognitive outcomes (Crooks et al., 2008; Noice et al., 2014). But most studies in this area are combined with physical activity and cognitive training, making it difficult to draw definitive conclusions (Baumgart, 2015; Cunningham, 2015). Lastly, cognitive engagement and interventions have displayed effective in improving immediate memory and delayed recall compared to control groups (Martin et al., 2011). But, due to most interventions being robust in nature evidence is inconclusive that such cognitive training is solely responsible for improved outcomes (Stern & Munn, 2009). Additionally, there is substantial evidence that asymptomatic SCD is correlated with increased likelihood of biomarker abnormalities consistent with AD pathology and with an increased risk for future cognitive decline and ADRD (Jessen et al., 2014). However, there is a scarcity of research examining the associations between SCD, position AD risk factors, and p-tau217. Risk factors associations with the novel biomarker may provide researchers with future directions to discover potential mechanistic insights to help practitioners implement protective measures.

Stages leading to dementia

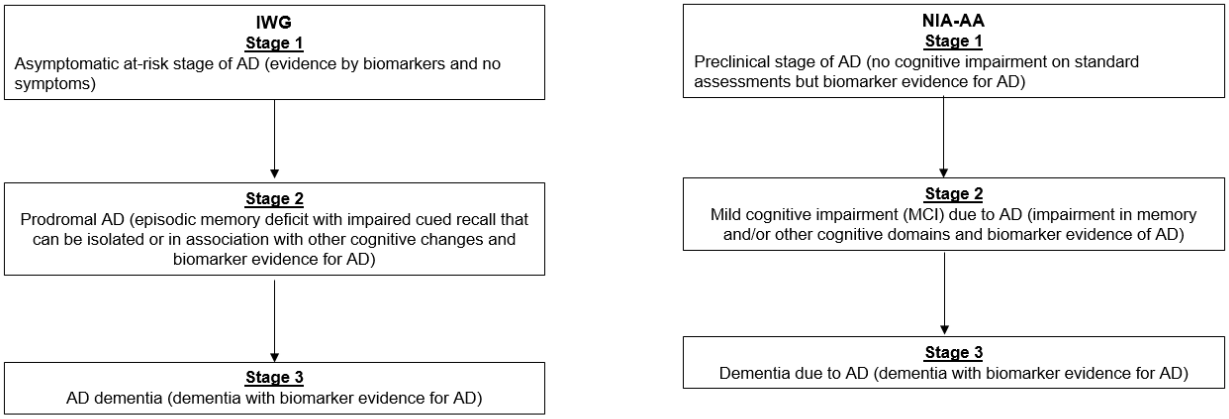

Figure 1. Stages of AD development

The International Working Group and National Institute on Aging-Alzheimer's Association (NIA-AA) propose similar stages of AD development (Figure 1). When examining high-risk

individuals (potentially stage 1), it is important to examine SCD, risk factors, and biomarkers before significant cognitive decline is present (stage 2). This proposed project examines high-risk people who are at risk for falling into the AD-continuum beginning at stage 1.

Chapter 3: Methodology

Participants

This was an exploratory, cross-sectional design where subjects were recruited on a rolling basis during data collection. We recruited 216 adults (male and female ages 45-75 years) at increased risk for AD (Table 2). During the visit, participants provided a blood sample, underwent a body composition analysis, and completed a suite of cognitive, physical and behavioral measures (described below). Women are at a higher risk for AD than men and also participate in health-based studies more than men; therefore, may be more interested in this study. We oversampled men to ensure the sample was representative if necessary but 60% female sample was acceptable. Inclusion and exclusion criteria are in Table 2.

Table 2. *Clinical Trial Inclusion and Exclusion Criteria*

Inclusion	Exclusion

• Age 45-75
• BMI 18.5 - 39.9 kg/m^2
• Fluent in English (written and spoken)
• Subjective cognitive decline with worry
• A minimum of 2 risk factors for AD on ANU-ADRI:
  • High school education or less
  • BMI 25-39.9 kg/m^2 (overweight, obese class I or II)
  • History of diabetes • History of hypertension
  • History of high cholesterol • History of smoking
• Maximum of 1 protective factor for AD on ANU-ADRI:
  • High level of physical activity • High fish consumption
  • High level of cognitive engagement
• Ability to send and receive text messages
• Access to a smartphone or tablet with a screen-side camera and reliable internet connection
• Ability to participate in light to moderate physical activity
• Willing to authorize release of medical records
	• Physician diagnosis of
	  • mental health condition (e.g., eating disorder, alcohol/substance use, schizophrenia, etc.)
	  • neurologic conditions (e.g., epilepsy, recent stroke, multiple sclerosis, Parkinson's disease, brain tumor, or severe traumatic brain injury)
	  • dementia, probable dementia, or mild cognitive impairment
	  • other significant health condition (e.g., congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, renal failure, chronic kidney disease, pulmonary hypertension)
	• Recent cardiovascular event or treatment for cancer (within the last year); on dialysis; or on active organ transplant list
	• Visual problems that prevent viewing screen at a normal distance (e.g., legal blindness, detached retina, occlusive cataracts)
	• History of learning disability
	• Currently participating in a cognitive training coaching program or other lifestyle change program (e.g., diabetes prevention program)
	• Currently pregnant or planning on becoming pregnant in the next two years

Biometric Assessments

Biometric assessments included height, weight, and body composition (fat free mass, fat mass, bone mineral density). Height was measured with a standing stadiometer (Seca; Hamburg, Deutschland). During this assessment, participants were asked to remove their shoes and stand up as straight as possible. Height was recorded to the nearest 0.1 cm. Weight was measured with a balance-beam scale (Detecto, Webb City, MO). Participants removed their shoes, any heavy clothing (sweaters, jackets, or coats), and empty their pockets. Weight was measured to the nearest 0.1 kg. Body composition was measured through a DEXA scan (General Electric Company, Madison, WI) during the initial visit.

Physical Function

Six-minute Walking Distance Test (6MWDT). The 6MWDT is a field measure of aerobic capacity which has a high test-retest reliability (ICC = .96), a minimal clinical important difference (MCID) of 20.0 meters, and stability over time (Teresa, 2002). From a standing start, participants were instructed to walk continuously for 6 minutes around a 200-meter track, at the fastest pace they feel they can maintain throughout the duration of the examination. Participants were told their goal is to cover as much ground as possible in 6 minutes. Participants were allowed to stop and stand or sit in chair if desire to rest is verbalized and they were instructed to walk again when they felt able. Distance walked will be recorded at the end of the test. This is a safe field submaximal aerobic capacity test; the 6MWDT is safer than the forester stepping test and more indicative of aerobic capacity than the YMCA submaximal bike protocol.

Hand-grip Strength. Hand-grip testing was used as a measure of isometric strength as it is highly correlated with overall strength and functional independence. All measurements were administered by a trained technician and measured in kilograms using a handheld dynamometer. All measurements were performed on each hand with the subject standing, arm down at the side,

wrist in neutral position, and interphalangeal joint of the index finger maintained at 90 degrees. Participants were instructed to maximally squeeze the handle for 5 seconds with standard encouragement provided. The test will be administered 3 times with 60s rest between attempts. This test has shown high test–retest reliability ICC of 0.95, MCID of 6.5 kg (19.5%) change (Perera et al., 2006). This strength test is safer for the population in the proposed study compared to one repetition maximum bench press, leg press, or back squat.

Lower-body Muscular Power. Sit-to-stand power will be measured using the Tendo Weightlifting Analyzer (Trencin, Slovac Republic). The Tendo will be attached to the side of each participant by securing a belt around the participant's waist. To ensure consistency, the Tendo will be placed on the participant's left side, with the Kevlar string positioned to be in the sagittal plane, when the participant is in the standing position. The Tendo will be attached to the participant by securing a belt around the participant's waist. From a seated position, with the arms placed across opposing shoulders, the participant will be instructed to stand as quickly as possible before slowly returning to the initial seated position (outcome measures only take into account the egress component of the STS). As the participant stands as quickly as possible, the Tendo's Kevlar string is pulled and average/peak power output (W) for each stand is recorded. Five repetitions will be recorded with a 60-second rest between each repetition. Average power is calculated as the mean power generated among all 5 repetitions and peak power is determined as the highest power recorded during any of the 5 repetitions. Average velocity is calculated as the mean velocity generated among all 5 repetitions and peak velocity is determined as the highest velocity recorded during any of the 5 repetitions. This measure was validated for use in middle-age and older adults (Glenn et al., 2015; Gray & Paulson, 2014); MCID of 17% change in average power and 9%

change in peak power. This assessment is a safer alternative to Olympic lifts (power clean, hang power clean, power snatch) examining an at-risk older population.

Dual-task. The dual-task walking assessment evaluated attention and executive function (Brustio, Magistro, Zecca, Rabaglietti, & Liubicich, 2017; Yogev-Seligmann, Hausdorff, & Giladi, 2008). This assessment has been described in detail elsewhere (Glenn, Vincenzo, Canella, Binns, & Gray, 2015). Dual-task assessments vary in protocol, but for the purposes of this study, participants were instructed to walk 20 meters at their usual speed while time was recorded by the researcher. There was a 5-meter distance before and after the 10-meter distance to account for acceleration and deceleration (Glenn et al., 2015). For the next part of the assessment, participants were instructed to walk as quickly and safely as possible without running. These two assessments were used as the baseline tests. For the dual-task conditions, participants were instructed to perform the same walking conditions and simultaneously perform serial subtractions (Hausdorff et al., 2001). A random 3-digit number between 199 and 999 was selected and participants were instructed to subtract three from each number while performing each walking condition. Four testing trials were completed, two at usual speed (dual-task habitual speed) and two at their maximal speed (dual-task maximal speed). Dual-task decrement was calculated as the difference between the walk trial while performing serial subtractions and the trial without subtraction. The walking speed trials (DT-HS and DT-MS) were averaged separately and used for all analyses. Dual-task is a valid and reliable method for assessing working memory in young and older adults (Montero-Odasso et al., 2009; McCulloch et al., 2009).

4-meter dual-task walk. Dual-task assessments vary in protocol, but for the purposes of this study, participants were instructed to walk 4 meters at their usual speed while time was

recorded by the researcher. For the next part of the assessment, participants were instructed to walk as quickly and safely as possible without running. These two assessments were used as the baseline tests. For the dual-task conditions, participants were instructed to perform the same walking conditions and simultaneously perform serial subtractions (Hausdorff et al., 2001). A random 3-digit number between 199 and 999 was selected and participants were instructed to subtract three from each number while performing each walking condition. Four testing trials were completed, two at usual speed (dual-task habitual speed) and two at their maximal speed (dual-task maximal speed). The walking speed trials (DT-HS and DT-MS) were averaged separately and used for all analyses. This test is a part of the short physical performance battery that has high test-retest reliability (Gómez Montes et al., 2013).

Surveys

ANU-ADRI. This is an evidence-based 79-itme risk assessment method to predict the risk of future AD development. It collection information on age, sex, education, body mass index, diabetes, depression, serum cholesterol, traumatic brain injury, smoking, alcohol intake, social engagement, physical activity, cognitive activity, fish intake, and pesticide exposure. This is a valid and reliable measure (Anstey et al., 2013).

Physical Activity. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), this is a component of the ANU-ADRI. IPAQ is a reliable and valid subjective tool for quantifying sedentary, moderate, and vigorous behaviors (Craig et al., 2003).

Subjective Cognitive Decline (SCD). Everyday Cognition (ECog-12) 12-item Assessment was utilized to evaluate subjective cognitive decline. ECog-12 is a self-report measure of level of independence in performing cognition-based daily tasks. This assessment contains 12 cognition-based questions for individuals to answer 1 (better or no changed compared to 10 years

ago) through 4 (consistently much worse). This test has been validated and has high test-retest reliability (Tomaszewski Farias et al., 2011).

Loneliness. The University of California, Los Angeles, 3-item Loneliness Scale was utilized to examine the degree of loneliness among participants (Hughes et al., 2004). Scores ranged from 3-9, with higher scores indicating greater levels of loneliness. Scores above 5 indicate loneliness.

Sleep. Quality of sleep was measured using Pittsburgh Sleep Quality Index. The 9-item assessment provides a score ranging from 0-27, with higher scores being associated with poor sleep. Individuals scoring ≥5 are deemed poor sleepers (Buysse et al., 1989).

Depression. The Patient Health Questionnaire was used to analyze depression, this is a 9-item questionnaire with scores ranging from 0-27. Higher scores indicate higher levels of depression (Martin et al., 2011).

Health-Related Quality of life. The 12-item Short Form Health Survey was used to evaluate quality of life. This is a valid and reliable measure for health-related quality of life in various populations (Ware, Kosinski, and Keller, 1996). There are two subscales: physical health and mental health. Scores range from 12-47, with higher scores associated with higher self-reported quality of life.

Anxiety. Anxiety was measured using the General Anxiety Disorder 7-item scale (Spitzer et al., 2006). This measure is valid and reliable anxiety tool among older adults (Löwe et al., 2008). Scores range from 0 to 21, with higher scores indicating higher anxiety severity.

Perceived Stress. Perceived stress was analyzed using the Perceived Stress Scale (Cohen et al., 1983). Scores ranged from 0-40, with lower scores related to lower perceived stress. Scores 0-12 show low stress, 14-26 indicates moderate stress, and >26 display high stress.

Asynchronous Cognitive Testing Battery

Image Pairs. Image Pairs is an eye tracking-based task that measures visual recognition memory and learning (Bott et al., 2018; Gills et al., 2019, 2020). The visual paired comparison portion of the test measured the participant's ability to recognize images they have already viewed during a familiarization phase. The paired recognition trial portion of the test measured the participant's ability to learn and identify image pairs they have been tasked with learning.

Symbol Match. Symbol Match is a processing speed and executive functioning task that utilizes a paired verification or rejection paradigm (forced choice). Participants were instructed to determine whether two symbols are equal or unequal utilizing a legend with nine number/symbol pairs. At the conclusion of the task, a brief implicit learning trial was administered without the legend present.

Arrow Match. The Arrow Match test is a measure of attention and processing speed. Participants were shown five arrows in the middle of the screen and were instructed to identify the direction of the middle arrow. The arrows can point in either the same direction or in the opposite direction from the other arrows. Participants were presented with 32 trials and scores are reported as the number of correct responses relative to the time elapsed during all trials.

Item Price. Item Price is a brief visual paired associates paradigm. This task required participants to learn eight food/price pairs and discriminate between target and foil (items previously present but not paired) pairs during a recognition trial. All items belong to the same semantic category (fruits, vegetables, etc.) and are presented in pseudorandom order using a blocking scheme.

Path Points. Executive function is assessed using the Path Points test. Similar to the paper-pencil Trail Making Test Part B (Lezak, 1995), Path Points is a digital version where participants connected a series of alternating numbers and letters from 1-A to 7-G. Scores were

reported as the amount of time required to complete the 14 responses. Only correct responses are allowed.

Light Reaction. Reaction time and inhibition are assessed with the Light Reaction test. Participants were presented with either a positive stimulus (green light) or negative stimulus (red light). If the positive stimulus appears, they were tasked with pressing a button. If the negative stimulus appears, they were tasked with refraining from pressing the button. Average response time for reacting to the positive stimulus (green light) was recorded.

RBANS Cognitive Assessment

Each participant was individually administered the RBANS assessment (RBANS; Forms A, B & C). The RBANS assessment was completed on an iPad along with paper and pencil. The RBANS assessment construction is explained in detail elsewhere (Dickerson et al., 2004). Briefly, the RBANS is made up of 12 subtests that are used to calculate five index scores and a total score. Test catalogues include: Immediate memory (list learning and story memory tasks), Visuospatial/constructional (comprised of figure comply and orientation tasks), language (picture naming and semantic fluency tasks), attention (digit span and coding tasks), and delayed memory (list recall, story recall, figure recall, and list recognition tasks). Each index score falls within an age-adjusted score (Dickerson et al., 2004). The index scores are combined to produce a total score, which is a summary score of the participant's performance on the RBANS. The RBANS test took approximately 30 minutes to administer and complete. Previous research showed the RBANS is significantly correlated with more extensive exams such as the Wechsler Adult Intelligence Scale III and the Wechsler Memory Scale III, it also has strong test-retest reliability (Hobart & Bartko, 1999; Wilk et al., 2002).

Venous Blood Draw

To evaluate biomarkers (p-tau217, ApoE, cholesterol, and glucose), a venous blood draw was taken at the beginning of the visit (subjects were on a 3-hour fast). Samples was stored at -80^0 C until analysis. P-tau217 was analyzed using enzyme-linked immunosorbent assays (ELISA) kits following instructions provided by manufacturers. Genetic testing through real time PCR was completed to asses ApoE ε4 in as an additional risk factor for AD. Cholesterol and glucose was examined through Cholestech (Stat-technolgies, Golden Valley, MN). ApoE will be analyzed by a third party laboratory.

SNP Genotyping

DNA was extracted from participant's whole blood. ApoE alleles were observed through SNPs rs7412 and rs429358 that were genotyped using real time PCR for 215 participants by a third party (CD Genomics, Inc., Shirley, NY). e_2 genotype was determined by T for a SNP rs7412 and T on SNP rs429358, e_3 genotype was determined by C for a SNP rs7412 and T on SNP rs429358, e_4 genotype was determined by C for a SNP rs7412 and C on SNP rs429358 (Sebastiani et al., 2019).

Statistical Analysis

All data was inspected to identify missing items and outliers. Conclusions were formed that are robust to different missing-data mechanisms (Raudenbush & Bryk, 2002). All data was subjected to quality control checks prior to proposed statistical analysis (e.g., homogeneity, multicollinearity). Assumptions for regressions and ANOVA were assessed including linearity, independence of error, homoscedasticity, heterogeneity, independence, and normality. Demographic and efficacy data was summarized by mean ± SD. Summary tables of continuous variables will present arithmetic mean, 95% CI, and SE. Summary tables of categorical variables will present counts and percentages. Hypothesis testing was carried out at the 5% (2-sided) significance level unless otherwise specified, and *P*-values was rounded to three decimal

places. SPSS (version 26) was used for descriptive calculations, ANOVA comparisons, and regression modeling.

Sample size and power calculation: Based on power analysis in G power to document that we have a sufficient sample size, we anticipated exceeding 95% power to detect meaningful associations between proposed variables during linear regressions and delineate differences in ANOVA. Power may decrease when looking at the differences between clusters and physical activity/genetic groups due to unequal and lower sample sizes. However, it is still important to understand which metabolic and behavioral factors affect cognition the most.

Question 1: A hierarchical cluster analysis was utilized to identify profiles based physical function levels among participants. A K-means cluster analysis was used to place participants in three clusters determined by the hierarchical cluster analysis. Physical function (Sit-to stand power variables, handgrip, 6MWDT, 4m fast, 10fast, 4mDTHab, 4mDTfast, 10mDThab, 10mDTfast) cluster individuals into specific clusters based on physical function scores. A one-way ANCOVA determined the differences in cognitive domain scores and blood biomarkers among each physical activity cluster. Age (not controlled for in digital cognitive tasks), sex, education, and APOE were co-variates in the model.

Question 2: iPAQ data was separated by top 50% and bottom50%. A 2x2 factorial ANCOVA was used to examine whether ApoE ε4 (carrier and non-carrier) mitigates PA (top 50%, bottom 50%) changes in cognition and blood biomarkers among each cluster and across clusters. Age, sex, education, and APOE were co-variates in the model.

Question 3: I used multiple linear regressions using age, education, sex, Ecog-12, metabolic and behavioral factors as predictor variables; and p-tau217 as the dependent variables. Independent variables in regressions: age, education, sex, BMI, glucose, HDL, LDL, blood pressure, physical

activity levels, SCD, triglycerides, depression, and social engagement. Dependent variables in regressions: P-tau 217.

Chapter 4: Results

Demographic information

Of the 216 subjects that completed the study, the mean age was 59.7 ± 14.1 years, 73.1% female (158 participants), and 97% Caucasian Americans represented the sample; additionally, participants had an average educational years in school of 17.9 ± 3.5 years. Participant's biometric information included: weight of 84.1 ± 19.9 kilograms, height of 165.9 ± 18.4 centimeters, and body mass index (BMI) of 30.1 ± 5.2 kg/m^2.

Physical Function Clusters

Based on the observed changes of the agglomeration schedule, a 3-cluster solution could best discriminate between measures of physical function and produce satisfactory division of individuals between clusters and was, therefore, selected for the subsequent analysis.

Cluster 1 (C1; *n* = 29) is characterized by high overall strength, power, faster dual-task walking time, and higher aerobic capacity. Cluster 3 (C3; *n* = 112) is described as the lowest strength, lower power output, slower dual task times and lowest aerobic capacity. Cluster 2 (C3; *n* = 74) is in-between clusters 1 and 3 for all values (Table 3). A posteri observed power for significant variables ranged from 0.65-0.93.

Table 3. Cluster centers

	Cluster1 (*n* = 29)	Cluster 2 (*n* = 74)	Cluster 3 (*n* = 113)	*p* –value
HG Right (kg)	37.99	31.66	26.61	< .001
HG Left (kg)	34.87	30.34	25.23	< .001
Average Power (W)	659.38	499.22	336.32	< .001
Average partial power (W)	548.16	421.54	296.59	< .001
Peak Power Average (W)	1508.42	1020.01	632.97	< .001
	Cluster1 (*n* = 29)	Cluster 2 (*n* = 74)	Cluster 3 (*n* = 113)	*p* –value

Average Velocity (m/s)	0.68	0.58	0.46	< .001
Peak Velocity (m/s)	1.16	0.99	0.77	< .001
Peak Force (N)	1504.19	1213.62	933.29	< .001
4m Fast (s)	2.16	2.32	2.40	.022
10m Fast (s)	4.94	5.35	5.63	.005
4 m DT Hab (s)	21.10	3.58	3.81	.043
4m DT Fast (s)	28.63	2.66	2.93	.041
10m DT hab (s)	7.87	8.30	9.11	.012
10m DT fast (s)	5.82	6.16	6.81	< .001
6MWDT (m)	566.8	546.6	517.6	.002

Note. Cluster means, HG=hand grip, DT= dual task, hab= habitual, m=meter

Cognitive scores. Significant differences were exhibited among global cognitive scores (RBANS total score) (F (2,198) = 3.73, p = .026; η^2_p =.036; figure 2, Table 4), C1 performed significantly better on RBANS than C3 (p = .021; figure 2). Visuospatial scores showed significant differences among groups (F (2,198) = 5.66, p = .004; η^2_p =.054; figure 3)*;* C1 performed significantly better on this task than C3 (p = .006; Table 4). Line orientation, a visuospatial test, scores were significantly different between groups (F (2,197) = 3.73, p = .001, η^2_p =.068; Table 4); C1 had significantly higher scores compared to C3 *(*p = .004) and C2 performed significantly better than C3 *(*p = .008). Furthermore, the figure recall exam, a delayed memory test, showed significant differences between groups *(*F (2,197) = 4.87, p = .012; η^2_p =.044; Table 4). C1 performed significantly better than C3 *(*p = .011). A significant trend was noticed between clusters for attention domains *(*F (2,198) = 2.78, p = .065; η^2_p =.027; Table 4).

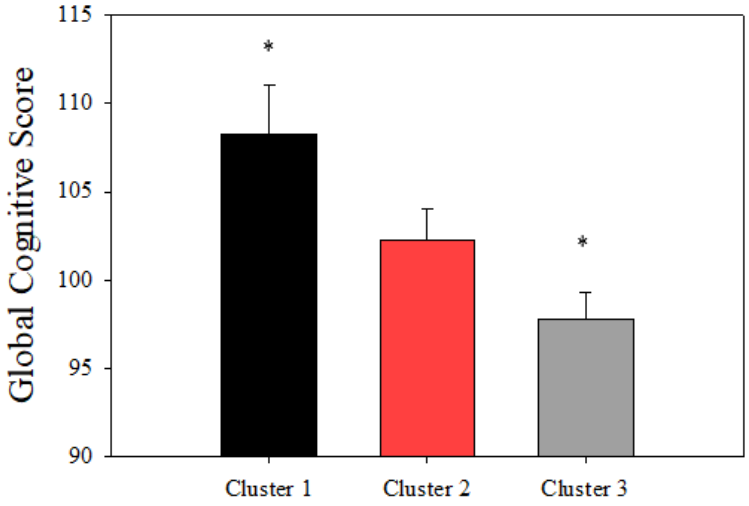

Figure 2. Global cognitive means with standard error bars for each cluster; * indicates significant differences between clusters.

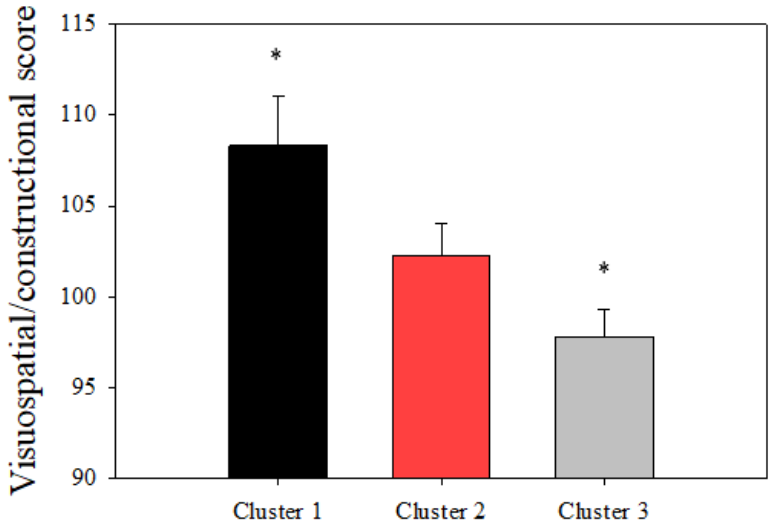

Figure 3. Visuospatial/constructional means with standard error bars for each cluster; * indicates significant difference between clusters.

Table 4. *Cluster cognitive domain data*

	Cluster 1 (n = 29)	Cluster 2 (n = 74)	Cluster 3 (n = 113)	p-value
Immediate Memory	105.0 ± 2.0	100.7 ± 1.6	102.7 ± 1.3	.137
Visuospatial/constructional	108.3 ± 2.7*	102.3± 1.7	97.8 ± 1.5*	.031
Language	100.8 ± 2.3	102.7 ± 1.1	102.1 ± 1.0	.224
Attention	115.1 ± 2.4	111.1 ± 1.5	108.2 ± 1.3	.264
Delayed Memory	105.9 ± 1.5	112.9 ± 9.0	102.7 ± 1.3	.249

	Cluster 1 (n = 29)	Cluster 2 (n = 74)	Cluster 3 (n = 113)	p-value
Total Score	109.0 ± 2.1*	104.3 ± 1.9	103.8 ± 1.1*	.026

Note. Mean ± SE

Among the digital cognitive tasks, there was a difference in path points (executive function) scores *(F* (2,190) = 6.05, p = .003; η^2_p =.06; Figure 4). C1 performed significantly better than C3 (p = .018), C2 also had significantly higher scores than C3 (p = .013). Moreover, significant differences were identified among the Item Price (associative learning) task *(F* (2,185) = 3.54, p = .031; η^2_p =.04; Figure 5). C1 performed significantly better than C3 (p = .044). No other significant differences were found between each cluster during the digital cognitive task.

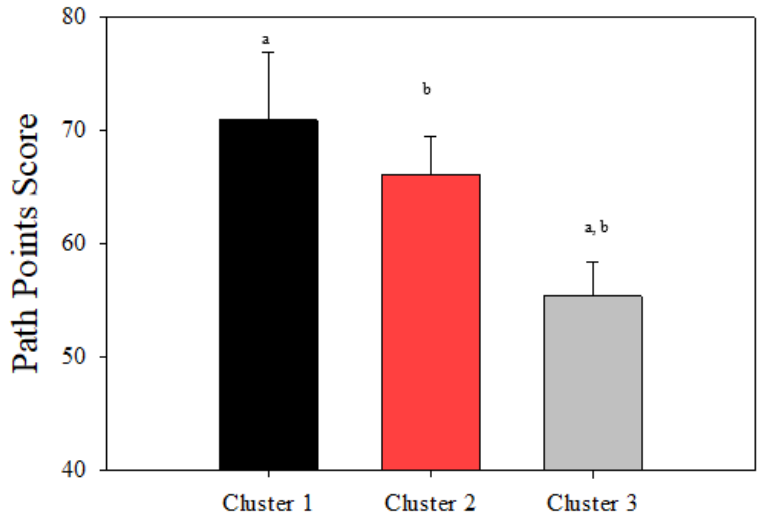

Figure 4. Path Points Score means with standard error bars for each cluster; a indicates significant difference between cluster 1 and cluster 3, b indicates significant differences between cluster 2 and cluster 3;

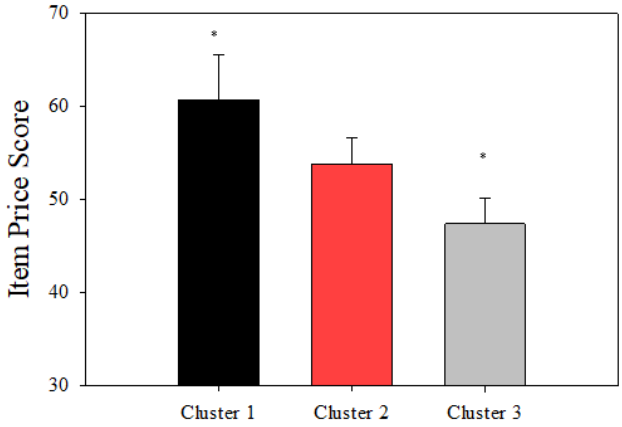

Figure 5. Item Price Score means with standard error bars for each cluster; * indicates significant difference between clusters.

Table 5. *Cluster individual exam cognitive data*

	Cluster 1 (*n* = 29)	Cluster 2 (*n* = 74)	Cluster 3 (*n* = 113)	*p*-value
Listen Learning (IM)	28.9 ± 0.7	28.1 ± 0.5	28.0 ± 0.4	.337
Story Memory (IM)	18.9 ± 0.5	17.7± 0.4	18.1 ± 0.3	.236
Figure Copy (V/C)	18.6 ± 0.4	18.1 ± 0.2	17.9 ± 1.0	.274
Line Orientation (V/C)	17.9 ± 0.4[a]	16.9 ± 0.3[b]	15.8 ± 0.3[a,b]	.001
Semantic Fluency (LAN)	21.9 ± 1.0	22.3 ± 0.5	21.9 ± 0.4	.266
Picture Naming (LAN)	9.7 ± 0.1	9.8 ± 0.1	9.6 ± 0.1	.283
Coding (ATT)	52.0 ± 1.3	49.7 ± 0.9	48.3 ± 0.9	.171
Digit Span (ATT)	13.0 ± 0.5	12.2 ± 0.4	11.6 ± 0.4	.201
List recall (DM)	6.3 ± 0.3	6.7 ± 0.2	6.6 ± 0.2	.836
Story Recall (DM)	9.9 ± 0.3	9.6 ± 0.2	9.6 ± 0.2	.582
Figure Recall (DM)	15.9 ± 0.5*	14.3 ± 0.4	13.1 ± 0.4*	.012
List Recognition (DM)	19.5 ± 0.2	19.3 ± 0.1	19.5 ± 0.1	.370
Arrow Match (attention)	37.5 ± 4.5	33.9 ± 3.0	32.3 ± 2.6	.726
Path Points (Exec Func)	70.9 ± 6.0[a]	66.1 ± 3.4[b]	55.4 ± 3.0[a,b]	.003
Light Reaction (Inhibition)	27.2 ± 4.5	29.1 ± 3.5	24.9 ± 2.5	.208
Symbol Match(Processing sp.)	40.0 ± 5.7	38.9 ± 3.1	37.2 ± 2.9	.339
Item Price (As. Learning)	60.7 ± 4.9[*]	53.8 ± 2.8	47.4 ± 2.7[*]	.031
Paired imaging (As. Memory)	40.3 ± 5.9	44.4 ± 4.1	46.6 ± 3.1	.920

Note. Mean ± SE, IM = Immediate memory, V/C = visuospatial/constructional, LAN = Language, ATT = Attention DM = delayed memory, Exec Func = executive functioning, processing sp. = processing speed, As. = associative.

Metabolic and Blood Biomarkers. There were no significant differences between clusters for total cholesterol, LDL, TC/HDL, HDL TRG, glucose, resting HR, blood pressure data, or BMI ($p > 0.05$; Table 6).

Table 6. *Cluster metabolic data*

	Cluster 1 (n = 29)	Cluster 2 (n = 74)	Cluster 3 (n = 113)	p-value
Age	56.9 ± 8.2	60.5 ± 8.0	64.2 ± 7.6	<.001
Sex (female%)	37.9	66.2	86.7	<.001
Weight	96.9 ± 23.2	89.7 ± 17.5	78.6 ± 14.6	.009
Height	174.7 ± 9.1	170.3 ± 9.0	163.8 ± 7.4	.002
BMI	31.5 ± 5.8	30.9 ± 5.7	29.1 ± 4.6	.090
Education	18.1 ± 2.8	17.9 ± 3.3	17.8 ± 4.2	.922
Resting SBP	126.0 ± 11.4	128.1 ± 10.8	128.6 ± 13.2	.608
Resting DBP	81.6 ± 9.5	82.3 ± 10.1	82.1 ± 10.4	.958
Resting HR	73.6 ± 14.5	71.2 ± 12.6	72.6 ± 9.6	.586
Total Cholesterol	199.5 ± 45.6	201.7 ± 41.9	204.9 ± 43.3	.142
LDL	118.9 ± 35.7	120.9 ± 33.9	122.8 ± 48.2	.906
HDL	50.4 ± .18.2	53.7 ± 17.8	59.4 ± 14.8	.704
TRG	159.7 ± 121.0	134.1 ± 66.9	136.7 ± 66.2	.308
Fasting Glucose	99.6 ± 14.8	106.5 ± 24.3	100.7 ± 21.7	.168

Note. Mean ± SD, BMI = Body Mass Index, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, LDL = Low density lipoprotein, HDL = High density lipoprotein, TRG = Triglyceride

Physical Activity and ApoE differences

Since there were only two ApoE ε4 carriers in the C1, carriers and non-carriers differences were analyzed through subjective IPAQ data (top 50% and bottom50% based on the median of 4450MET per minute). Observed power for significant variables ranged from .53-.79.

Metabolic and blood biomarker data. BMI had a significant interaction effect between ApoE and physical activity groups ($F(1,198) = 4.01$, $p = .047$; $\eta^2_p = .02$). ApoE carriers that were physically active individuals had lower BMI compared to the physically inactive individuals

(Table 7). However, the ApoE non-carriers who were physically inactive had lower BMI compared to the physically active group. Moreover, a significant trend was identified in triglycerides non-carriers who were physically active had higher triglycerides than physically inactive but ApoE carriers who were physically active had lower triglyceride levels than physically inactive individuals ($F(1,192) = 3.25$, $p = .073$; $\eta^2_p = .02$; Table 7). The high physical activity group showed significantly higher resting heart rates compared to low physical activity group ($F(1,198) = 4.87$, $p = .028$; $\eta^2_p = .02$; Table 7). In addition, carriers had significantly lower resting HR than non-carriers ($F(1,198) = 6.23$, $p = .013$; $\eta^2_p = .01$; Table 7). No other differences were found in metabolic and blood biomarker data between ApoE carriers and non-carriers or physical activity groups ($p > .05$).

Table 7. Metabolic and blood profiles of ApoE and physical activity levels

	ApoE ε4 carriers		ApoE ε4 non-carriers		
	PA ($n = 32$)	PIA ($n = 20$)	PA ($n = 72$)	PIA ($n = 79$)	p-value
Age	61.6 ± 1.5	60.6 ± 1.8	62.6 ± 0.9	62.0 ± 0.9	.860
Education	16.1 ± 0.6	18.3 ± 0.7	17.9 ± 0.4	18.7 ± 0.4	.215
BMI	28.0 ± 0.9	30.7 ± 1.1	30.6 ± 0.6	30.0 ± 0.6	.047
Resting SBP	130.4 ± 2.1	126.7 ± 2.5	129.0 ± 1.3	126.3 ± 1.3	.799
Resting DBP	82.8 ± 1.8	80.1 ± 2.2	83.2 ± 1.2	81.2 ± 1.2	.818
Resting HR	65.6 ± 1.9	71.9 ± 2.3	72.4 ± 1.2	73.6 ± 1.2	.131
Total Cholesterol	209.1 ± 7.8	194.8 ± 9.4	201.7 ± 9.4	203.4 ± 4.9	.256
LDL	128.1 ± 7.9	120.3 ± 9.8	117.8 ± 5.3	123.1 ± 4.9	.362
HDL	56.6 ± 2.8	51.9 ± 3.4	56.5 ± 1.8	57.3 ± 1.8	.286
TRG	118.1 ± 13.4	148.9 ± 16.6	147.8 ± 9.0	134.4 ± 8.5	.073
Fasting Glucose	99.4 ± 3.9	102.1 ± 4.8	100.7 ± 2.6	104.8 ± 2.5	.845

Note. Mean ± SE, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, PA = physically active, PIA = physically inactive

Cognition. Physically inactive showed higher RBANS scores than physically active ($F(1,196) = 4.53$, $p = .034$; $\eta^2_p = .023$). ApoE carriers had significantly higher language scores

than non-carriers ($F(1,196) = 5.79$, $p = .0.017$; $\eta^2_p = .006$). No significant differences were found between carriers and non-carriers or physical activity groups among remaining RBANS domain and individual test scores ($p > .05$; Table 8).

In the digital cognitive test, results showed that physically inactive individuals had significantly higher associative learning scores than physically active ($F(1,183) = 7.82$, $p = .0.006$; $\eta^2_p = .041$). Moreover, a significant trend was found in the associative memory task ($F(1,123) = 3.74$, $p = .055$), ApoE non-carriers showed better scores than carriers. No other significant differences were found for the remaining four digital cognitive tests ($p > .05$; Table 8).

Table 8. *Cognitive scores* of ApoE and physical activity levels

	ApoE ε4 carriers		ApoE ε4 non-carriers		
	PA ($n = 32$)	PIA ($n = 20$)	PA ($n = 72$)	PIA ($n = 79$)	p-value
Immediate Memory	99.7 ± 2.3	105.8 ± 2.8	101.5 ± 1.5	102.7 ± 1.4	.229
Visuospatial/Constr.	103.7 ± 2.9	103.9 ± 3.6	99.1 ± 1.9	100.0 ± 1.8	.889
Language	104.0 ± 1.7	106.6 ± 2.1	102.3 ± 1.1	100.0 ± 1.7	.181
Attention	109.6 ± 2.4	104.0 ± 1.7	110.1 ± 1.6	109.9 ± 1.5	.289
Delayed Memory	105.7 ± 8.5	99.9 ± 10.6	103.7 ± 5.6	112.2 ± 5.4	.361
Total Score	101.8 ± 2.3	110.2 ± 2.9	104.2 ± 1.5	104.9 ± 1.5	.073
Arrow Match (ATT)	29.2 ± 4.7	33.4 ± 5.7	35.3 ± 3.1	31.7 ± 2.9	.360
Path Points (Exec. Func.)	59.0 ± 5.5	63.7 ± 6.9	63.2 ± 3.6	58.2 ± 3.6	.343
Light Reaction (Inhibition)	20.3 ± 4.9	28.4 ± 5.8	28.9 ± 3.1	25.4 ± 3.1	.189
Symbol Match(Processing sp.)	31.1 ± 5.3	42.9 ± 6.4	38.1 ± 3.4	39.6 ± 3.3	.283
Item Price (As. Learning)	46.2 ± 4.8	62.8 ± 6.1	46.6 ± 3.1	55.4 ±	.379
Paired imaging (As. Memory)	28.9 ± 6.1	45.2 ± 7.6	45.7 ± 3.8	49.6 ± 3.7	.271

Note. Mean ± SE, ATT = Attention, Exec Func = executive functioning, processing sp. = processing speed, As. = associative.

P-tau217 Associations

The model used explained 55% of the variance for p-tau217 but was not significant ($F(20,7) = 2.65$; $p = .095$). Moreover, BMI ($r = .42$; $p = .013$), gender ($r = .35$; $p = .033$) were the

only significant correlations with p-tau217. However, this model had multi-collinearity issues with perceived stress and resting DBP being the highest; and HDL and LDL overlapping with total cholesterol. So, a second model was created to resolve the multi-collinearity issues.

The second model explained 49% of the variance for p-tau217 but was not significant (F (17, 10) = 7.90; p = .068). Again, BMI (r = .42; p = .013), gender (r = .35; p = .033) were the only significant associations with p-tau217.

These models are underpowered due to the lack of p-tau217 data due to the ELISA kit detection range being too high to identify the amount of protein in all samples (28 samples were detected and used in this analysis).

Table 9. *Descriptive statistics for AIM 3*

	N	Mean
Age (years)	26	62.5 ± 0.6
Sex (female)	26	58%
Height (cm)	26	170.2 ± 10.5
Weight (kg)	26	83.9 ± 19.1
Education (years)	26	18.4 ± 4.5

Note. Mean ± SD

Table 10. *The relationship between risk factors and p-tau217 in at-risk individuals*

Dependent variable: p-tau217 concentration (ng/mL)						
	Model 1			Model 2		
Predictors	Estimate (B)	LL 95% CI	UL 95% CI	Estimate (B)	LL 95% CI	UL 95% CI
Age	0.45	-1.64	7.1	0.24	-2.38	5.26
Gender	0.44	-17.74	113.07	0.32	-25.17	94.80
Education	-0.39	-18.32	4.50	-0.24	-13.88	5.59
ApoE	-0.54*	-114.05	-2.76	-0.64*	-122.50	-15.10
Physical Function	-0.57*	-81.17	-2.83	-0.67*	-85.95	-12.85
QoL	-0.48	-13.71	3.38	-0.62	-14.58	1.34
Sleep	-0.67*	-28.57	-1.10	-0.38	-19.52	2.82
Anxiety	0.02	-11.07	11.70	0.30	-4.92	15.07
Depression	-0.99*	-28.57	-4.21	-0.99	-28.41	-4.60
Loneliness	0.07	-12.64	17.92	0.08	-11.42	17.09
Subjective Cog. Dec.	-.027	-9.01	2.62	-0.21	-8.26	3.21

	Model 1			Model 2		
Predictors	Estimate (B)	LL 95% CI	UL 95% CI	Estimate (B)	LL 95% CI	UL 95% CI
BMI	0.12	-3.82	2.45	0.40	-0.26	7.09
Resting SBP	-0.17	-3.83	2.45	0.13	-1.23	2.31
TRG	0.20	-0.24	0.61	0.09	-0.29	0.48
GLU	0.41	-0.38	2.12	0.27	-0.44	1.56
Resting HR	0.69	-0.07	6.68	0.50	-0.60	5.38
Total Cholesterol**				0.01	-0.43	0.44
LDL	-0.32	-1.15	0.34			
HDL	-0.06	-1.60	1.25			
Resting DBP	0.38	-2.05	5.89			
Perceived Stress	.52	-1.32	10.07			
F-statistic for linear model			$F_{20,7} = 2.65$			$F_{17,10} = 7.90$

*$p < 0.05$. Abbreviations: 95 CI = confidence intervals; ApoE apolipoprotein *e*4 allele; B = standardized beta value from linear model; BMI = body mass index, LL = Lower Level; UL= upper limit; QoL = Quality of life; cog. Dec. = cognitive decline; SBP = systolic blood pressure; DBP = Diastolic Blood Pressure; TRG = triglycerides; GLU = Glucose; HR = Heart rate; LDL = low-density lipoprotein; HDL = High density lipoprotein.

Chapter 5: Discussion

The first aim of this study was to examine if higher physical function clusters would produce better cognitive scores than lower physical function cluster. To my knowledge, this is the first study to examine physical function variables clustered together and examining the cognitive differences between each cluster. My *a priori* hypothesis predicted higher physical function cluster would display higher cognitive domain scores compared to lower physical function clusters. My hypotheses was supported; higher physical function exhibited better global cognitive scores and other cognitive domains than the lower clusters. Moreover, visuospatial domain scores, attention tests, and delayed memory recall performance were significantly better in the higher physical function cluster (Cluster 1) compared to lower physical functional clusters (Cluster 2 and 3). Additionally, both higher functioning clusters exhibited better scores on executive functioning and associative learning digital tasks than the lower functioning clusters. Lastly, there were no significant differences identified in blood biomarkers between clusters.

The second aim of this study was to examine if ApoE ε4 carriers would mitigate physical activity benefits among physically active individuals. My *a priori* hypothesis predicted ApoE ε4 carriers physical active (>50% on IPAQ) and inactive individuals (<50% on IPAQ) would have lower cognitive scores and worse metabolic data than ApoE ε4 non-carriers. My hypotheses was not supported; ApoE ε4 carriers that were physically active had lower BMI compared to the ApoE ε4 carriers who were physically inactive. In addition, there was a trend towards significance for lower triglycerides levels among ApoE ε4 carriers that were physically active compared to ApoE ε4 carriers who were physically inactive, the reverse trend was observed in non-carriers. ApoE ε4 carriers had significantly lower resting HR than non-carriers. Moreover, ApoE ε4 carriers had significantly higher language scores than non-carriers. While, physically inactive individuals showed higher global cognitive scores than physically active. Additionally,

physically inactive individuals had higher associative learning scores. But, ApoE ε4 non-carriers were trending towards significantly better scores on the associative memory task.

My final aim of the study was to evaluate the relationship between p-tau217 and metabolic and behavioral risk factors. My *a priori* hypothesis suggested metabolic risk factors and subjective cognitive decline will be associated with greater likelihood of elevated p-tau217 plasma levels. Both models retained the null hypothesis, metabolic and behavioral factors could not predict p-tau217 values. My hypotheses was not supported but more research is needed because the model was underpowered. But, women and higher BMI values were significant correlations with elevated p-tau217. Since both models were underpowered, additional participants are needed to examine these potential relationships.

My exploratory analyses showed that greater physical function clusters were associated with greater global cognitive functioning. Physical activity and exercise studies have shown men and women who are active in mid and late life are at lower risk for global cognitive decline (Barnes et al., 2003; Hagan et al., 2016; Kirk-Sanchez & McGough, 2013; Weuve et al., 2004). Although some of these investigations were longitudinal, researchers found that higher walking levels and average metabolic equivalents have greater cognitive benefits and neuroprotection. Moreover, our study found that executive functioning and delayed memory tasks were greater for the higher physical function cluster compared to the lowest physical functioning cluster. The Doetinchem Cohort Study exhibited the similar results with 6-11 year follow-up analyses (Angevaren et al., 2007). Researchers found that the intensity and variation of physical activities was positively associated with processing speed, memory, mental flexibility, and overall cognitive function, interestingly duration was not associated with better cognitive functioning.

Likewise, a cross-sectional study found greater executive functioning among older men and women with higher physical activity and greater energy expenditure rates (Bixby et al., 2007).

Similarly, this current study showed our highest cluster exhibiting greater muscular fitness (handgrip and lower body power) values than the lowest. Previous investigations indicate that higher handgrip values are associated with executive function, attention, memory, and overall cognition, this was seen in this current study (Buchman, Boyle, et al., 2007; Buchman, Wilson, et al., 2007; Rand & Eng, 2011). Moreover, higher physical function clusters showed higher lower body power and velocity values as well. My results are similar to previous literature in that higher muscular power and velocity scores had strong relationships with overall cognition and executive function scores (Cherup et al., 2018; Petrella, 2004; Yoon et al., 2017). To my knowledge, there are no studies examining lower body muscular power variables clustered together, in aging adults, effect on cognition. Results will add to the literature and should be explored more due to the neural component of power and velocity. Additionally, higher dual-task velocity and fast walking speeds are associated with normal cognitive functioning (Gills et al., 2020; Glenn et al., 2015; Gray et al., 2021). While cognitive differences were found between clusters, there were no differences in blood and metabolic markers between the groups. Higher physical functioning and more physically active groups usually have better metabolic profiles than lower active groups (American College of Sports Medicine, 2018), but this is a specific population at higher risk for cognitive decline. The requirements for this study were that participants were overweight/obese, higher cholesterol, blood pressure, etc. So, the study design deterred heterogeneity in the dataset among metabolic and blood biomarker profiles. Despite the lack of blood and metabolic biomarker difference, participants with higher physical function variables exhibited better cognitive outcomes. Combining these variables into physical function

clusters may be a more efficient way of evaluating cognitive decline. Practitioners could use these techniques to measure decline; however, more research completed is warranted to understand cut-off values for normal cognitive function without increased risk compared to individual's at-risk and individuals with significant decline; as well as comparison to early biomarker data.

Factoring in genetics with biomarker data, participants showed mixed results similar to the literature (Colovati et al., 2021; Stringa et al., 2020). Physically active ApoE carriers showed lower BMI and triglyceride (TRG) levels which may indicate that despite carrying the ApoE ε4 gene, physical activity is still protective in metabolic/biomarker data. However, previous data have demonstrated higher TC and LDL, but not TRG, in ApoE carriers than non-carriers (Wang et al., 2020). But, Wu and Colleagues (2016), found in a Taiwanese population that higher c-reactive protein levels were associated with higher TRG levels in ApoE carriers compared to non-carriers (Wu et al., 2016). The data shown in this current study suggest that higher physical activity levels may have a protective effect on ApoE carriers' metabolic profiles. Further analysis is needed to determine if inflammation plays a role in TRG levels in at-risk individuals. Moreover, carriers also had higher language scores than non-carriers, but no interactions were observed in cognitive data when controlling for age, sex, and education. However, previous longitudinal studies and interventions have shown that physically active ApoE carriers have better cognitive performance than inactive ApoE carriers (Ferrari et al., 2013; Jensen et al., 2019; Shih et al., 2018; Smith et al., 2016; Solomon et al., 2018). Furthermore, physically active ApoE carriers may curb their risk for dementia (Ferrari et al., 2013). A larger sample size is needed to understand true differences in cognitive and metabolic data between ApoE and exercise. Also, an

objective measure to examine physical activity would be a better method delineating accurate interactions between physical activity and genetics.

Lastly, the underpowered model did not predict p-tau 217 levels. However, associations were noticed with p-tau217. Higher BMI and sex were related to increased p-tau217 values. These results contradictory to the literature on BMI and cognition since being overweight is neuroprotective over time (Sun et al., 2020). Tracking this interaction longitudinally may be useful when trying to identify if higher BMI is a risk factor for p-tau217. Moreover, women had higher p-tau217 values than men which corresponds with previous investigations where women have a higher likelihood of AD than men (Brookmeyer et al., 2011). While the survey results do not coincide with the cognitive decline and ADRD literature, a larger sample size may reveal significant correlations with p-tau217 and behavioral data. A recent investigation found that higher quality of life predicted reduced risk of cognitive decline and dementia over time (Phyo et al., 2021). Moreover, several additional studies found that quality of life was associated longitudinal subjective cognitive decline and MCI (Pusswald et al., 2015; Roehr et al., 2017). Additionally, this current investigation found no significant association between subjective cognitive decline and p-tau217 values. Subjective cognitive decline and AD biomarker elevation are indicators of stage 1 of cognitive decline outlined by the National Institute of Aging (Jessen et al., 2014). Moreover, lower loneliness scores were not associated with higher p-tau217 plasma values. Previous findings suggest loneliness or lack of social interaction is associated with a 40% increased risk for dementia (Sutin et al., 2020). Moreover, lower sleep quality was not associated with elevated p-tau217 in this current study. But, previous investigations have linked sleep deprivation to elevated p-tau CSF levels (Barthélemy et al., 2020). While several of these current independent variables may not be linked to p-tau217 in this study, more research is

needed to evaluate their relationship. This model was underpowered because of the low sample size due to ELISA detection range being too low to detect unimpaired individual's p-tau217 levels. The average unimpaired individual is 1.9 pg/mL but the detection range lower end on the ELISA kit used was 3.0 pg/mL (Palmqvist et al., 2021). Further research is needed to draw complete conclusions in these relationships. If relationships are found and substantiated through longitudinal studies and larger sample sizes, this provides insights to specific mechanisms that can be targeted to reduce elevated plasma p-tau217.

This current investigation had several limitations due to the sample and sample size. The sample was mainly Caucasian Americans which limits the generalizability of the results. Heterogeneity in different populations may change current results from this study due to education, genetics, and other social determinants of health. Moreover, this study sample size hindered the conclusions that could be made from the physical activity, biomarker, and genetic results. More robust sample size should be used to examine each variable on cognition. Also, convenience sampling was used to find participants for this current study which limits generalizability of the study. Lastly, cross-sectional data were used to evaluate these current findings which hinders the conclusions that can be made because it only examines a single time point. These findings would have to be measured longitudinally to confirm conclusions.

This is the first study examining cognitive differences among clustered physical function variables. Current data suggests evaluating cognition through physical function/exercise variables clustered together could provide a more efficient way of evaluating exercise on cognition. Cluster 1 surpassed the minimal clinically important differences of >3.3 against both cluster 2 and cluster 3 (Kivipelto et al., 2013). This indicates the value in cluster physical function variables instead of examining a singular domain of physical fitness, each domain and

measures of mobility can be grouped together. More research is needed on a larger scale to incorporate genetics into the equation to determine if higher functioning cluster values can offset genetic risk variants. This is a prospective method of evaluating cognitive decline that is less invasive and cost-efficient. Also, significant associations were noticed between BMI, gender, and p-tau217. Further longitudinal and larger sample sizes are required to confirm relationships. Identifying these particular risk factors can help health care practitioners target specific mechanisms to mitigate cognitive decline.

In conclusion, the results of this current study showed that clustering individuals by physical function variables can discriminate global cognitive functioning. Moreover, it delineated differences in spatial, delayed memory, associative learning, and executive functioning scores. Higher physical activity rates in ApoE carriers demonstrated to lower BMI and triglyceride levels but no cognitive differences were identified between physical activity levels and ApoE. Lastly, elevated p-tau217 levels were related to higher BMI and women.

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