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Association Study: APOE Alleles Association with Neurodegenerative Disorders in the Hispanic Population

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ASSOCIATION STUDY: APOE ALLELES ASSOCIATION WITH NEURODEGENERATIVE DISORDERS IN THE HISPANIC POPULATION

A Thesis

by

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ABSTRACT

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The purpose of this study was to assess the impact of phenotypic variables and Apolipoprotein E (APOE) alleles and its effect on cognitive statues. APOE is a gene found vastly in the Hispanic community, speculated to be linked to neurodegenerative disorders such as Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI). Compared demographic, clinical, and genetic features among Hispanics who were diagnosed with Alzheimer's Disease, Mild Cognitive Impairment, and psychiatric disorders (e.g., anxiety and depression) in the efforts to assess the role of APOE. In past research, APOE has been considered a pathological hallmark for neurological diseases.

Past research has demonstrated that Hispanics have a younger age onset of neurodegenerative disorders and more clinical symptoms. In this research, is meant to test the association of the APOE ε2, ε3, and ε4 alleles across the different cognitive statues; additionally, determining the association of APOE with gender, age, education and BMI.

DEDICATION

The completion of my studies and reason for my hard work is simply to honor those who have accompanied me on my journey. A million blessings to my mother Veronica Moreno, my father Armando Moreno, and my two sisters Carolina and Veronica Moreno for all their love and support.

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CHAPTER I

INTRODUCTION

Statement of the Purpose

In previous studies, apolipoprotein E (APOE) alleles have emerged as hallmarks for neurodegenerative disease and have been used to study the susceptibility of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) (Ponomareva et al., 2013; Yin & Wang, 2018). Research studies have identified APOE alleles, specifically ε4, heighten the risk for AD (Burke et al., 2016; González et al., 2019a; Sando et al., 2008). A meta-analysis explored the association of APOE allele and AD, by age and gender, demonstrating that being homozygous for ε4 increases the risk by 14 times in Whites, and the same can be seen with heterozygous (ε2/ε4 odd ratio (OR):2.6; ε3/ ε4 OR:3.4 increase) (Farrer et al., 1997; Liu et al., 2013a; Nitrini et al., 2009). At the same time, the same study found APOE ε4-AD had a weak association in Hispanics, and mentioned it should be further investigated (Farrer et al., 1997; Reitz & Mayeux, 2014). A previous TARCC study, 'Biomarkers of Alzheimer's disease among Mexican Americans', demonstrated that the biomarkers profile of AD in Hispanics differentiate from other non-Hispanic groups, demonstrating the importance of further research with APOE-AD association in Hispanics (O'bryant et al., 2013). The inclusion of the following covariates: age, BMI, education, and gender have been associated as contributing risk factors to AD and MCI (Jefferson et al., 2015; W. A. Rocca et al., 2014; *What Causes Alzheimer's Disease? | Alz.Org*, n.d.; Yin & Wang, 2018). It would be valuable information to understand additional factors that have a contribution to AD and MCI, to correctly assess the association of APOE alleles with AD

and MCI. Additionally, the study will also focus on psychiatric disorders and their prevalence in AD and MCI as well as, their association with APOE ε4 allele with AD participants.

Overall, the purpose for this research is to further investigate APOE association with AD, MCI and psychiatric disorders (anxiety and depression) . Adjustment of confounding factors, such as gender, BMI, education, and age, that may contribute to AD, MCI, and psychiatric disorders, were assessed to determine the true association of APOE. The question addressed is 'Does APOE alleles have an association with AD, MCI and/or psychiatric disorders and if yes, can it be statistically justified?'. It is hypothesized that U.S. Hispanics suffering from AD, or MCI will have an association with APOE alleles, specifically ε4, and the prevalence of certain psychiatric disorders would depend on allele status, but the association with APOE might not be as prominent as it is in White population. This study was exclusively conducted in U.S. Hispanics, in the efforts to provide a clear reflective nature of APOE gene in this target group.

This information is valuable for the field of pharmacogenomics, which intergrades information on the individual's responses to a medication and the information of their unique genetic makeup (e.g., SNPs) and produce individualized medication (Shukla, 2020). Association studies, such as this one, are being utilized to identify genes that contribute to certain diseases and are paving the road for future research, by deducing genetic variants worth further researching and identifying Single Nucleotide Polymorphism (SNPs) that may predict susceptibility to diseases and responses to medication (Marais, 2019; Shastry, 2009; Weiss, 2014). Therefore, findings in this study can serve as a platform for future research. A future direction for this project would be to conduct haploid analysis, the addition of SNPs biomarkers such as Presenilin 1, FOXO3-A, TOMM40 and many more SNPs related to AD and MCI, and recruit for a larger sample size. A further future possibility could be to conduct a pharmacogenomics study in collaboration with

other researchers and medical practitioners and which could build on the information obtained from this association study.

Statement of the Problem

Recent studies have found to be inconsistent in relation to APOE alleles in Hispanic populations due to the genetic heterogeneity in the different ethnic groups found in Hispanics (Conomos et al., 2016; González et al., 2018; Rajabli et al., 2020). Hispanics population is genetically heterogenous with a vast categorization of different ethnicities and by placing them in the same classification, can show inconsistencies on the reflection of the APOE allele frequency distribution and the association it may have with neurogenerative diseases (Chernin et al., 2010; González et al., 2018; Granot-Hershkovitz et al., 2020; Lee et al., 2010). APOE alleles should be further studied because the alleles have been attributed to different levels of associations with AD and MCI and the association vary depending on varying factors, such as race and gender (*Ancestry-Specific Genetic Variation at APOE Alzheimer's Gene Modifies Disease Risk - Memory and Brain Wellness Center*, n.d.; *APOE and Gender | Cognitive Vitality | Alzheimer's Drug Discovery Foundation*, n.d.; Bell et al., 2017; Farrer et al., 1997; Morris et al., 2019). Hispanics population have yet to be studied as an inclusive group, impacting the outcome of current research conducted; as a result, Hispanics need to be studied in-depth on the risks between APOE alleles and neurogenerative disorders (Blue et al., 2019; Campos et al., 2013; Farrer et al., 1997)

In 2016, around 12.2% of Hispanics, 65 years and older, were diagnosed with AD in the U.S. and it is expected by 2060 that the percentage would double, affecting 3.2 million Hispanics (U.S. Burden of Alzheimer's Disease, Related Dementias to Double by 2060 | CDC Online Newsroom | CDC, n.d.; Vega et al., 2018). A cross-analysis study demonstrated that Hispanics were more likely to develop symptoms of AD 6.8 years earlier than Whites and are more likely

to be burdened with psychiatric disorders (Clark et al., 2005; Hernandez et al., 2005). It is well understood that AD is a result of interactions between genetics and non-genetic factors (e.g., such as age, genetics, coexisting medical conditions and lifestyle) (Can Alzheimer's Be Prevented? | Alzheimer's Association, n.d.).

Additionally, prevalence of MCI is also increasing and currently, it is estimated that the prevalence of MCI in Hispanics is close to 9.8%, but may vary per subgroup (e.g., Mexican Cuban etc.) (González et al., 2019a). As previously mentioned, APOE ε4 allele has been considered a risk factor in developing AD, the same association has been established between the APOE ε4 allele and MCI (Granot-Hershkovitz et al., 2020; Jefferson et al., 2015; Safieh et al., 2019). Yet, some studies have found no association between APOE ε4 allele and MCI nor in increasing the risk of MCI, while others have (González et al., 2019a; Qian et al., 2017).

There is a lack of association studies being conducted on APOE alleles with AD and MCI in the Hispanic population. For example, as of December 19, 2020, using the following keywords '((APOE) AND (Hispanics)) AND (Alzheimer's)' in Pubmed.gov, only retrieved 135 results (publishing year ranged from 1993 to 2020) while in caparison, the following key words '((APOE) AND (Whites)) AND Alzheimer's) retrieved 745 results (publishing year ranged from 1993 to 2020); Whites were more likely to be incorporated in research and had 5 times the number of publications. Hispanics are under studied and underrepresented in research studies and even though they make at least 16.3% of the population in the US in 2010, they make a meager percentage in research (*Population of the United States by Race and Hispanic/Latino Origin*, n.d.; *The Importance of Latinos in Clinical Trials – NHCOA*, n.d.). Hispanics face many barriers when it comes to participating in research studies, with the initial issue being language. Many prefer or

can only speak their native language, whether it be Spanish, or a regional dialect and participation is limited if the study is conducted in English (SEONAE YEO, 2004).

Overall, Hispanics tend to develop AD symptoms at an earlier point in their lives compared to other populations and it is expected for those affected with AD and MCI, will increase. Common symptoms of AD and MCI are anxiety and depression, psychiatric disorders, and some studies suggest that APOE ε4 allele can increase the probability of developing comorbidity with psychiatric disorders, but most of the results are inconclusive (Burke et al., 2016; Forero et al., 2018; *Gene Variant May Increase Psychiatric Risk after TBI*, n.d.). Lack of research in this population can result in many limitations such as lack of accurate statistical power in the results which may cause false positive or false negative results that represents the Hispanic population. Therefore an increase in genetic studies in this population is needed since the data obtained from these studies can help formulate clinical trials and aid in assessing the risk of AD and MCI in this target group (Qian et al., 2017).

CHAPTER II

REVIEW OF LITERATURE

APOE Gene

APOE is a gene found on chromosome 19 that creates the multifunctional protein called Apolipoprotein E, which is composed of a total of 299 amino acids (Frieden, 2015; Huang & Mahley, 2014). APOE proteins distributes lipids in the central nervous system to maintain lipid homeostasis, allows for the repair of injured neurons, and maintains synaptic-dendritic connections and aids in the production of Apolipoprotein E (Mahley et al., 2006). Apolipoprotein E protein functions within the central and peripheral nervous system as a lipid carrier where it supports membrane homeostasis and the repair of injuries to the brain (Zhao et al., 2018).

The alleles are differentiated in the amino acid residues 112 and 158 by having either cysteine (Cys) and/or arginine (Arg),ε2 :Cys 112, Cys 158; ε3:Cys 112, Arg 158; ε4: Arg 112, Arg 158, and influence binding of lipids and amyloid β (Aβ) clearance differently (Liu et al., 2013b). Research has demonstrated that APOE plays a role in Aβ aggregation, with evidence demonstrating that Aβ deposits are more abundant in APOE ε4 carriers, in comparison to non-carriers (Chia-Chen Liu, Takahisa Kanekiyo, 2013). Over the years, the accumulation of Aβ can lead to the buildup of plaque and neurofibrillary tangles that damage the synapses, leading to neurodegeneration disorders (O'Brien et al., 2012).

APOE gene exhibit three alleles: ε3, ε2 and, ε4. Out of the three isoforms, the most common one, APOE ε3 allele, has been found to be present in about 75% of the population, while also believed to be a neutral allele (Sebastiani et al., 2019). APOE ε2 isoform is believed to be a protective allele against neurological diseases, such as AD, because it reduces neuroinflammatory responses and is found in 5% of the population (Sebastiani et al., 2019). Yet, very little is known on how ε2 allele expresses neuroprotection and its functions and effects in Hispanics (González et al., 2018; Kuo et al., 2020; Sebastiani et al., 2019). APOE ε4 allele, found in 20% of the population, is deemed as an allele that increases the risk and accelerates the rate of cognitive decline (Sebastiani et al., 2019). In previous studies, APOE ε4 allele disturbs normal cognitive aging and leads to cognitive impairments, such as memory decline, motor disturbance, and reasoning (Burke et al., 2016). While looking at APOE allele frequency in those suffering from AD in Hispanics and in other populations, several studies found that more than half the individuals were ε4 carriers(Jensen et al., 2019; Rippon et al., 2006). This results could vary by race and the percentage could be higher or lower for example, 70% of AD individuals were ε4 carriers in the region of Northern Europe, which were predominately White (Jensen et al., 2019; Wu & Zhao, 2016). Even a single copy of ε4 allele has been correlated with an increased risk of developing AD, cerebral amyloid angiopathy and MCI (Boyle et al., 2010; Liu et al., 2013a).

Hispanics

Research on APOE alleles, in the Hispanic population have been inconsistent due to the heterogeneous background of the sub-populations (González et al., 2018). A meta-analysis demonstrated that APOE ε4 allele was found to be lower in Hispanics than in Whites non-Hispanics (Farrer, 1997). Further investigations have revealed the APOE ε2 allele to be

associated with longevity but not among Hispanics, even with their record of low mortality rates (González et al., 2018). Moreover, Hispanics have not been rigorously studied as a single group to determine an associated between the APOE alleles and neurodegenerative disease risks (Campos et al., 2013).

About 12% of older Hispanics are diagnosed with AD, showing symptoms at an earlier age (Mehta & Yeo, 2017). On average, Hispanic develop symptoms of AD at the age of 70 (Santos et al., 2019). Yet, after ten years, the Hispanic have a longer survival rate (67%) versus the other two ethnicities: Whites (40%) and African Americans (16 %) (Santos et al., 2019). Hispanics develop the symptoms at an earlier age but lived longer, approximately 12 years longer from the onset of AD till death, than other ethnicities (Santos et al., 2019).

Hispanics are less likely to seek out psychiatric help with only 20% of people, who experience symptoms, will discuss with a doctor and only 10% will seek professional help (*Latinx/Hispanic Communities | Anxiety and Depression Association of America, ADAA*, n.d.). Due to the inability or refusal to seek help, the symptoms will persist longer, due to the lack of treatment (Humberto Marin, 2003). Therefore, in a study conducted, Hispanics (27.3%) shows to have a lower rate than the Whites population (46.3%) regarding a mental illness (Vega et al., 2017).

In Hispanic communities a prominent psychiatric disorder addressed to a healthcare professional is anxiety (Cohen et al., 2016). Anxiety is displayed in 3 out of 4 individuals with AD, leading us to believe there is a correlation between the two disorders (*Alzheimer's Disease and Anxiety: Guidance and Tips*, n.d.). In several studies, anxiety is one of the first of many symptoms of AD, a prodrome. To support this, a longitudinal association study, demonstrated the correlation between psychiatric disorders and an early indication of pre-diagnosed AD

(Donovan et al., 2018a). Meaning that, anxiety and depression, can be pre-clinical symptoms of AD.

Neurodegenerative Disorders

Alzheimer's disease (AD) is a type of dementia that causes cognitive impairment. Its prevalence and severity increase gradually with age, making it a progressive disease. More than 5 million people are diagnosed with AD in the U.S. alone (Vega et al., 2018). This disorder causes brain cells to degenerate and die, leading patients to lose the ability to take part in their everyday activities. Consequently, affecting the patient's caregiver, resulting in a physical responsibility and financial deficit.

AD displays psychiatric symptoms in all stages. A person can develop AD due to many factors and interactions between genetic and environmental factors. Common symptoms for AD are delusions, agitation, and apathy. In more advanced stages, an AD patient can suffer from a severe loss of neurological functions, which are vital to carry out daily necessities. Unfortunately, there is no cure, however it can be treated to help temporarily alleviate the symptoms. An average person with AD tends to live three to eleven years after being diagnosed, depending on its severity. The Hispanic community is made up of different ethnic groups, making it difficult to study how AD affects certain individuals or sub-populations (González et al., 2019b).

Mild Cognitive Impairment (MCI) can be defined as the middle ground for normal and atypical aging cognitive decline. The main characteristics of MCI are forgetting details, confusion, losing items, and/or impaired communication skills (*What Is Mild Cognitive Impairment? | National Institute on Aging*, n.d.). Approximately, 15% to 20% of people 65 or

older will be diagnosed with MCI (Langa & Levine, 2014). MCI can interfere with the routine of a person but does not change the capability to conduct their daily activities. MCI does not meet the clinical criteria for dementia, but their degree of clinical impairment is beyond that which is expected for their current age (Petersen, 2009). In a longitudinal study, subjects were followed over a period of time and those diagnosed with MCI tend to progress to clinical probable AD at a rate of 12% per year, while other epidemiological studies have yielded lower progression rates of 8-10% per year (Petersen, 2009). When looking at the Hispanic population, it is estimated that 9.8% are diagnosed with MCI (González et al., 2019c); however, this number is projected to increase due to population growth within the Hispanic community (*U.S. Burden of Alzheimer's Disease, Related Dementias to Double by 2060 | CDC Online Newsroom | CDC*, n.d.). Additionally, Hispanics in comparison with Whites have demonstrated to have a higher rate of cognitive decline and memory disturbance, leading us to believe that AD and MCI may be more prevalent in Hispanics, than in the Whites population (*U.S. Burden of Alzheimer's Disease, Related Dementias to Double by 2060 | CDC Online Newsroom | CDC*, n.d.).

Covariates

Body Mass Index (BMI) is used to indirectly measure the adiposity body fat tissue in an individual. In the last couple of decades, many longitudinal studies have evaluated the relationship between adiposity and AD. Several have reported that an increase of BMI can be a risk factor for AD (Xu et al., 2011). One of the aims of this study is to assess if BMI can be a risk factor for AD and MCI while adjusting for confounding factors, such as gender, education and APOE alleles.

The incidence of AD is higher in females than in males and the estimated lifetime risk for AD is also greater. An important contributor to the sex difference between AD has been

attributed to the expanded lifespan of females but overall, it does not explain the higher frequency and lifetime risk in women (Nebel et al., 2018). The results based on a meta-analysis has demonstrated that the gender differences can be a result of education and occupational opportunities within the region the participants resides, with some studies finding significant differences while others do not (Nebel et al., 2018; L. G. Rocca et al., 2017; W. A. Rocca et al., 2014). Two studies, predominately White, showed that after the age of 80, the incident of neurodegenerative disease is higher for females than in males, but before the age of 80 incident rate is higher in males (Letenneur et al., 1999; Ruitenberg et al., 2001). This type of information is limited for the Hispanics population and the information that is available shows no observing that prevalence of AD differed by gender (Santos et al., 2019). It is one of the many focuses of this study, to highlight the relationship between AD and gender and to address if APOE allele has significance with AD once it has been stratified by gender.

Previous studies have shown that a person with a higher level of education has an increased verbal/nonverbal performance when conducting their daily tasks while suffering from MCI/AD, in comparison to its counterparts, a person with lower to no education level (Vadikolias et al., 2012). Additionally, some studies have attributed a higher level of education to higher cognitive reserves, referring to the ability to maintain cognitive function despite damage and can act as a protection against neurodegenerative diseases such as AD (Katzman, 1993; Stern, 2009).

Age is the most well-known risk factor for AD with the initial symptoms of AD appearing as early as age 60. As time progresses, the number of people with AD will double every 5 years beyond the age of 65 (Matthews et al., 2019). It is evident that the risk for both MCI and AD, increase as age progression (Tampi et al., 2015)

Psychiatric Disorder

Studies show that the increase of beta-amyloid proteins, characteristic of AD, have a direct correlation with depression and anxiety, inevitably increasing the probability of a person developing AD/MCI in the future (Donovan et al., 2018b). Depression has been recognized as a risk factor for AD but there is debate in whether depression is a risk factor or if it is a prodrome of the disease (Karlsson et al., 2015). AD patients dealing with depression have adverse consequences such as impairment in daily activities, poorer quality of life, a rapid decline in cognition and higher mortality rates (Delano-Wood et al., 2008).

A longitudinal study evaluating the association between anxiety and MCI demonstrated that those suffering from anxiety had a higher probability of their diagnosis statues changing to AD (Donovan et al., 2018a). Some studies have hypothesized that anxiety may speed up AD onset in those suffering with MCI (Donovan et al., 2018a; Rozzini et al., 2009). Anxiety has been described as a risk factor for AD but the relation between the two should be further investigated due to mixed results (Becker et al., 2018). Anxiety has been shown correlation with psychiatric morbidity, disability and mortality in AD patients and in the general population (Teri et al., 1999). It is a common symptom in those diagnosed with MCI and AD, with 3 out 4 suffering from some level of anxiety (*Alzheimer's Disease and Anxiety: Guidance and Tips*, n.d.). Both depression and anxiety are debilitating disorders that take their toll on the brain by damaging brain cells (Dennis Thompson Jr, n.d.)

CHAPTER III

METHODOLOGY AND FINDINGS

Methods

This study is an analysis of data collected by the Texas Alzheimer's Research and Care Consortium (TARCC) (N=1,320) in combination with our own data, Initial Study of Longevity and Dementia from the Rio Grande Valley (ISLD-RGV, N=62); resulting in a total of 1,382 subjects. The studies' protocols were approved by the corresponding Institutional Ethics Committees and Institutional Review Boards; in our case ISLD-RGV, IRB-19-0024, PI, Dr. Xu. A written informed consent was obtained from each participant or their legally authorized proxies before data collection began.

The 1st data collection was from ISLD-RGV. Controls were matched to cases based on their age, gender, and ethnicity (Hispanic subjects). Patients with AD, MCI, psychiatric disorders, and normal cognitive participants were recruited from the Lower Rio Grande Valley (LRGV), which included the regions of Brownsville and McAllen, Texas. Recruitment took place in different locations (e.g., community events, clinics, and home visits), and signed letters of support from three independent adult day care centers were obtained, granting us access to their facility. Recruitment was done by identifying and evaluating participants by native Spanish speaking research assistants Victoria Padilla and Kimberly Moreno, whose one of their many duties consisted of arranging meetings with the adult daycare centers in search for potential participants

Inclusion and exclusion critical: Inclusion criteria (1) included diagnosed with AD, MCI or AD-related phenotypes by their private medical practitioner, and (2) the inclusion of normal cognitive participants that were family members of those diagnosed with a neurodegenerative disorder. Exclusions were done (1) if the participant could not provide medical documentation and (2) those with normal cognitive that were not related blood related, were excluded.

This process was done in a year with the initial phase being to establish a relationship with an adult care facility. Once a meeting has been organized with the participants, a consent form was signed and the saliva samples were taken for genetic study, and a token of our gratitude was given in exchange. The research assistants documented the data using the subject's self-report which was later confirmed by the daycare records and a physician statement. Additionally, all questionnaires, lifestyle (10 questions,(Haines et al., 1999)), medical history, and familism factors (10 questions modified based on (Steidel & Contreras, 2003), were provided either in Spanish or in English and were collected during the interview. Psychiatric disorder diagnosis was obtained by individuals self-reporting on the questionnaire meaning.

The 2nd data collection was from the Texas Alzheimer's Research and Care Consortium (TARCC) study, which is well-characterized, ethnically diverse (e.g., U.S Hispanic subjects »1320) convenience sample with annual longitudinal follow-up described in detail in a previous study (Waring, 2018).

Based on combined two sample sets, our own and TARCC, the study design consisted of (1) testing demographic factors (e.g., age and education) association with three clinical phenotypes, AD, MCI, and psychiatric disorders (anxiety and depression); (2) conducting a genetic association between APOE alleles with the three clinical phenotypes. The initial cohort consisted of 1,320 participants that were sub-divided as followed: 1,019 controls and 301 cases

in the AD analysis, 993 controls and 327 cases in the MCI analysis, 127 controls and 174 cases in the anxiety analysis and 119 controls and 182 cases in the depression analysis (ref. Table 1 and 9). All participants were ethnically matched between controls, and cases, those who suffered from AD, MCI, depression and anxiety.

DNA Isolation and Genotyping

Genetic data was collected to study genetic determinants of APOE polymorphic alleles associated with AD, MCI, and psychiatric disorders. DNA extraction was performed by two different methods: saliva samples collection (ISLD-RGV, N=62 participants) and blood samples collection (TARCC, N=1,320). For the collection of ISLD-RGV saliva samples (N=62), participants who consented to the study were asked to provide 1-2 ml of saliva. The samples were collected using Oragene DISCOVER (OGR-500), a self-collection kit, from the company DNA Genotek Collection and done according to OGR-500 protocols (*DNA Genotek - Genetic Academic Research - Sample Solutions*, n.d.). The saliva samples were stored at a temperature of 4°C until DNA extraction. DNA isolation from saliva was performed following the standardized laboratory protocol described by DNA Genotek (*Laboratory Protocol for Manual Purification of DNA from Whole Sample Ethanol Precipitation Protocol and PrepIT®•L2P Reagent for the Purification of Genomic DNA from Oragene® Products and ORAcollect® Formats OC-175, OCD-100 and OCR-100. Not for Use with OCD-100A*, 2018). DNA isolation and genotyping of TARCC's data have been described in detail in other TARCC publications (O'Bryant et al., 2010).

DNA genotyping was determined by two separate methods, as well. TaqMan SNPs assays were used for the analysis of the SNPs rs7412 and rs429358 to identify the three main APOE alleles, ε3, ε2, ε4. TARCC utilized Affymetrix Genome-Wide human SNP Array 6.0 to collect SNPs rs7412 and rs429358 data, referencing the methods from their previous studies (*Data and*

Sample Information and Requests – Texas Alzheimer's Research and Care Consortium, n.d.). APOE alleles (ε3, ε2, and ε4) were determined by SNPs rs7412 and rs429358 from both data sets. SNPs data was identified as either 'Carriers' (ε2+, ε3+, ε4+) or 'Non-carriers' (ε2-, ε3-, ε4-). Carriers were participants who had at least one copy of the allele (either heterozygous, with one allele or homozygous with two identical alleles), while Non-carriers were participants who did not carry a single copy of the allele.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 26 and Intellectuals Statistics were used to perform statistical analysis: chi-square, t-test and logistical regression. To test whether the APOE alleles were independently associated with several phenotypes (e.g., gender or BMI) in the subjects. Initially, an independent t-Test and chi-square test were used to statistically examine the role of each allele and the phenotypes with the presence of neurodegenerative diseases (AD and MCI) and psychiatric disorders (exclusively in those classified with AD). Binary logistic regression was used to adjust for all the potential risk factors (e.g., sex, and education) and included phenotype alleles that showed significances in the previous two test, Chi-square, and T-test. Significance, in all three tests were indicated with a $P<0.05$. The Odds Ratio (OR) was used to determine the risk value between alleles and phenotypes. Additionally, our data was tested for Hardy-Weinberg Equilibrium before data analysis, $PHWE>0.05$. Statistical Power Analysis was performed to determine power (78.2), based on sample size of 1000 controls and 300 cases using Genetic Power Analysis (http://zzz.bwh.harvard.edu/gpc/) (Purcell, Chery & Sham,2003). This analysis was based on sample size, an estimate of 1000 control subjects and 300 cases with disease phenotypes (e.g., AD or MCI), while utilizing variance components analysis with the following parameters: disease prevalence, 0.01; D′0 between disease and SNP alleles, 0.8; alpha, 0.05 and

case-control statistics of allelic 1 df test (B versus b) allelic 1 df test. Plus, using the marker allele frequency of 0.2, since the frequencies being studied are of the minor allele frequencies of the tested SNPs/markers.

Statistical analysis was performed according to APOE statues 'Carriers' (ε2+, ε3+, ε4+) and 'Non-carriers' (ε2-, ε3-, and ε4-). Those considered carriers had either one or two copies of the given allele and could be either homozygous or heterozygous. In total, several variables were used to generate statistical reports from the responses. Categorical phenotypes were assigned no more than two values denoted by 0 and 1. For example, to specify the presence or absence of anxiety (or other clinical phenotypes) the value of 0 denoted 'Absent' and 1 indicated 'Present'

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Results

Demographic Information

The results were obtained by statistically analyzing AD and MCI data. As previously mentioned, the data was derived from TARCC and ISLD-RGV, and was merged to become a single data set, which was composed of only Hispanic participants from various regions of Texas. Initially, originally the study included 1,382 participants, of which all phenotypic data, DNA samples and consent forms were obtained. However, due to the ongoing 2020 global pandemic, only 1,320 participants were genotyped for APOE allele data. The demographic information, in Table 1, for this portion of the study is as follow: majority of the participants were female (69.9%) with a mean ± SD age of 70±10 (range, 50-98 years). Additionally, 301 participants' cognitive statues were classified with AD, with 65% being female with mean ± SD age of 78±8, and 327 with MCI, with 66% being female and a mean ± SD age of 74±9.

AD

There were observed differences between certain baseline characteristics within AD and MCI. The frequency of APOE ε4 allele was 11% higher in AD participants than MCI participants, yet no differences were observed in age, education, BMI, and the other baseline characteristics.

The frequency of the APOE alleles within the participants with AD, APOE ε2 allele, 5%; APOE ε3 allele, 93%; APOE ε4 allele, 31%, Table 1. As previous research results demonstrated, APOE ε3 allele, the neutral allele, was the most frequent allele, followed by APOE ε4 and lastly, the rarest, APOE ε2. The distribution of the APOE alleles in the AD group, Table 1, did not deviated from previous results in study conducted in Hispanics by González et al., 2018 and Blue et al., 2019. The associations between the phenotypes of categorical variables and APOE alleles with AD, based on the chi-square analysis were shown in Table 2, and phenotypical continuous variables based on T-test were in Table 3. The results after controlling potential confounding factors (e.g., age, BMI, education) using logistical regression were shown in Table 4-6. Additionally, the Variance Inflation Factor (VIF) test was conducted for each logistical regression, but no multicollinearity was detected, with all values displayed as being less than or equal to 1.05. Differences with probability values of $P<0.05$ were found to be statically significant. The odds ratio (OR) was used to determine the risk value between alleles and phenotypes

The chi-square statistical analysis tests categorical data, resulting in the $P<0.05$ being statistically significant. The chi-square analysis demonstrated that sex, $P= .045$, was significantly associated to AD. Due to the observed values being greater than the expected values in males (OR:1.32) and a risk value greater than the females, it is 1.32 times more likely to observe males

suffering from AD than females due to risk value for females (OR: .757) were lower. To break down the data, the results showed that APOE ε4 allele, P < .001, and APOE ε3 allele, P = .046, were statistically significant and suggested they were associated and could be risk for AD. Those who had APOE ε4 allele significantly displayed, were 2.06 times more likely to suffer from AD, while APOE ε3 were 1.64 times. On the contrary, for APOE ε2, P=.264, no significance was detected and suggested that APOE ε2 and AD could be independent of one another because the observed frequencies were not significantly different from the expected frequencies; additionally after transforming the data values, no significant values were observe to justify the possibility of the allele being a protective allele. To summarize, those who were APOE ε4 carriers more likely to suffer from AD when compared to the other two APOE alleles, ε3 and ε2.

Independent T-test was used to statistically measure categorical data, with a P < 0.05 considered significant. The p-value for BMI, P < .001, and age, P < .001, were significant with AD, meaning that the means were significantly different between the cases and controls. In past research, education was considered a significant factor associated with AD, but no association was found in this study. Education was not significant *P* = .599, suggesting the mean for education between cases and controls categories of AD were not significantly different. It can be noted that both means between cases and controls of AD were the same, with a mean of 10 years.

Logistical regression was used to determine the relationship of APOE status to AD, while controlling for covariates; the model was evaluated based on an alpha of 0.05. The covariates used (e.g., age, education, BMI, and gender) were utilized to adjust the logistical regression models. Gender was not a significant role in predicting AD in this study. The regression coefficient for sex was not significant, P = .862, indicating that sex did not have a significant

effect on the odds of observing AD. Contradictory to the previous results of the chi-square test, it is important to keep in mind that chi-square is a descriptive test used to find associations between two variables and is not a statistical model. On the other hand, logistical regression takes into consideration multiple variables, both categorical and continuous, and is a statistical model in which the dependent variable is predicted by the independent variables (Steyn Peter, n.d.). As previously seen, APOE ε2 was not significant, P = .086 and has no effects in the possibility of observing AD while APOE ε3, P = .711, did not maintain its significant value. Lastly, APOE ε4, P < .001, was significant which indicates the presence of this particular allele, APOE ε4, increases the odds of observing AD, therefore ε4 carriers had an increased risk of developing AD compared to participants who did not carry the allele.

Previous research has demonstrated the importance of education as a variable in understanding cognition (Letenneur et al., 1999; Livney et al., 2011). When examining the association of education and its significances to AD, the logistical regression model demonstrated education, P = .641, was not significant. Due to the means of education being the same for both groups (AD cases and controls of AD), it demonstrated that levels of education did not associate with AD, Table 4-6, in Hispanic population however, these findings need to be confirmed in a large sample data.

BMI has been incorporated into many studies as a reliable assessment to roughly measure body fat and categorizes the score into a range between healthy and an unhealthy BMI (Bhaskaran et al., 2014). A closer look into the logistical model demonstrated BMI, P = .315, as a non-significant factor in predicting AD in this research. Both groups, AD cases and control groups, demonstrated to have a mean BMI value equal to or above 30, a high BMI considered ‘obese’ can be observed both cases and controls groups in our studied population.

Due to humans normal aging process, the body undergoes indefinite changes and encounters age-related disorders, which is also supported by our current study (*The Truth About Aging and Dementia | CDC*, n.d.). AD has been considered an age-related disorder with the risk increasing as age increases, as it is observed in this study and in others (Corrada et al., 2010). Age, $P < .001$, was a significant factor in predicting the presences of AD, since majority of the participants were older, they had an increased probability of developing AD. As the results demonstrated, those suffering from AD were older by at least 11 years and the odds of observing AD increased by 16%. APOE ε4 and age were associated with AD after controlling potential confounding factors (e.g., BMI, education) using the logistical regression analysis.

MCI

The demographic characteristics for MCI (N=317), a subpopulation in this study, are described in Table 1. There were no significant differences between the cases with MCI and controls, in respect to the demographic characteristics (i.e., education and gender) and APOE alleles frequency. The three APOE allele frequencies on those suffering from MCI are as followed APOE ε3, 92%; APOE ε4, 20%; APOE ε2, 7%. The APOE allele frequency was analyzed using Chi-square (Table 7), T-test (Table 8); in all analyzations a $P<0.05$ was considered significant. In chi-square and T-test analysis, age, $P < .001$, demonstrated significances, referring to means age the cases with MCI and the controls differentiated. Additionally, physiatrist disorders, anxiety ($P = .004$) and depression ($P=.023$) also showed significance (Table 7), suggesting there is a possibility for these factors to be dependent of AD. Due to lack of significances in the chi-square and t-tests results with APOE alleles, the logistical model (not shown) was conducted with anxiety and depression instead, while controlling for confounding factors (e.g., age, BMI, education and sex); no association was detected.

MCI is an age-related disorder, and it was observed that MCI increased by 8% with every unit increase, meaning as the time progressed the change of developing MCI would increase by 8%, in this study. The logistical model showed not significances for depression nor anxiety.

Psychiatric disorders. In the final section of the results, focuses on the relationship of psychiatric disorders, depression and anxiety, exclusively in AD participants and their association with APOE ε4 (ref. Table 9). Amongst the 301 patients with AD, 174 participants suffered from anxiety and 182 from depression, Table 9.

APOE ε4 allele association with anxiety amongst participants with AD, a psychiatric disorder in AD participants, was statistically analyzed. The categories controls (N=127) and cases (N=174) frequencies can be observed in Table 9; a 4% increase in prevalence of anxiety in APOE ε4 carriers. According to our chi-square results in Table 10 and Independent T-Test results, Table 11, the APOE ε4 allele was not associated with anxiety in participants diagnosed with AD.

APOE variants (e.g., ε4 allele) has been associated as with AD and it has also demonstrated to increase the risk for depression in those with AD (Delano-Wood et al., 2008; Klengel & Binder, 2013; Pauline, 2017). For depression, the groups consisted of controls (N=119) and cases (N=182), whom have APOE genotype data and diagnosed with AD. The analysis of allele frequency demonstrated that APOE ε4 alleles frequencies were not significantly different between AD with depression (34%) and control (28%). The result of the chi-square analysis (Table 12) and the t-test (Table 13) demonstrates no association of APOE ε4 allele was found with APOE ε4, and other confounding factors (e.g., BMI, education, sex and age).

Overall, this study demonstrates a lack of association between psychiatric disorders (anxiety and depression) and APOE ε4 allele in AD participants and suggests that anxiety and depression are associated with AD or could be prodrome of the disease. As previously mentioned, a larger sample is needed to confirm these finding.

CHAPTER IV

SUMMARY AND CONCLUSION

Summary

Overall, the results of the study show that AD was significantly associated with APOE ε4 allele (including participants with one or two copies of the allele), however no association of APOE ε2 and ε3 allele were observed with AD ($P>0.05$). Overall, these findings demonstrate the association of APOE alleles with AD, correlating with past research, such as González et al., 2018 and O'bryant et al., 2013, and highlighting the possibility of targeting APOE for early intervention for dementia (AD and MCI) prevention.

The results have established that both age and APOE ε4 allele contribute to the probability of developing AD, with the data provided supporting the statement. Association was established between APOE ε4 allele and AD in our studied population, Hispanics and other populations (Farrer et al., 1997; Murrell et al., 2006). Yet, the statistical results should not be interpreted as APOE alleles were the sole contributor for the development of AD; it is important to understand that 'association does not imply causation'. This study did not investigate the possible mechanisms in which AD. MCI and psychiatric disorders and APOE can be linked; this study only tested for significant association via statistical measures. It is important to keep in mind that AD has been attributed to many mixed factors such as genetics, lifestyle and other factors that interact together and impact the probability of developing AD. For example, lifestyle

factors such as smoking has been linked to smoking-related cerebral oxidative stress that is considered to be a risk for AD (Durazzo et al., 2014). To account for phenotypic factors that contribute to AD, MCI and psychiatric disorders, covariates that were previously associated with the disorders were utilized to adjust the logistical regression.

It is important to know that the ages of the participants included into this study, ranged from the age of 50 to 97, relatively proportioned between middle age and late age however, the mean age of AD and MCI were between their early and late 70 years of age. Further expanding, the mean age of those diagnosed with AD, 77 years of age, suggest that the onset of AD can be categorized as late onset AD (onset >65), but unfortunately, that data was not available. It can only infer that the majority are facing the disorders at a later year of 77, an age close to late onset AD (onset> 65).

Years of Education had no association with the risk of developing AD, MCI nor psychiatric disorders (anxiety and depression). This can be attributed to low education levels in the Hispanic population with the mean years of education being equivalent to 10^{th} grade or lower than a high school level. Although, BMI did not contribute to any of the disorders in the studied population, it can be noted that the mean BMI of 30, of all the participants, showed a higher BMI compared to normal BMI of 18.5-24.9, but correlating with Hales et al., 2017, stating 44.8% of Hispanics were obese (*Body Mass Index (BMI): Chart, Calculation, & Healthy BMI Ranges*, n.d.; Center for Health Statistics, 2018; Hales et al., 2017).

To fully address complexity of causes and risk involved in AD and MCI in Hispanic population, it is needed to investigate other factors such as traditions, socioeconomical, migration status and access to education plus health care. To fully access the association between AD and APOE alleles, specifically APOE ε4 allele, in Hispanics population, more data must be

obtained to fully understand the penetrance of APOE alleles as a risk factor for AD in the Hispanics population.

To address the limitation for this section of the results, the sample size was relatively small and the lack of data that can pose valuable information in understanding the association between APOE alleles and AD in Hispanics is missing (e.g., onset of the disorders, clinical dementia ratings (CDR) scores and other cognitive measures) . Not enough diversity in the subgroup of Hispanics to analyze the risk by subgroup (e.g., Venezuelans, Puerto Ricans) nor enough data to address the healthcare disparities between the Hispanic population and its impact on AD.

Our results of the psychiatric disorder show that APOE ε4 allele was not associated with anxiety nor depression exclusively in AD participants. Due to lack of association, it can be concluded that the psychiatric disorders that were prevalent in AD participants and be considered a prodrome or associated with AD but independent of APOE.

The 2nd limitations of this study include (1) no interaction between APOE alleles and psychiatric disorders as a predicting factor for AD, due to lack of data; (2) A longitudinal study was not conducted, which impedes us from addressing the predicting factor of APOE ε4 allele and psychiatric disorders in MCI progressing to AD (3) Lack of data to investigate synergistic effect of interactions between genetic factors and environmental factors involved in AD and MCI development.

Conclusion

Overall, the only risk factors associated with all neurological disorders is age. The current study confirms the findings of previous research results: APOE ε4 allele is a risk factor for AD however neither MCI nor with psychiatric disorders in those with AD, in the studied

population. As a closing statement, more research is required to validate our findings by a larger sample size, and/or longitudinal study, and more homogenous Hispanic population, such as subdividing the Hispanic population according to their appropriate regions.

Table 1: Demographic Table of AD and MCI

	AD		MCI	
	Controls (n=1019)	Cases (*n*=301)	Control (n=993)	Cases (n=327)
AGE Mean ± SD	66.93 ± 8.58	77.52 ± 7.72	67.83 ± 9.26	73.97 ± 8.67
BMI (Mean ± SD)	32.12 ± 6.73	30.13 ± 6.31	31.61 ± 6.80	31.83 ± 6.32
Education (Mean ± SD)	10.19 ± 4.70	10.35 ± 4.44	10.22 ± 4.59	10.22 ± 4.80
SEX				
Female (%)	725 (71%)	196 (65%)	704 (71%)	217 (66%)
Male (%)	294 (29%)	105 (35%)	289 (29%)	110 (34%)
Anxiety				
Absent (%)	761 (75%)	127 (42%)	689 (69%)	199 (61%)
Present (%)	258 (25%)	174 (58%)	304 (31%)	128 (39%)
Motor Disturbance				
Absent (%)	954 (94%)	197 (65%)	867 (87%)	284 (87%)
Present (%)	65 (6%)	104 (35%)	126 (13%)	43 (13%)
Depression				
Absent (%)	666 (65%)	119 (40%)	608 (61%)	177 (54%)
Present (%)	353 (35%)	182 (60%)	385 (39%)	150 (46%)
APOE ε2				
Non-carrier (%)	950 (93%)	286 (95%)	932 (94%)	304 (93%)
Carrier (%)	69 (7%)	15 (5%)	61 (6%)	23 (7%)
APOE ε3				
Non-carrier (%)	107 (11%)	20 (7%)	101 (10%)	26 (8%)
Carrier (%)	912 (89%)	281 (93%)	892 (90%)	301 (92%)
APOE ε4				
Non-carrier (%)	835 (82%)	207 (69%)	779 (78%)	263 (80%)
Carrier (%)	184 (18%)	94 (31%)	214 (22%)	64 (20%)

Table 1. Demographic Table of Neurodegenerative disorders *Note.* Due to rounding errors, column wise percentages may not equal 100%. SD, standard deviation; (%) percentage by column.

Table 2: Chi-Square Analysis for AD

AD	Controls (n=1019)	Cases (*n*=301)	χ^2	OR	*p*
SEX					
Female (%)	725 (71.1%)	196 (65.1%)	4.01	1.32	.045
Male (%)	294 (28.9%)	105 (35.9%)			
Anxiety					
Absent (%)	761 (74.7%)	127 (42.2%)	111.40	4.04	< .001
Present (%)	258 (25.3%)	174 (57.8%)			
Depression					
Absent (%)	666 (65.4%)	119 (39.5%)	64.29	2.86	< .001
Present (%)	353 (34.6%)	182 (60.5%)			
Motor Disturbance					
Absent (%)	954 (93.6%)	197 (65.4%)	165.20	7.74	< .001
Present (%)	65 (6.4%)	104 (34.6%)			
APOE ε4					
Non-carrier (%)	835 (81.9%)	207 (68.8%)	24.25	2.06	< .001
Carrier (%)	184 (18.1%)	94 (31.2%)			
APOE ε2					
Non-carrier (%)	950 (93.2%)	286 (95%)	1.25	0.72	0.264
Carrier (%)	69 (6.8%)	15 (5.0%)			
APOE ε3					
Non-carrier (%)	107 (10.5%)	20 (6.6%)	3.97	1.64	0.046
Carrier (%)	912 (89.5%)	281(93.4%)			

Table 2. Chi-Square Analysis for AD and Categorical Phenotypes *Note.* Due to rounding errors, column wise percentages may not equal 100%. SD, standard deviation; (%) percentage by column; χ^2, chi-square value; p, p-value 0.05.

Table 3: T-Tests Table of AD

AD	Controls (n=1019)		Cases (*n*=301)		
Variable	*M*	*SD*	*M*	*SD*	*p*
AGE	66.93	8.58	77.52	7.72	< .001
BMI	32.12	6.73	30.13	6.31	< .001
Education	10.19	4.70	10.35	4.44	0.599

Table 4. Two-Tailed Independent Samples t-Test for Age, BMI and Education by AD *Note.* N = 1320. Degrees of Freedom for the *t*-statistic = 1318. M, mean; SD, Standard Deviation; p, p-value;

Table 4: Logistical regression for AD and APOE ε4

AD	*B*	*SE*	χ^2	*p*	*OR*	95% CI
Sex	0.03	0.16	0.03	.862	1.03	[0.74 1.41]
Age	0.15	0.01	202.79	< .001	1.16	[1.13, 1.18]
Education	0.01	0.02	0.22	.641	1.01	[0.97, 1.04]
BMI	-0.01	0.01	1.01	.315	0.99	[0.96, 1.01]
APOE ε4	0.65	0.17	13.94	< .001	1.91	[1.361, 2.69]

Table 4. Logistic Regression Results with Sex, Age, Education, BMI, and ε4 Predicting AD.

Note. $X^2(5) = 336.98$, $p < .001$, McFadden $R^2 = 0.24$. B, unstandardized Beta coefficient; SE Standard Error; χ^2, chi-square value; p, p-value; OR, Odd Risk; 95% CI, 95 confidence Intervals

Table 5: Logistical regression for AD and APOE ε3

AD	*B*	*SE*	χ^2	*p*	*OR*	95% CI
SEX	0.04	0.16	0.05	.824	1.04	[0.75, 1.42]
Age	0.15	0.01	204.50	< .001	1.16	[1.13, 1.18]
Education	0.01	0.02	0.28	.594	1.01	[0.97, 1.04]
BMI	-0.02	0.01	1.48	.224	0.98	[-0.04, 1.01]
APOE ε3	0.11	0.29	0.14	.711	1.11	[0.63, 1.96]

Table 5. Logistic Regression Results with Sex, Age, Education, BMI, and ε3 Predicting AD.

Note. $X^2(5) = 323.44$, $p < .001$, McFadden $R^2 = 0.23$. B, unstandardized Beta coefficient; SE Standard Error; χ^2, chi-square value; p, p-value; OR, Odd Risk; 95%CI, confidence Intervals

Table 6: Logistical regression for AD and APOE ε2

AD	*B*	*SE*	χ^2	*p*	*OR*	95% CI
SEX	0.03	0.16	0.04	.842	1.03	[0.75, 1.41]
Age	0.15	0.01	206.93	< .001	1.16	[1.13, 1.18]
Education	0.01	0.02	0.34	.561	1.01	[0.97, 1.04]
BMI	-0.02	0.01	1.48	.223	0.98	[0.95, 1.01]
APOE ε2	-0.57	0.33	2.94	.086	0.56	[0.29, 1.08]

Table 6. Logistic Regression Results with Sex, Age, Education, BMI, and ε2 Predicting AD

Note. $X^2(5) = 326.45$, $p < .001$, McFadden $R^2 = 0.23$. B, unstandardized Beta coefficient; SE Standard Error; χ^2, chi-square value; p, p-value; OR, Odd Risk; 95% CI, 95 confidence Interval

Table 7: Chi-Square Analysis for MCI

MCI	Control (n=993)	Cases (n=327)	χ^2	OR	*p*
SEX					
Female	704 (71%)	217 (66%)	2.40	0.37	0.121
Male	289 (29%)	110 (34%)			
Anxiety					
Absent	689 (69%)	199 (61%)	8.13	0.78	0.004
Present	304 (31%)	128 (39%)			
Motor disturbance					
Absent	867 (87%)	284 (87%)	0.05	0.24	0.829
Present	126 (13%)	43 (13%)			
Depression					
Absent	608 (61%)	177 (54%)	5.14	0.71	0.023
Present	385 (39%)	150 (46%)			
APOE ε2					
Non-carriers	932 (94%)	304 (93%)	0.33	4.02	0.567
Carriers	61 (6%)	23 (7%)			
APOE ε3					
Non-carriers	101 (10%)	26 (8%)	1.39	1.65	0.238
Carriers	892 (90%)	301 (92%)			
APOE ε4					
Non-carriers	779 (78%)	263 (80%)	0.58	0.45	0.447
Carriers	214 (22%)	64 (20%)			

Table 7. Chi-Square analysis for MCI. *Note.* Values formatted as Observed (Percentage) x^2, *c*hi-square value; p, p-value; OR, Odd Risk

Table 8: T-Test for MCI

MCI	Control (n=993)		Cases (n=327)		
	M	*SD*	*M*	*SD*	*p*
Age	67.83	9.26	73.97	8.67	< .001
Education	10.22	4.59	10.22	4.80	0.983
BMI	31.61	6.80	31.83	6.32	0.593

Table 8. Two-Tailed Independent Samples t-Test for Continues Variables: Age, Education and BMI by MCI *Note.* N = 1320. Degrees of Freedom for the *t*-statistic = 1318. M mean; SD, Standard Deviation; p, p-value.

Table 9: Demographic table for Psychiatric disorder in AD participants

	Anxiety (N=301)		Depression (N=327)	
	Controls (N=127)	Cases (N=174)	Controls (N=119)	Cases (N=182)
Age (mean ± SD)	76.92 ± 7.61	77.97 ± 7.79	78.41 ± 7.47	76.96 ± 7.84
Education (mean ± SD)	10.57 ± 4.37	10.18 ± 4.49	10.72 ± 4.42	10.10 ± 4.40
BMI (mean ± SD)	30.51 ± 6.53	30.03 ± 5.72	29.68 ± 5.80	30.60 ± 6.23
SEX (%)				
Female (%)	75 (59%)	121 (70%)	71 (60%)	125 (69%)
Male (%)	52 (41%)	53 (30%)	48 (40%)	57 (31%)
APOE ε4				
Non-carrier (%)	90 (71%)	117 (67%)	86 (72%)	121 (66%)
Carrier (%)	37 (29%)	57 (33%)	33 (28%)	61 (34%)

Table 9. Frequency Table for Anxiety and Depression in AD *participants Note.* Due to rounding errors, column wise percentages may not equal 100%. SD, Standard Deviation; (%), percent by column

Table 10: Chi-Square Analysis for Anxiety and categorical variables in AD participants

Anxiety	Controls (N=127)	Cases (N=174)	χ^2	OR	*p*
SEX					
Female (%)	75 (59%)	121 (70%)	3.55	0.63	0.059
Male (%)	52 (41%)	53 (30%)			
APOE ε4					
Non-carrier (%)	90 (71%)	117 (67%)	0.45	1. 85	0.503
Carrier (%)	37 (29%)	57 (33%)			

Table 10. Chi-square analysis for Anxiety in AD participants. SD, standard deviation; (%) percentage by column; χ^2, chi-square value; p, p-value 0.05.

Table 11: T-Test for Anxiety and continues variables in AD participants

Anxiety	Controls (N=127)		Cases (N=174)		
	M	*SD*	*M*	*SD*	*p*
AGE	76.92	7.61	77.97	7.79	0.247
BMI	30.51	6.53	30.03	5.72	0.497
EDUCATION	10.57	4.37	10.18	4.49	0.460

Table 11. Two-tailed independent samples t-test for age, BMI, and education by anxiety in AD participants *Note.* N = 301. Degrees of Freedom for the *t*-statistic = 299. M, mean; SD, standard deviation; p, p-value.

Table 12: Chi-Square Analysis for Depression and categorical variables in AD participants

	Depression				
	Controls (N=119)	Cases (N=182)	χ^2	OR	*p*
Sex					
Female (%)	71 (60%)	125 (69%)	2.58	0.67	0.109
Male (%)	48 (40%)	57 (31%)			
APOE ε4					
Non-carrier (%)	86 (72%)	121 (66%)	1.12	1.31	0.290
Carrier (%)	33 (28%)	61 (34%)			

Table 12. Chi-square analysis for Depression and categorical variables *Note.* N = 301. Degrees of Freedom for the *t*-statistic = 299 SD, standard deviation; (%) percentage by column; χ^2, chi-square value; OR, Odd risk; p, p-value 0.05.

Table 13: T-Test for Depression and continues variables in AD participants

Depression	Controls (N=119)		Cases (N=182)		
	M	*SD*	*M*	*SD*	*p*
Age	78.41	7.47	76.95	7.84	0.107
Education	10.72	4.42	10.10	4.44	0.234
BMI	29.68	5.80	30.60	6.23	0.202

Table 13. Two-tailed independent samples t-test for age, BMI, and education by Depression in AD participants *Note.* N = 301. Degrees of Freedom for the *t*-statistic = 299. M mean; SD, Standard Deviation; p, p-value.

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BIOGRAPHICAL SKETCH

Kimberly Moreno is a first-generation college student and first in her family to attend graduate college, which is a tremendous honor for her. She graduated from JCECHS and STC on Spring 2015, with a dual enrollment program, allowing her to obtain an Associate`s Degree in Interdisciplinary Studies and a High School diploma, simultaneously. In Fall 2015, she went on to pursue her bachelor's degree in Biology and during her time as an undergrad, she volunteered in numerous locations such as local hospitals, health clinics, humanitarian respite centers and as a volunteer in service-learning trips in Peru. She obtained her undergraduate degree in August 2019. Soon after graduating she enrolled in a graduate program, Biochemistry and molecular biology. During her time as a graduate, Kimberly took part in research with Dr. Xu, an associate professor of the Biomedical Science department in UTRGV. As a graduate, she mentored undergraduates in Dr. Xu's lab and worked along her PI to obtain data for her research, ISLD-RGV. Additionally, she worked as a graduate teaching assistant and graduate research assistant during her graduate program. Finally, as a graduate from a master's program, Biochemistry and Molecular Biology from University of Texas Rio Grande Valley in December 2020, she hopes to continue her education until the maximum capacity, a doctorate.

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