

# Alzheimer's Disease Risk Genes and Cognitive Decline in a Healthy Population

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### Abstract

**Introduction:** Alzheimer's disease (AD) is a devastating, progressive, irreversible brain disorder. Previous research has identified genes associated with the risk of developing AD. Variations in the Apolipoprotein E (APOE) gene show the largest effect size, with the  $\epsilon$  4 isoform associated with highest risk. Genome Wide Association Studies (GWAS) have found other genes associated with AD, yet none with effects as large as APOE. Because AD diagnosis is often preceded by a long period of cognitive decline, we investigated the relationship between previously determined AD risk genes and cognitive decline to determine whether we could detect individuals at risk of imminent decline and at a high priority for clinical intervention.

**Methods:** Cognitively healthy participants from the Duke "MURDOCK" study based in Kannapolis, NC participated in the study. They were aged 55+, had contributed DNA, and undergone two waves of cognitive assessments 4 years apart (n=713). An AD genetic risk score (AD-GRS) was derived for each individual based on the known 9 AD genes from recent meta-analyses. APOE was modeled separately. Scores were based on number of risk alleles and the associated odds ratio for each gene. To determine optimal measure of cognitive decline, the available cognitive tests were evaluated individually and in three different composite measures (1.Global; 2.Learning/Memory; 3.Memory-Weighted). Post-hoc analyses evaluated interactions between AD-GRS, APOE risk-score, combined risk-score, cognition, and cognitive decline as measured by composites and individual assessments.

**Results:** APOE risk-score was associated with cognitive decline as measured by all of the composite measures. APOE risk-score was most highly associated to the newly constructed Predict Composite (composed of assessments most associated to risk genes), followed by the Memory-Weighted, the Learning/Memory, and lastly the Global Composite. APOE risk-score was associated with individual assessments except delayed recall. The AD-GRS was not associated with cognitive decline but associated with baseline cognition as measured by composites weighting memory. The combined risk-score was less associated with cognitive decline than APOE alone.

**Conclusions:** APOE was associated with cognitive decline as best captured by the composites that weighted memory. Although associated with AD, the other risk genes were not associated with cognitive decline, yet are related to baseline cognition best captured by composites weighting memory. This suggests that for identifying individuals at risk of cognitive decline, focusing on APOE will be more useful than other AD risk alleles, and that the optimal composite for capturing change associated with AD appears to be one that is weighted with memory.

## 1. Introduction

Alzheimer disease (AD) is a devastating, progressive, irreversible brain disorder (Welsh-Bohmer, 2016). AD is identified as the most common cause of dementia in later life, affecting nearly 10% of individuals over the age of 65 and 25-40% of those over the age of 85 (Brayne, 2007; Breitner, 2006). Cognitively, the impairment in episodic memory, such as impaired recent memory function / learning and difficulty in word retrieval and general memory recall, is recognized very early in the progression of the disease (Perry, Watson, & Hodges, 1998; Paola et al., 2007; Reid et al., 1996). This is followed by difficulties in executive function, including top down controlled functions such as decision-making, planning, self-monitoring, behavior initiation, organization and inhibition as well as complex problem solving, spatial judgment and motor performance during sensorimotor tasks that require thought (Baudic et al., 2005; Anderson & Tranel, 2002). These impairments are correlated with the severity and duration of the disease (Double et al., 1996). Ultimately, as the disease develops and neural destruction progresses, demise in global cognition and function result and those that survive to the late stages of AD typically succumb to the disease due to complications related to severe brain compromise (Brunnström & Englund, 2009).

a) Neuropsychology of AD: The presentation of AD is largely exhibited as a notable impairment in episodic memory, specifically the processing and learning of recent memories. This impairment is often the most influenced area of cognition as the disease progresses and is believed to occur due to the involvement of the medial temporal lobe early in the illness (Hyman, Van Hoesen, Damasio & Barnes, 1984). More specifically, the affected cells of AD are

in the hippocampus, the structure that processes memory. The destruction of these cells results in the loss of key input and output pathways and therefore results in impaired consolidation of newly learned information into long term memory stores located across interconnected neocortical structures.

AD is defined by its clinical presentation of profound rapid forgetting of recent events and other cognitive problems which appear to be tightly linked to the underlying neuronal cell loss in the hippocampus and other cortical structures (Fleisher et al., 2008). The cognitive measures most closely associated with the core symptoms of disease progression are tests tapping into episodic memory decline, executive function decline, and orientation dysfunction (Donohue et al., 2014). In neuropsychological testing, memory deficits of AD are presented as rapid forgetting of and inability to recall new information after a brief delay (Welsh, Butters, Hughes, Mohs, & Heyman, 1991). It has been found that the most sensitive cognitive measures of disease for episodic memory decline are for verbal memory after a delay, such as a word list recall test or delayed memory recall test (Hayden et al., 2014). It has also been concluded that deficits in multiple cognitive domains are characteristic of AD prior to clinical diagnosis and therefore multiple brain structures and functions are affected years before diagnoses. Patients in the mild prodrome of AD often exhibit the characteristic memory deficits of advanced AD, but may also show mild deficits in executive function, language expression, visuoception, and attention (Bäckman et al., 2005). A diagnosis of mild cognitive impairment (MCI) can be made at this early symptomatic stage based on cognitive assessments. MCI is defined as usually

early stage AD and can begin with a cognitive impairment other than memory (Storandt, Grant, Miller & Morris, 2006).

As AD advances, other cognitive domains become progressively more affected, demonstrating the spread of neuropathological involvement throughout the brain, specifically the lateral temporal areas, parietal cortex, and frontal neocortical areas. While rapid loss of new information is a highly sensitive indicator of AD, changes in lexical-semantic processing, visuospatial functions, expressive language, and higher executive control are superior determinants of the progressive course of the disease (Storandt, Grant, Miller & Morris, 2006; Welsh, Butters, Hughes, Mohs, & Heyman, 1992). At later stages of the disease, semantic knowledge impairments manifest as anomia and impaired semantic fluency. Faulty word search and circumlocution are common tendencies (Bayles, Boone, Tomoeda, Slauson & Kaszniak, 1989). Furthermore, in late stages of AD, visuospatial complications become more prominent, giving rise to apraxia, affecting ability to perform purposeful motor acts and familiar motor acts (Benke, 1993). Spatial processing difficulties, manifested as topographical disorientation or difficulties routing familiar drives, can be identified with formal spatial judgment and visual organization assessments (Rizzo, Anderson, Dawson & Nawrot, 1999). Impaired performance of flexible behavior and executive function tests, such as poor scores on the Trail Making Test Part B, are common (Hayden et al., 2014).

Mental status tests, which are sensitive to global cognition and include the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination

(MMSE), are used by doctors to quickly screen memory and other cognitive functions previously described (Costa et al., 2014; Ayutyanont et al., 2014). Furthermore, recent studies have determined that a composite (a test score derived from two or more different cognitive tests) is most sensitive to detecting and tracking the progression of AD (Ayutyanont et al., 2014). The mental status tests, MoCA and MMSE, bear some similarity to a composite of multiple cognitive tests due to their very nature of briefly assessing a number of cognitive functions. Composite cognitive tests consisting of measures of episodic memory, executive function, and general cognition have been found to best capture the progressive change in brain function throughout AD (Burnham et al., 2015). Additionally, composites simplify data to reduce the number of comparisons and decrease the possibilities of a Type 1 error. Yet, the question of what is the best overall approach for measuring cognitive change in all instances is debated among varying reports. For example, one study focuses primarily on assessments of memory decline as an indicator of AD as longitudinal rate of memory change is the hallmark of AD and including assessments of other cognitive domains causes undesired noise in the data (Marden, Walter, Tchetgen Tchetgen, Kawachi, & Glymour, 2014). In our study, we examined three composites of cognitive tests for association with genetic risk to see what is most useful. The first, a global cognitive composite, consists of assessments that test for episodic memory, executive function, and global deficits. The second composite, a learning and memory composite, consists of multiple episodic memory assessments as previous research has proposed that there is a greater association of AD risk genes

with memory decline specifically. Lastly, a memory-weighted global composite, which consists of mainly memory assessments in addition to executive function and global cognitive deficit assessments.

b) **Biology of AD:** Neurobiological research has identified three pathological hallmarks of Alzheimer's disease; "amyloid plaques"- abnormal aggregation of a viscous small peptide,  $\beta$  amyloid peptide, surrounded by debris around the neuron, "neurofibrillary tangles" - tangled bundles of neurons, and loss of synaptic connections between neurons. These characteristic changes are usually confined to specific cellular laminar areas within the medial temporal lobe area and additionally throughout the association cortices of the frontal, temporal, and parietal lobes (Welsh-Bohmer, 2015; Arnold, Hyman, Flory, Damasio, & Van Hoesen 1991). The presence of these biological features allows firmest diagnose of AD. However, in the absence of pathological information or biomarkers, diagnosis is made based on clinical features such as the characteristic memory loss and cognitive change over time without a known cause.

c) **Genetics of AD:** Efforts to understand the underlying causes of AD have resulted in much recent attention directed at the genetics associated with the disease. It has been found that early onset AD is associated with a mutation in the B-amyloid precursor protein gene (Chartier-Harlin et al., 1991). Recently, efforts have turned to identify genes responsible for the more common form of AD, the sporadic, late onset Alzheimer Disease (LOAD). The apolipoprotein E (APOE)  $\epsilon$  4 allele is a well-known risk factor of LOAD, and has been linked to faster cognitive decline for those who possess one or more of the  $\epsilon$  4 alleles (Breitner et

al., 1999; Hayden, 2009; Farrer et al., 1997). APOE is an important gene in cholesterol metabolism, and plays a role in immunity, inflammation, and endosomal vesicle recycling. Notably, the gene has also been found to have an effect on amyloid precursor protein trafficking and amyloid- $\beta$  production (Welsh-Bohmer, 2015).

Recent advances in Genome Wide Association Studies (GWAS) have led to the discovery of other associated genes, but none with an association as substantial as APOE. Additionally, not all of these genetic associations have sustained replication attempts (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). However, 21 genes in addition to APOE have been identified across many studies to be associated with AD onset (Lambert et al., 2013; Marden et al., 2016). While the reported effects of the individual 21 genetic loci associated with AD (not including APOE) have been found to be generally small, polygenic risk scores have been utilized to evaluate the joint effects of the genetic variants, which may have effects too small to detect individually. (Marden, Walter, Tchetgen Tchetgen, Kawachi, & Glymour, 2014).

More recently, efforts have focused on exploring structural variants within these genetic regions of interest. One variant that has been found to contribute to cognitive performance in aging and therefore AD risk is a polymorphic T homopolymer in the TOMM40 gene which is known to encode the essential, mitochondrial protein import translocase (Translocase of the Outer Mitochondrial Membrane, 40kD). (Roses et al., 2010; Hayden et al., 2012). The TOMM40 poly-T is found adjacent to and in linkage disequilibrium with the APOE region and

appears to provide information regarding LOAD not accounted for by APOE individually, yet this assertion is not universally supported by replication attempts as some studies show that it is duplicative with information provided by APOE (Jun et al., 2012). Understanding these genes and their reliable association with AD may allow better therapies and give a strategy to identify vulnerable individuals.

d) Predicting AD risk and onset: With no current cure or comprehensive understanding of AD, and a rapidly aging population with great increase in incidence of AD, efforts are turning to determine an effective preclinical treatment. This type of intervention is started in the absence of MCI or dementia and is intended to delay the onset, reduce the risk of, and possibly prevent the clinical stages of AD (Reiman, Langbaum, & Tariot, 2010). Therefore, there is a great need for a reliable method of identifying people at risk of developing AD.

One approach to finding a risk group is to build an AD specific genetic risk algorithm and use this AD genetic risk score (AD-GRS) to see how well it predicts people who eventually develop the disease. It has been reported that the greater possession of the AD risk alleles, specifically APOE, is associated with faster rate of memory decline. (Marden, Walter, Tchetgen Tchetgen, Kawachi, & Glymour, 2014). Because the disease develops over decades, a focus on memory or cognitive decline is a more practical approach than using a diagnostic outcome, like AD dementia, which will take years to affirm. With this approach, cognitive decline acts as a precise “endophenotype” tightly linked to the early biological changes occurring in advance of full AD symptom onset and years before the

patient shows the full dementia. Endophenotypes are defined as measurable intermediate phenotypes that are generally more associated to the action of the gene and more proximal to the underlying biology of the disease than affection status. Endophenotypes are therefore characteristics genetically correlated with disease yet can be measured in both affected and unaffected individuals (Gottesman & Gould, 2003; Reitz & Mayeux, 2009).

In this study, we will look at how the AD-GRS relates to overall cognition and various domains affected by AD in a population-based sample and whether these genes predict cognitive change over a 3 to 4-year interval. Within this context, we will test various approaches to constructing composite scores of cognition to determine which of these is optimal for measuring cognitive decline related to AD. Longitudinal studies have indicated that a decline in episodic memory precedes the symptomatic onset of AD, and therefore composites weighting assessment of memory decline are suggested as a measure for detecting the early cognitive deficits of at-risk individuals (Baxter, Caselli, Johnson, Reiman, & Osborne, 2003).

e) The Measurement to Understand Reclassification of Disease of Cabarrus/Kannapolis (MURDOCK) study cohort for studies of memory and aging: The Bryan Alzheimer Disease Research Center (ADRC) has longitudinally observed cohorts that have been tested over two time points, 4 years apart, with neurocognitive measures of memory, executive function, and global cognition. These cohorts include the PREPARE cohort in Durham and the MURDOCK Memory and Cognitive Health cohort in Kannapolis NC. The latter study had

genetics information and had completed both waves of assessment at the inception of this project; whereas the PREPARE project was still in the process of completing the second assessment wave (Romero et al., 2014). Therefore we focused on the MURDOCK study to explore the predictive relationship between AD risk genes and cognitive ability and cognitive decline in older adults (age 55+) who were cognitively healthy by self-report at the baseline examination.

In this study, the nine most reliable AD risk genes (excluding APOE), known to date, were used to calculate the AD-GRS for each individual participant based on their genotypes at each of the nine risk alleles. The AD-GRS was calculated by applying the odds ratios for each of the AD risk as reported in the meta-analysis on AlzGene website and then summed for each individual, as described in the Methods section (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). Four mutually exclusive risk groups were determined based on APOE  $\epsilon$  4 allele and the total AD-GRS risk. This method of risk group construction was extrapolated from a previous study with a similar set up (Hayden, Lutz, Kuchibhatla, Germain & Plassman, 2015). APOE was modeled as a separate risk factor due to the possibility of the strength of its association with cognitive deficits masking the genetic effects of the other nine risk genes. The four risk groups were:

- *APOE+ GRS+ (very high risk)*
- *APOE+ GRS- (high risk)*
- *APOE- GRS+ (relatively lower risk)*
- *APOE- GRS- (lowest risk)*

APOE  $\epsilon$  4 has previously been found to function as a both a risk factor for cognitive impairment in normal aging across a broad spectrum of domains as well as

exhibiting detectable effects in early prodromal AD (Bretsky, Guralnik, Launer, Alber & Seeman, 2003). It has also been determined that  $\epsilon 4$  carriers are more vulnerable to greater cognitive decline in the presence of other risk factors, such as environmental and physical health risks (Christensen et al., 2008). Therefore, genetic risk algorithms that include all known AD risk genes in addition to the presence of APOE  $\epsilon 4$  may improve our ability to identify those at risk for AD. It is hypothesized that the AD-GRS will supplement the APOE risk in its association with cognitive decline, therefore concluding that the nine AD risk genes affect LOAD progression independently of APOE.

In efforts to determine whether these genes predict cognitive decline and whether some measures are more optimal for this purpose, we examined different measures and domains of cognition in relationship to these AD risk genes. Global measures of cognition (MoCA and the Global Composite) are used as a surrogate for all causes of dementia that occur with aging, AD being the most common cause. In order to explore the phenotype linked to AD genes specifically, commonly referred to as the endophenotypes of disease, the individual domains most affected in AD dementia (episodic memory) were emphasized and contrasted to other domains that are sensitive to healthy aging in addition to AD (executive function as measured by Trails B) (Gottesman, 2003).

Hypothesis: We hypothesize that the most predictive genetic risk algorithm will be related to cognitive decline as measured by a summary composite of various measures in our battery - Montreal Cognitive Assessment (MoCA), Trail Making Part B (Trails B), and the Consortium to Establish Registry for Alzheimer's Disease (CERAD) Word List Memory task (WLM). Furthermore, we predict that the genetic algorithm will be related

to the various individual domains, such as episodic memory (CERAD WLM), executive function (Trails B), and global cognition (MoCA), but to a lesser extent than the Memory-Weighted cognitive composite, which integrates multiple domains yet focuses on memory decline.

If we could understand the genetic risk relationships of AD we could perhaps develop better therapeutic compounds. Furthermore, we might be able to use this genetic information and identify high-risk subjects in order to intervene early when treatments become available. Because AD involves cognitive decline well in advance of the diagnosis, we investigated the relationship between the most reliable AD risk genes known to date and cognitive decline. We examined various composite measures and individual domains in relationship to APOE and the other risk genes (GRS) to determine whether we might be able to detect subjects at risk of future decline and AD.

## **2. Methods**

### *2.1 Participants*

Data were collected from a community study, the Measurement to Understand Reclassification of Disease of Cabarrus/ Kannapolis (MURDOCK). The MURDOCK Study Community Registry and Biorepository recruited study participants from the 55+ adult population of Cabarrus County and the city of Kannapolis, NC. Participants were involved in two waves of assessment. The two waves of assessments were spread out by 4 years. The first baseline wave was completed between the years 2011-2013 and the second wave in 2015-2016.

### *2.2 Measures*

Basic demographic information was collected on all participants including age, sex, marital status, race, ethnicity, employment, and education level. Age was calculated as the time between self-reported date of birth and interview date. Race was classified as White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or other race. Ethnicity was classified as Hispanic or Latino or neither. Education levels were defined as less than high school, high school, some college or associate's degree, bachelor's degree, and master's or higher professional degree. Participants were subsequently measured for height, weight, and body mass index (BMI) was calculated. Information on blood pressure, heart rate, vision, hearing, previous tobacco use were all collected. Health information was gathered and included medication use, family history of illnesses (including dementia), and medical history including vascular risk conditions (diabetes, hypertension, stroke, and cardiovascular disease) and history of depression. Subject's views regarding their

personal physical and mental health were collected in addition to behavioral and functional assessments.

### *2.3 Neuropsychological Testing/ Cognitive and Clinical Evaluations*

The MURDOCK cognitive assessment battery was comprised of 4 measures, the Montreal Cognitive Assessment (MoCA), the Trail Making Part B (Trails B), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory task (WLM), and the Alzheimer's Disease Cooperative Studies (ADCS) Mail-In Cognitive Function Screening Instrument (MCFSI) (Morris et al., 1989; Nassreddine et al., 2005; Reitan, 1992; Walsh, Raman, Jones, & Aisen, 2006). The MoCA is a global cognitive function test developed to detect early stages of AD, the Mild Cognitive Impairment (MCI) stage (Nassreddine et al., 2005). The MoCA assesses various cognitive domains including attention, executive function, language, memory, orientation, and visuospatial function. Furthermore, it has been found to have a higher level of sensitivity and specificity for the detection of the earliest stages of AD than the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). Scores for MoCA range from 0-30, where higher scores indicate better cognitive function. Scores below 26 (after education correction) is considered to represent cognitive disorders, and cut-point of 16 reflects AD patients. Therefore, individuals scoring lower than 16 were excluded from the study.

The Trails B is a timed test of executive function which requires set switching as participants are required to connect alternating numbers and letters in order. For example, successful participants are required to draw a line from 1 to A to 2 to B to 3 to C, ... to 13. Participants have 300 seconds to complete this attention and task-switching test. It is

a commonly used metric to measure speed of processing and flexible behavior associated with the frontal lobe. Trails B test has been found to be sensitive to detecting cognitive impairment associated with AD, and more generally, dementia (Reitan, 1992).

The CERAD WLM task was developed as part of the CERAD protocol neuropsychological battery for the assessment of dementia and has further been proven to be a sensitive test for mild impairment as well. The WLM task consists of a 10-item word list with three learning trials in which words are read to the participant and they are asked to immediate recall as many of the 10 words that they remember. On subsequent trials the same list is read with the words presented in a different order to allow all words the opportunity to be remembered thereby mitigating primacy and recency effects. Total learning across the three learning trials is the sum of the recall for each trial (range 0-10 for each trial, 0-30 total amongst all 3 trials). After a brief delay, spontaneous recall for the list is again queried (delayed recall), which has proven to be a highly sensitive measure of early, mild AD (Welsh et al., 1991). Lastly, recognition is tested with 20 words, the 10 correct words, and 10 incorrect words and the total correctly identified yes and no responses were added and ranged 0-20 (Morris et al., 1989). Lastly, the ADCS MCFSI is a self-report memory questionnaire that was developed for the detection of cognitive change in large prevention trials. It is a 14-item brief questionnaire consisting of questions about memory, daily activity, and function (Walsh, Raman, Jones, & Aisen).

#### *2.4 Genotyping*

Participants provided blood samples for genetic studies. The DNA from one aliquot was extracted and these samples were then genotyped at the APOE locus along with the other 9 SNPs previously found to be associated with AD by investigators of

Clinical Translational Science Award (CTSA) blinded to all clinical data. The 9 SNPs genotyped include the following (Gene, SNP): (CR1, rs6656401); (BIN1, rs6733839); (CD2AP, rs10948363); (EPHA1, rs11771145); (CLU, rs9331896); (MS4A6A, rs983392); (PICALM, rs10792832); (ABCA7, rs3752246); (CD33, rs3865444). Errors in genotypic assays were recorded as missing values (Lambert et al., 2013).

### 2.5 Genetic Risk Score Calculation

The AD-GRS was derived using the odds ratios for the 9 identified AD risk alleles (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). The AD-GRS was calculated by multiplying each individual's risk allele count for each locus by the log of

Equation 1: $\text{GRS} = \sum \log_{10}(\text{odds ratio}) \times \text{number of minor alleles}$
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the Odds Ratio (OR) for that polymorphism and summing the

products of all 9 loci (Equation 1). The OR is the odds of disease with a minor allele of the specific risk gene and was derived from a meta-analysis of over 74,000 individuals (Lambert et al., 2013; Marden et al., 2016). Therefore, each polymorphism is weighted in proportion to its anticipated effect on AD risk. The resulting continuous risk score (AD-GRS) was then dichotomized at the score of 0 into high and low scores (positive values are high risk, negative values are low risk).

The AD-GRS is the probability of dementia as predicted by the 9 risk alleles. These probabilities were determined based on the strength of associations between the 9 alleles and disease prevalence as estimated in previously published GWAS and meta-analysis. The various scores based on different combinations of risk alleles (and individual alleles) are examined to assess the extent the loci contribute information in predicting cognitive deficits (Marden et al., 2016).

An APOE risk score was similarly calculated as the log of the OR multiplied by the number of  $\epsilon 4$  alleles.

Four mutually exclusive genetic risk groups were determined based on the calculated AD-GRS and APOE  $\epsilon 4$  risk score. The APOE allele is modeled separately of the other top 9 risk alleles because of the strong association between APOE and cognitive function. Furthermore, this association differs from all of the other identified AD risk alleles used to determine the AD-GRS, which individually have effects too small to reliably detect AD. Those who have at least one copy of the APOE  $\epsilon 4$  allele (APOE risk score  $>0$ ) will be identified as high risk based on APOE (APOE+) and those with no copies of the APOE  $\epsilon 4$  allele will be identified as low risk based on APOE (APOE-). In this study, the reference group had no APOE  $\epsilon 4$  and a low AD-GRS (APOE-/low GRS). The alternative groups consisted of those with no APOE  $\epsilon 4$  and a high AD-GRS (APOE-/high GRS), those with APOE  $\epsilon 4$  and a low AD-GRS (APOE+/ low GRS) and those at highest risk, with APOE  $\epsilon 4$  and a high AD-GRS (APOE+/ high GRS) (Hayden, Lutz, Kuchibhatla, Germain & Plassman, 2015).

## *2.6 Cognitive Composites*

Three composites of cognitive tests were tested for association with genetic risk.

*1. Global Composite:* CERAD WLM delayed recall+ MoCA +Trails B

*2. Learning/Memory Composite:* CERAD WLM total learning + CERAD WLM delayed recall + CERAD WLM Word List recognition

*3. Memory-Weighted Composite:* CERAD WLM word list total learning + CERAD WLM delayed recall + CERAD WLM recognition+ MoCA+ Trails B

Total scores for the MoCA, Trails B, and WLM assessments were standardized by using age-specific sample means and standard deviations (SD) to calculate z-scores for each participant. The normative data used was extracted from previous studies of age appropriate healthy populations (Rossetti, Lacritz, Cullum & Weiner, 2011; Welsh-Bohmer, et al., 2009). The Z-score was calculated by taking the value for the measure at that visit, subtracting the normative mean for the individual's specific age group for that measure, and then dividing by the normative standard deviation for that measure. The Z-scores of each component are summed to form the composite. The composite is then standardized by dividing by the number of assessments constituting the composite.

### *2.7 Data Analysis*

To understand the impact of missing observations (dropouts: those who participated in the first wave of cognitive tests but were absent for the follow up wave), we compared the demographics and cognitive test scores at baseline between the two groups using Chi Square and t-tests in SAS programming. In those for whom we had two time points, we also examined the demographic characteristics across the four mutually exclusive genetic risk groups using generalized linear models (SAS PROC GLM) and Chi Square tests (Laird & Ware, 1982). The measure of individual cognitive decline as valued by the change in the various cognitive assessments was the dependent variable for the main analysis while controlling for baseline cognitive performance. Models were additionally adjusted for the covariates baseline age (squared), sex, and education level (Hayden, Lutz, Kuchibhatla, Germain & Plassman, 2015).

### 3. Results:

Of the 1,597 adults who provided DNA for genetic analysis and participated in the first wave of assessment, 880 individuals completed the second wave of assessment (55.10% retention). Difference between participants and nonparticipants are shown in Tables 1A and 1B. Table 1A summarizes the drop out data, whereas Table 1B shows the data for the completers. Table 1C is data for all participants and nonparticipants.

The 717 dropouts were found to be older ( $p=0.03$ ), have lower mean education level ( $p<0.0001$ ), and perform worse on cognitive assessments than those that completed both waves of assessments (Tables 1A, 1B, and 1C).

Of the 880 individuals who completed both cognitive assessments, 812 self-identified as White (92%) and only 12 were lower than high school education level. Demographic characteristics of the final sample by age are shown in Table 1B.

SNP frequencies within the sample were found to accurately represent population frequencies determined from large-scale meta-analyses studies (Table 2; Lambert et al., 2013).

Of the 880 individuals who completed both waves of cognitive assessments, 723 individuals had blood samples that provided information of all nine AD- risk SNPs and APOE. The demographic characteristics of the 723 individuals with all SNPs by genetic risk group are shown in Table 3. Genetic risk group was not related to sex and age, but was related to education level ( $\chi^2(12)=23.98$ ,  $p=0.02$ : this relationship was not monotonic, as the 2<sup>nd</sup> highest risk group had the highest education and the lowest risk had the least education with no relationship in between). Since genetic risk group was related to education, to test for confounders we also looked at education by the cognitive

composite scores. Generally, those with more education performed better on the individual and composite cognitive assessments. Furthermore, genetic risk group (high- vs.-low risk of AD) was not related to any cognitive variables at baseline.

The various genetic risk groups were not related to cognitive decline as measured by the various composites when controlled for baseline score of the respective composite, age<sup>2</sup> (as cognitive decline is curvilinear with age), education level, and sex in a linear regression model. Yet trends between risk group's cognitive decline could be seen primarily in the Learning/Memory Composite and the Memory-Weighted Composite in association with the risk groups containing individuals with one or more APOE  $\epsilon 4$  alleles.

To further evaluate this phenomenon, we ran post-hoc linear regression models with both AD-GRS and APOE as independent risk scores (based on odds ratio) rather than using the genetic risk groups previously constructed. In this analysis we modeled AD-GRS and APOE risk score as continuous rather than categorical variables. The linear regression models were controlled for the same confounders previously described (Table 4 and 5). Through this analysis, we found that APOE risk score is significantly associated to decline in all three composites (Table 4): the Global Composite ( $\beta=-0.19$ , SE= 0.062,  $p=0.0021$ ), the Learning/Memory composite ( $\beta =-0.211$ , SE= 0.0855,  $p=0.0139$ ), and the Memory-Weighted composite ( $\beta =-0.212$ , SE= 0.0651,  $p=0.0012$ ). To understand the association of these composites, we then looked at the individual assessments and found that APOE risk score was associated with change in MoCA ( $\beta =-0.205$ , SE= 0.0798,  $p=0.0105$ ), Trails B ( $\beta =-0.311$ , SE= 0.0963,  $p=0.0013$ ), WLM total learning ( $\beta =-0.227$ , SE= 0.0994,  $p=0.0225$ ) and WLM recognition ( $\beta =-0.325$ , SE=0.153,  $p=0.0337$ ).

Surprisingly, APOE risk score was found to not be significantly associated with WLM Delayed Recall decline ( $\beta = -0.154$ ,  $SE = 0.105$ ,  $p = 0.1426$ ) (Table 5).

Additionally, it was found that none of the composites were associated with the AD-GRS composed of the 9 SNPs (Table 4). Yet, AD-GRS was found to be associated with change in MoCA ( $\beta = 0.408$ ,  $SE = 0.206$ ,  $p = 0.0483$ ) and showed a trend with WLM Learning ( $\beta = 0.493$ ,  $SE = 0.255$ ,  $p = 0.0538$ ) but its association was in the opposite direction as APOE (lower risk score associated with cognitive decline) (Table 5).

With this knowledge, we created a new composite, which was empirically derived to include only the individual tests with the strongest relationships to the AD genetic risk scores. This composite, titled “Predict Composite”, consisted of MoCA, Trails B, WLM Learning, and WLM Recognition. When we compared the various composites that we had derived by logical properties (e.g. Global; Memory-Weighted; Learning/Memory composites) to this empirically derived “Predict” composite, the latter showed the strongest relationship with APOE risk score ( $\beta = -0.249$ ,  $SE = 0.0676$ ,  $p = 0.0003$ ) (Table 4).

Additionally, we ran another post-hoc linear regression model using a combined risk score of the SNPs and APOE, the sum of AD-GRS and APOE risk score. In this analysis we found slightly different results than when APOE risk score and AD-GRS are modeled separately. It was found that decline in the Learning/Memory Composite was no longer significantly associated to genetic risk, but the combined GRS was associated to decline in the Global Composite ( $\beta = -0.122$ ,  $SE = 0.0578$ ,  $p = 0.0348$ ), the Memory-Weighted composite ( $\beta = -0.142$ ,  $SE = 0.0604$ ,  $p = 0.0187$ ) and was most associated to the Predict Composite ( $\beta = -0.180$ ,  $SE = 0.0627$ ,  $p = 0.0041$ ) (Table 4). Figure 1 illustrates the

association of decline in the Predict Composite and combined risk score, which is largely driven by the APOE risk relationship as demonstrated by the three distinct dense areas (representing the three possible outcomes of APOE risk: 0, 1, or 2  $\epsilon 4$  alleles). The combined risk score was also associated with decline in the individual assessments Trails B ( $\beta = -0.267$ ,  $SE = 0.0886$ ,  $p = 0.0027$ ) and WLM recognition ( $\beta = -0.327$ ,  $SE = 0.141$ ,  $p = 0.0205$ ) (Table 5).

To further understand our results, we looked at the relationship between overall cognition cross-sectionally (at baseline) and the genetic risks while controlling for age, sex, and education. It was found that of all the assessments and composites, only the baseline Memory-Weighted composite score and baseline Predict Composite score were associated to AD-GRS and combined risk scores (Table 6 and 7). AD-GRS was associated with the baseline Memory-Weighted Composite score ( $\beta = -2.046$ ,  $SE = 0.976$ ,  $p = 0.0364$ ) and the baseline Predict Composite score ( $\beta = -1.78$ ,  $SE = 0.757$ ,  $p = 0.0189$ ). The combined risk score was associated with the baseline Memory-Weighted Composite score ( $\beta = -0.740$ ,  $SE = 0.374$ ,  $p = 0.0482$ ) and the baseline Predict Composite score ( $\beta = -0.62$ ,  $SE = 0.289$ ,  $p = 0.0325$ ).

#### 4. Discussion:

Our original analysis of cognitive decline using the four genetic risk groups did not produce statistically significant results, yet trends were noted. For example, the groups containing a positive APOE risk score demonstrated more cognitive decline than the other risk groups. The reason for non-significant results is most likely due to the small sample size, which was further sub-divided into the risk groups. Therefore, we decided to run a post hoc analysis using a continuum for the AD-GRS, APOE risk score, and a combined risk score to test for association.

Through this analysis, we saw that in this population-based study of cognitively healthy individuals over the age of 55, APOE was largely associated with cognitive decline over a 3 to 4-year-interval. The APOE risk score was associated with all of the cognitive composites but most associated with the composites weighting memory (Predict Composite and Memory-Weighted Composite) and least associated with the Global Composite. This is consistent with our hypothesis, that APOE is most strongly related to AD-related cognitive endophenotypes (specifically memory decline) and that composites, particularly those weighting memory, will be more sensitive to the cognitive decline related to AD.

Previous studies have similarly determined that possession of one or more  $\epsilon 4$  alleles results in faster decline in episodic memory in cognitively healthy subjects (Reitz & Mayeux, 2009). Our results supplement these findings in demonstrating that composites of multiple cognitive assessments are more associated to APOE risk than simply individual assessments of memory. Furthermore, the Predict Composite and the Memory-Weighted Composite (which include assessments of global cognition and

executive function in addition to multiple memory assessments) were the most associated to APOE risk. Demonstrating that, while memory is an endophenotype tightly linked to AD, other domains of cognition are associated with the genetics of AD in unaffected individuals (as also demonstrated by the association of APOE with MoCA, Trails B, WLM total, and WLM recognition individual assessments). APOE risk was strongly associated with decline in the Trails B assessment, and therefore this test should be included in composites designed to be sensitive to very early cognitive decline.

Surprisingly, APOE risk was not associated with change in WLM delayed recall assessment. The measure used, CERAD WLM, may simply be too easy for healthy adults and therefore result in a reduction in range of values. The WLM test was developed to assess mild dementia and is therefore relatively easy for cognitively healthy individuals. The assessment consists of a small, simple word list with a very short delay interval, and is therefore insufficient for picking up memory deficiencies in a relatively healthy population. Previous studies have also found that healthy individuals often improve on the WLM delayed recall test due to practice effects and therefore association with genetic risk cannot be determined, as the scores in WLM delayed recall fail to capture cognitive decline in healthy individuals (Zehnder, Bläsi, Berres, Spiegel & Monsch, 2007).

Currently, global cognition assessments and mental status tests are utilized as the standard cognitive measure for AD diagnoses due to their ability to cover a wide range of domains in a short period of time (Welsh-Bohmer, 2016; Burnham et al, 2015). Yet, this study demonstrates that a global composite uniformly composed of multiple domains is not as sensitive to the cognitive changes associated with APOE in healthy individuals as the composites that weighed memory.

This finding was supported with another post-hoc analysis using a combined risk score (the sum of the risk associated with the nine SNPs and APOE) to test for association with the various composites. It was found that the Predict Composite and Memory-Weighted composite were again the most significantly associated to all of the risk genes combined. Yet, APOE was more strongly associated than the combined risk score to all of the composites, indicating that the effect of established AD genes on cognitive decline independent of APOE, was contributing relatively little to cognitive decline.

When looking at cognitive change over two time points, it was found that the risk SNPs (other than APOE) actually had a positive effect on cognitive change as measured by MoCA (also seen as a trend in the other individual assessments and cognitive composites). It is possible that this is due to scaling, and that with a small, healthy sample many participants are scoring near the maximum, which could skew the association. Yet it could also be possible that these risk genes act in a protective fashion, which renders the effect of these genes an area for future inquiry.

Previous studies have found similar and mixed results using risk scores calculated in nearly the same manner (Hayden, Lutz, Kuchibhatla, Germain & Plassman, 2015). There are several explanations for why the joint effect of the AD genes (apart from APOE) was found to not be related to cognitive decline. Primarily, this indicates that the influence of these genes on cognition is extremely subtle and a larger sample would be necessary to pick up on associations. Another possibility is that these AD risk genes, interact solely with environmental risk factors also associated with AD but do not cause cognitive decline. Lastly, it is possible that the AD risk genes studied are not the causal

variants of cognitive decline, but are in linkage disequilibrium with them (Verhaaren et al., 2013).

While there was no risk of AD genes (independent of APOE) associated with cognitive decline, it was found that these genes were related to overall cognition when analyzed at a single time point. At baseline, the composites weighting memory were negatively associated with the AD-GRS, demonstrating that performing worse on these composites at one time point would indicate carrying more risk genes.

Altogether, these results demonstrate that AD-risk genes (not including APOE) are most sensitive to cognitive deficits at one time point, while APOE risk is most sensitive to cognitive decline over a 4-year-interval. Composites that include tests of executive function and global cognition yet weight memory assessment are most sensitive to the deficits as predicted by the AD-GRS at one time point, in addition to the cognitive decline as predicted by APOE risk over a time interval and should therefore be utilized to predict people at risk of AD.

We believe that it is crucial to understand how the various genes associated with AD function differently in order to begin to comprehend this complex multifactorial disease. It has been recognized that genetics of AD must be understood in order to identify subjects at high risk of developing AD, which is necessary for early prognosis and intervention. Currently, disease diagnoses are based almost entirely by clinical features (memory impairment, general cognitive decline, etc) and ruling out treatable disorders. By using cognitive screeners like our Predict Composite and our Memory-Weighted Composite, we may be able to screen more effectively for individuals in the pre-symptomatic stage of disease for earlier intervention. There are currently no effective

therapies that target the underlying biology of AD. If we can better understand the role of the genes in the disease, we might be able to tailor future therapies towards these highly specific mechanisms of disease. Furthermore, in addition to the genetics, the precision medicine approach to AD diagnoses should include environmental factors, lifestyle, and specific clinical presentation (Hampel et al., 2016). In order to avert this global epidemic, the understanding of genetic, environmental, and cognitive components must be utilized for early prediction, precise intervention, and hence prevention of AD.

*Limitations:*

The analysis comparing the dropouts (those who completed only the initial wave of cognitive assessments) and the completers (those who completed both waves of assessments) demonstrates the possibility of sample bias in this study. Those who did not complete the second wave of assessment were generally older, less educated, and performed worse on cognitive assessments. Therefore, the composition of our sample may not have allowed us to pick up on further associations present that would have been identified in those who were most likely to decline. This limitation can be overcome with a larger sample size.

Likewise, a primary limitation of this study is small sample size in general, which renders this study as exploratory. While significant genetic associations cannot be concluded, as the study is underpowered, general trends of the relationship between AD endophenotypes and AD risk genes can be determined. Furthermore, because the effects of the risk genes relative to APOE are small, larger samples will be needed in all likelihood to see these effects. Future research should take this model and apply it to a

larger sample for more power and the possibility of finding associations between the risk genes and cognitive decline that cannot be determined with this sample size.

Additionally, a methodological concern is the limited number of cognitive assessments in the battery completed by participants. While the cognitive assessments in the battery used in this study include assessments of global cognition, executive function, and episodic memory, there are many more cognitive domains that have been determined to be affected by AD and should be included in the study's battery of assessments.

Although the contribution of the genes other than APOE to cognitive decline appears small, we note that we might see different results with the inclusion of other cognitive domains (such as language or visuospatial function) not included in the MURDOCK battery.

It should also be recognized that the possibility of practice effects on the neuropsychological assessments could skew the measure of cognitive decline. This test-retest effect often results in cognitively healthy individuals performing better on the 2<sup>nd</sup> wave of assessment than the 1<sup>st</sup>. As mentioned earlier, memory tests may be too easy for this population and particularly prone to ceiling effects and effects of practice. Therefore, analyzing the difference in cognitive assessment scores may be insufficient to pick up on the underlying cognitive decline (Zehnder, Bläsi, Berres, Spiegel & Monsch, 2007).

We also note that the 9 SNPs selected for this study were identified in the Alzgene top associated genes list. This list is continually updated with new information from GWAS and there are likely genes associated with AD not included in the genetic risk-score as they have not been identified in existing literature. There are other identified

genetic variants that should be studied for association with cognitive decline such as the polymorphic T homopolymer in the TOMM40 gene.

## 5. Conclusions:

In summary, using a sample of cognitively healthy, community representative participants, age 54 and older, our results show (1) for measuring cognitive decline, a composite of multiple cognitive assessments which puts added weight on memory, is most closely associated to the known AD risk genes; (2) specifically, the  $\epsilon 4$  allele of the APOE gene is the largest risk factor for picking up cognitive decline over time; (3) the combined effects of all other known AD risk genes (excluding APOE) was not found to be associated with cognitive decline over the short 4-year interval; (4) Further, while APOE was powerful in predicting cognitive decline, particularly memory decline, all of the other genes were associated with lower cognition when measured cross-sectionally at a single time point with composites weighting memory.

Taken together, these findings suggest that for identifying individuals at risk of cognitive decline, focusing on APOE genotype will be more useful than the other AD risk alleles. Furthermore, cognitive composites weighted more heavily with memory are more sensitive to both lower cognition at baseline and cognitive decline over a short interval associated with AD risk genes.

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Table 1A: Data of Drop-Outs by Age

<b>A</b>	Sex (% female)	Race (%White)	Race (%AA)	Education Level Mean	MoCA Mean (SD)	MSFSI Mean (SD)	Trails B Mean (SD)	WLM Total Mean (SD)	WLM Recall Mean (SD)	WLM Recognition Mean (SD)	Total
54-59	68.42	86.47	11.28	3.17	25.50 (3.74)	2.91 (2.91)	93.41 (54.23)	21.10 (3.77)	8.00 (7.71)	19.52 (1.96)	133
60-64	78.79	86.36	13.64	3.07	25.57 (3.28)	3.02 (2.80)	104.43 (58.00)	20.98 (3.14)	7.06 (1.71)	19.57 (1.81)	132
65-69	62.05	92.17	7.23	3.12	24.40 (3.54)	2.86 (2.64)	104.18 (45.08)	19.48 (3.97)	6.19 (2.08)	19.34 (1.93)	166
70-74	53.54	92.91	6.30	2.80	23.08 (23.73)	3.19 (2.56)	130.36 (59.77)	18.32 (3.72)	5.81 (2.16)	19.30 (2.90)	127
75-79	62.67	93.33	4.00	2.95	22.21 (3.50)	3.73 (2.96)	147.09 (56.29)	17.28 (3.99)	5.20 (1.94)	18.90 (2.51)	75
80-84	60.42	100.00	0.00	2.94	22.38 (3.90)	3.40 (2.50)	162.88 (74.78)	17.48 (3.98)	5.17 (2.72)	18.96 (3.11)	48
85-89	50.00	96.43	0.00	2.89	19.90 (2.68)	5.04 (3.49)	217.27 (71.68)	15.08 (3.71)	4.15 (1.99)	18.35 (1.74)	28
90-95	75.00	87.50	12.50	3.00	16.86 (3.85)	4.63 (2.47)	221.67 (83.39)	14.67 (4.84)	2.83 (2.48)	14.43 (6.92)	8
Total	64.44	90.93	7.95	3.02	23.79 (3.85)	3.19 (2.80)	119.09 (63.01)	19.30 (4.09)	6.36 (3.99)	19.49 (6.70)	717

Table 1A Legend: Abbreviations: GRS: genetic risk score, AA: African American, WLM: word list memory task, MSFSI: mail in cognitive function screening instrument

Education levels: 1. less than high school; 2. high school; 3. some college or associate’s degree; 4. bachelor’s degree; 5. master’s or higher professional degree

Table 1B: Data of Completers by Age

<b>B</b>	Sex (% female)	Race (%White)	Race (%AA)	Education Level Mean	MoCA Mean (SD)	MCFSI Mean (SD)	Trails B Mean (SD)	WLM Total Mean (SD)	WLM Recall Mean (SD)	WLM Recognition Mean (SD)	Total
54-59	78.13	90.63	8.13	3.54	26.39 (2.64)	2.80 (2.57)	80.15 (37.47)	22.08 (3.52)	7.56 (1.72)	19.80 (0.54)	160
60-64	67.89	86.32	11.58	3.46	25.71 (2.72)	2.62 (2.46)	91.28 (43.48)	21.14 (3.33)	7.20 (1.91)	19.78 (0.54)	190
65-69	65.16	93.21	5.88	3.43	25.80 (2.68)	2.43 (2.17)	93.43 (47.97)	20.95 (3.688)	7.12 (1.75)	19.70 (0.65)	221
70-74	60.00	93.79	5.52	3.26	24.82 (2.89)	2.74 (2.19)	101.23 (40.60)	19.07 (3.70)	6.26 (2.07)	19.58 (0.77)	145
75-79	57.00	100.00	0.00	2.93	24.02 (3.06)	3.06 (2.35)	136.54 (65.62)	18.94 (3.75)	5.95 (2.20)	19.26 (1.10)	100
80-84	76.74	93.02	6.98	3.33	23.65 (3.18)	2.99 (2.29)	154.55 (70.37)	18.98 (4.22)	5.65 (2.32)	19.30 (1.12)	43
85-89	64.71	100.00	0.00	3.29	22.41 (2.92)	2.79 (1.41)	153.40 (53.93)	17.53 (3.56)	4.88 (2.32)	19.35 (0.79)	17
90-95	25.00	100.00	0.00	3.25	20.50 (4.51)	4.51 (1.25)	135.00 (40.31)	15.50 (2.38)	5.25 (0.50)	19.50 (0.58)	4
<b>Total</b>	<b>66.70</b>	<b>92.27</b>	<b>6.70</b>	<b>3.36</b>	<b>25.59 (3.17)</b>	<b>2.60 (2.37)</b>	<b>100.82 (52.24)</b>	<b>20.47 (4.04)</b>	<b>6.83 (2.11)</b>	<b>19.67 (0.79)</b>	<b>880</b>

Table 1B Legend: Abbreviations: GRS: genetic risk score, AA: African American, WLM: word list memory task, MSFSI: mail in cognitive function screening instrument  
 Education levels: 1. less than high school; 2. high school; 3. some college or associate’s degree; 4. bachelor’s degree; 5. master’s or higher professional degree

Table 1C: Data of All Participants (Dropouts and Completers) by Age

<b>C</b>	Sex (% female)	Race (%White)	Race (%AA)	Education Level Mean	MoCA Mean (SD)	MCFSI Mean (SD)	Trails B Mean (SD)	WLM total Mean (SD)	WLM recall Mean (SD)	WLM recognition Mean (SD)	Total
54-59	73.72	88.74	9.56	3.37	25.99 (3.21)	2.84 (2.72)	86.04 (46.08)	21.64 (3.66)	7.75 (5.33)	19.67 (1.38)	293
60-64	72.36	86.34	12.42	3.3	25.24 (3.01)	2.78 (2.61)	96.51 (50.09)	21.08 (3.25)	7.14 (1.83)	19.70 (1.23)	322
65-69	63.82	92.76	6.46	3.29	25.20 (3.15)	2.62 (2.39)	97.96 (47.02)	20.33 (3.87)	6.73 (1.95)	19.55 (1.36)	387
70-74	56.99	93.38	5.88	3.04	24.01 (3.42)	2.95 (2.38)	114.44 (52.16)	18.73 (3.87)	6.05 (2.12)	19.45 (1.52)	272
75-79	59.43	97.14	1.71	2.94	23.25 (3.37)	3.35 (2.64)	140.77 (62.08)	18.25 (3.93)	5.64 (2.12)	19.11 (1.83)	175
80-84	68.13	96.70	3.30	3.12	22.98 (3.62)	3.20 (2.40)	158.71 (72.29)	18.20 (4.14)	5.40 (2.53)	19.12 (2.37)	91
85-89	55.56	97.78	0.00	3.04	20.86 (3.01)	4.17 (3.05)	191.38 (71.68)	16.05 (3.80)	4.44 (2.13)	18.74 (1.51)	45
90-95	58.33	91.67	8.33	3.08	18.18 (4.29)	3.96 (2.30)	172.64 (72.64)	15.00 (3.89)	3.80 (2.25)	16.27 (5.95)	12
Total	65.69	91.67	7.26	3.21	24.64 (3.47)	2.92 (2.56)	108.73 (57.84)	19.95 (4.00)	6.61 (3.06)	19.57 (4.49)	1597

Table 1C Legend: Abbreviations: GRS: genetic risk score, AA: African American, WLM: word list memory task, MSFSI: mail in cognitive function screening instrument  
 Education levels: 1. less than high school; 2. high school; 3. some college or associate’s degree; 4. bachelor’s degree; 5. master’s or higher professional degree

Table 2: 9 Genes, SNPs, and Frequencies used in AD-GRS

Gene	SNP	Sample Frequency	Population Frequency
CR1	rs6656401	0.178	0.197
BIN1	rs6733839	0.397	0.409
CD2AP	rs10948363	0.259	0.266
EPHA1	rs11771145	0.388	0.338
CLU	rs9331896	0.417	0.379
MS4A6A	rs983392	0.401	0.403
PICALM	rs10792832	0.341	0.358
ABCA7	rs3752246	0.165	0.190
CD33	rs3865444	0.314	0.307

Table 3: Demographics By GRG

Characteristic	Low Risk		High Risk		Total
	Group1 APOE4-/ low GRS	Group2 APOE4-/ high GRS	Group3 APOE4+/ low GRS	Group4 APOE4+/ high GRS	
N (%)	347 (47.99)	172 (23.79)	128 (17.70)	76 (10.51)	723
Mean Baseline Age (SD)	67.49 (7.80)	66.51 (7.38)	67.00 (7.08)	66.12 (7.94)	67.03
Sex: Female (%)	229 (65.99)	113 (65.70)	83 (64.84)	52 (68.42)	477 (65.98)
Male (%)	118 (34.01)	59 (34.30)	45 (35.16)	24 (31.58)	246 (34.02)
Education Level:					
Less than high school graduate (%)	13 (3.75)	2 (1.16)	1 (0.78)	3 (3.95)	19 (2.63)
High School graduate or equivalent (%)	64 (18.44)	31 (18.02)	26 (20.31)	13 (17.11)	134 (18.53)
Some college or associates degree (%)	153 (44.09)	59 (34.30)	35 (27.34)	29 (38.16)	276 (38.17)
Bachelors Degree (%)	64 (18.44)	48 (27.91)	40 (31.25)	16 (21.05)	168 (23.24)
Masters or higher professional degree (%)	53 (15.27)	32 (18.60)	26 (20.31)	15 (19.74)	126 (17.43)
Mean Baseline Performance (SD):					
MoCA	25.28 (3.01)	25.37 (2.66)	25.30 (3.44)	25.55 (2.61)	25.33 (2.98)
Trails B	99.04 (50.04)	100.46 (54.04)	101.36 (55.91)	104.27 (54.25)	96.89 (45.85)
WLM Total	20.55 (3.74)	20.54 (3.60)	20.80 (3.71)	20.39 (4.01)	20.57 (3.73)
WLM Recall	6.76 (2.08)	6.87 (1.84)	6.95 (1.95)	6.75 (2.07)	6.82 (2.00)
WLM Recognition	19.63 (0.74)	19.73 (0.65)	19.68 (0.76)	19.53 (0.82)	19.65 (0.73)
MSFSI	2.64 (2.25)	2.72 (2.61)	2.95 (2.35)	2.97 (2.34)	2.75 (2.37)
Global Composite (standardized)	0.66 (0.70)	0.66 (0.61)	0.67 (0.78)	0.60 (0.71)	0.66 (0.69)
Learning/Memory Composite (standardized)	0.17 (0.90)	0.23 (0.83)	0.24 (0.91)	0.07 (1.03)	0.17 (0.93)
Memory-Weighted Composite (standardized)	0.49 (0.70)	0.51 (0.59)	0.54 (0.73)	0.38 (0.78)	0.49 (0.70)

Table 3 Legend:

Abbreviations: WLM: word list memory task, MSFSI: mail in cognitive function screening

Table 4: Change in Cognitive Composites by Genetic Risk

	Global Composite Difference			Learning/Memory Composite Difference			Memory-Weighted Composite Difference			Predict Composite Difference		
	$\beta$ value	Standard error	P-value	$\beta$ value	Standard error	P-value	$\beta$ value	Standard error	P-value	$\beta$ value	Standard error	P-value
APOE $\epsilon$ 4	-0.193	0.0624	0.00210	-0.211	0.0855	0.0139	-0.212	0.0651	0.00120	-0.249	0.0676	0.000300
AD-GRS	0.314	0.160	0.0506	0.198	0.219	0.367	0.292	0.167	0.0811	0.247	0.174	0.156
Combined GRS	-0.122	0.0578	0.0348	-0.154	0.0790	0.0514	-0.142	0.0604	0.0187	-0.180	0.0627	0.00410

Table 4 Legend: General Linearized Models controlled for baseline score, age<sup>2</sup>, sex, and education level

Abbreviations: GRS: genetic risk score

Table 5: Change in Individual Assessments by Genetic Risk

	MoCA Difference			Trails B Difference			WLM Learning Difference			WLM Delayed Recall Difference			WLM Recognition Difference		
	$\beta$ value	Standard error	P-value	$\beta$ value	Standard error	P-value	$\beta$ value	Standard error	P-value	$\beta$ value	Standard error	P-value	$\beta$ value	Standard error	P-value
APOE $\epsilon$ 4	-0.205	0.0798	0.0105	-0.311	0.0963	0.00130	-0.227	0.0994	0.0225	-0.154	0.105	0.143	-0.325	0.153	0.0337
AD-GRS	0.408	0.206	0.0483	-0.000663	0.246	0.998	0.493	0.255	0.0538	0.381	0.269	0.157	-0.339	0.392	0.387
Combined GRS	-0.122	0.0742	0.102	-0.267	0.0886	0.00270	-0.128	0.0921	0.1657	-0.080	0.0968	0.412	-0.327	0.141	0.0205

Table 5 Legend: General Linearized Models controlled for baseline score, age<sup>2</sup>, sex, and education level

Abbreviations: GRS: genetic risk score WLM: word list memory task

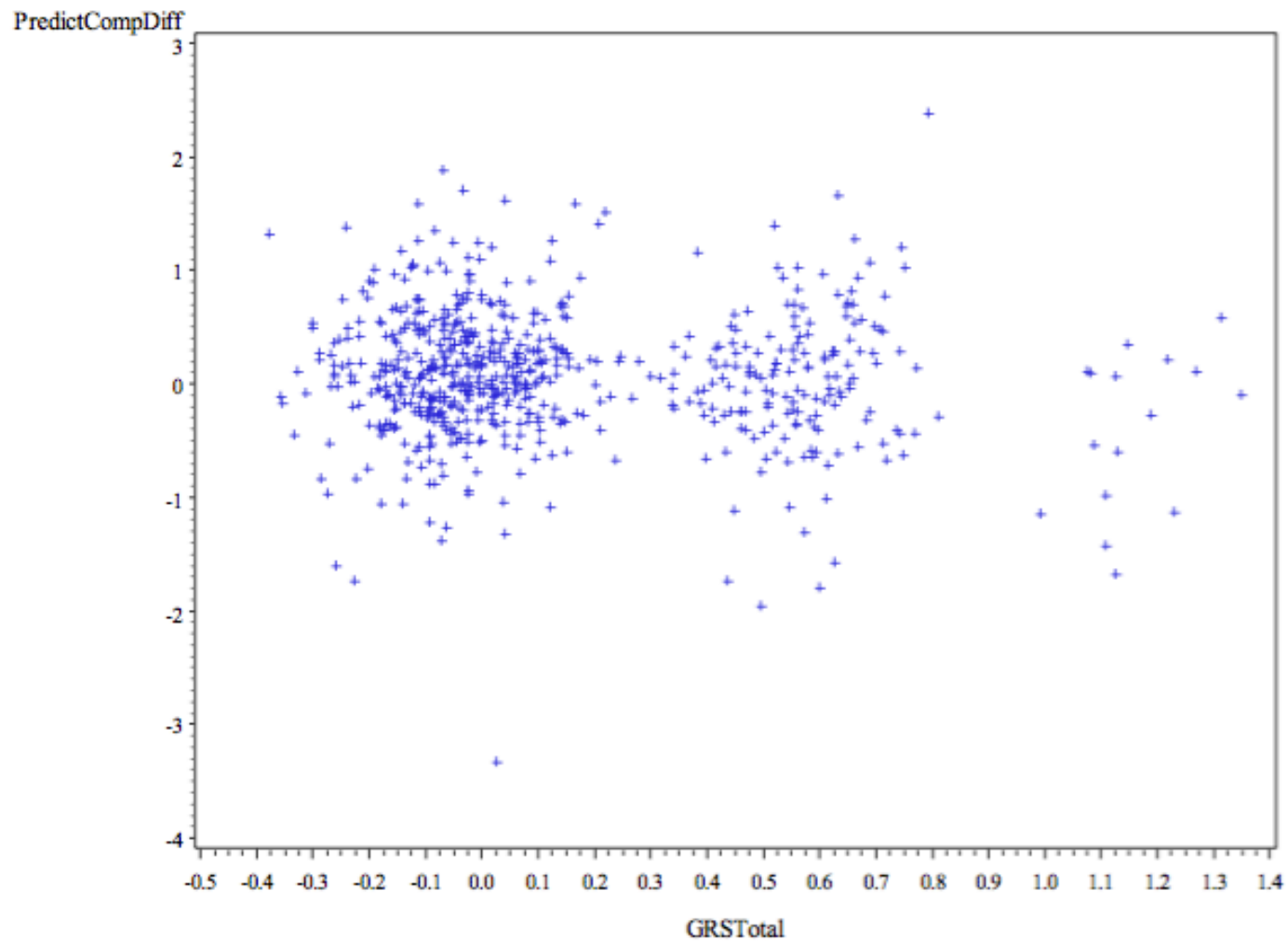


Figure 1: Association of cognitive decline as measured by the Predict Composite and Combined Genetic Risk Score

**Table 6: Baseline Individual Assessments by Genetic Risk**

	MoCA Initial			Trails B Initial			WLM Learning Initial			WLM Delayed Recall Initial			WLM Recognition Initial		
	$\beta$ Value	Standard Error	P-value	$\beta$ Value	Standard Error	P-value	$\beta$ Value	Standard Error	P-value	$\beta$ Value	Standard Error	P-value	$\beta$ Value	Standard Error	P-value
APOE $\epsilon$ 4	-0.0965	0.0882	0.274	-0.156	0.116	0.177	-0.111	0.116	0.336	-0.103	0.120	0.390	-0.200	0.164	0.222
AD-GRS	-0.362	0.212	0.0885	-0.370	0.270	0.171	-0.412	0.288	0.154	-0.181	0.291	0.534	-0.295	0.392	0.452
Combined GRS	-0.117	0.0819	0.152	-0.178	0.107	0.0967	-0.145	0.107	0.178	-0.106	0.112	0.343	-0.196	0.152	0.199

**Table 6 Legend: General Linearized Models controlled for age<sup>2</sup>, sex, and education level**  
 Abbreviations: GRS: genetic risk score WLM: word list memory task

Table 7: Baseline Cognitive Composites by Genetic Risk

	Global Composite Initial			Learning/Memory Composite Initial			Memory-Weighted Composite Initial			Predict Composite Initial		
	$\beta$ Value	Standard Error	P-value	$\beta$ Value	Standard Error	P-value	$\beta$ Value	Standard Error	P-value	$\beta$ Value	Standard Error	P-value
APOE $\epsilon$ 4	-0.329	0.243	0.176	-0.422	0.316	0.182	-0.570	0.404	0.159	-0.465	0.314	0.138
AD-GRS	-0.993	0.580	0.0875	-0.883	0.767	0.250	-2.05	0.976	0.0364	-1.78	0.757	0.0189
Combined GRS	-0.399	0.225	0.0764	-0.452	0.293	0.124	-0.740	0.374	0.0482	-0.620	0.289	0.0325

Table 7 Legend: General Linearized Models controlled for age<sup>2</sup>, sex, and education level

Abbreviations: GRS: genetic risk score