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Differences in Cognitive and Neuropsychiatric Symptoms and their Correlates in Individuals with Alzheimer's Disease across Different Racial/Ethnic Groups

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Abstract

[Alzheimer's disease (AD) is the most common form of dementia and is characterized by the formation of neurofibrillary tangles and amyloid-beta plaques. The three aims of the study were to examine whether the severity of cognitive impairment and neuropsychiatric symptoms (NPS) in AD patients varies with racial/ethnic status, to examine whether the relationship between cognition and NPS differs with race/ethnicity, and to examine whether the relationship of Apolipoprotein E (ApoE) status to cognition and NPS varies with race/ethnicity. Final sample consisted of 10,014 participants, of which 80.27% identified as White, 11.64% identified as African-American and 8.09% identified as Hispanic/Latinx. With regard to the first aim, scores on two cognitive tests significantly differed between the groups, with Mini Mental State Exam (MMSE), $F(2,8877)=14.483$, $p<.001$, and Clinical Dementia Rating (CDR), $F(2,10009)=14.485$, $p<.001$, with the White group generally performing best and the Hispanic/Latinx group performing worst. Furthermore, total Neuropsychiatric Inventory (NPI) scores showed differences between groups of different racial/ethnic identities, $F(2,9754)=30.899$, $p<.001$ and a pattern similar to that of cognition was observed. With regard to the second aim, the general pattern was that worse cognition was related to worse NPS scores, but that the relationship of NPS to cognitive scores did not seem to differ by racial/ethnic group. ApoE status did not seem to differ by racial/ethnic groups since all three racial/ethnic group was equally affected by the ApoE ε4 allele. In conclusion, there were some racial/ethnic differences in cognitive impairment and NPS across the three racial/ethnic groups. However, their relationship to one another and to a risk factor for AD, such as ApoE status, did not differ by racial/ethnic groups. Racial/ethnic differences that occurred that cannot be explained by socioeconomic differences and a greater number of minority groups into studies is needed.]

Keywords: Alzheimer's disease, neuropsychiatric symptoms, racial differences, diverse populations

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that was first described in the 1900s by Dr. Alois Alzheimer. AD is a prevalent disease in older adults that results in atrophy of white and gray matter in the brain. The deterioration of neurons in the brain is characterized by the formation of neurofibrillary tangles and amyloid plaques and may lead to a wide range of deficits, including aphasia, memory impairment, mild cognitive decline which eventually develops into dementia, and neuropsychiatric symptoms (NPS) such as anxiety, delusions, depression, agitation and more (Alzheimer's Association, 2010). Tangles and plaques in the brain may begin more than 25 years before the clinical signs of AD in some individuals (Burke et al., 2016). The early development of tangles and plaques is not used to diagnose AD because they are difficult to detect in situ and many people have amyloid plaques but no signs of dementia, cognitive decline or AD (Johnson et al., 2013). However, evidence suggests that tangles and plaques are hallmark features in the pathological diagnosis of AD (Albert et al., 2011). Because they are difficult to detect, AD is clinically diagnosed based on the presence of cognitive decline and NPS.

Cognitive Symptoms in AD

Some symptoms, such as memory decline and NPS, may appear before the diagnosis of AD (Tarawneh et al., 2012) and are part of the diagnostic criteria as described by the National Institute of Neurological and Communicative Diseases and Stroke/ Alzheimer's Disease and Related Disorders Association, or NINCDS/ADRDA (Albert et al., 2011, McKhann et al., 2011). Being able to properly identify these symptoms may aid in detecting AD earlier and may lead to better treatment and preventative measures; no current treatment can prevent the eventual progression of AD, and no current treatment is particularly effective (Salloway et al., 2014).

Cognitive symptoms seen in AD include the inability to learn new information, memory impairment, difficulty performing multistep tasks, and language changes. The progression of cognitive decline usually occurs in three general stages – mild cognitive impairment (MCI), moderate impairment, and severe impairment, commonly referred to as dementia (Alzheimer's Association, 2010). AD is known to be the most frequent cause of dementia (Galvin & Karantzoulis, 2011). Prevalence of dementia has been shown to increase exponentially with increasing age and doubles every five years of age after age 65 (Jolley & Jorm, 1998). The cognitive symptoms of dementia lead to difficulty performing basic everyday functions (Galvin & Karantzoulis, 2011).

The cognitive symptoms in AD are clearly related to the anatomical brain changes seen in AD. Studies have shown that hippocampal volume loss is significant in AD patients, which may explain why memory decline is a prevalent symptom of the disease (Jack et al., 2013; Seab et al., 1988, Sperling et al., 2011). Disruptions in white matter are suggested to lead to subtle cognitive impairments (Lockhart et al., 2014). In addition, other studies have noted other neurophysiological changes in AD and their correlation with cognition. For example, it has been hypothesized that accumulation of neurofibrillary tangles in the prefrontal cortex is reflected in deficits in executive function, while neurofibrillary changes in the hippocampus and the entorhinal cortex may be linked to changes in episodic memory (Weintraub et al., 2012). As the disease begins to progress, many of the cognitive symptoms are coupled with behavioral and psychological symptoms.

Neuropsychiatric Symptoms (NPS) in AD

NPS seen in AD include the non-cognitive, psychological and behavioral symptoms of the disease, such as apathy, depression, agitation, psychosis, aggression, psychosis, and more (Li et al., 2014). These symptoms are also likely related to the neurophysiological changes seen in the brains of individuals with AD. Recent research has shown how neuronal connections exist between the epicenters

of two parts of the brain that deal with emotions and cognition (Geda et al., 2013), the association and limbic areas of the cerebral cortex. For example, Rafii et al. (2014) reviewed the relationship between regional neocortical atrophy and psychotic symptoms in adults with AD and showed that atrophy rate of the lateral frontal lobe was most associated with the presence of psychotic symptoms. Hirao et al. (2015) also reviewed the literature on structural and functional brain findings related to psychiatric symptoms in AD and concluded that the presence of psychotic symptoms is related to abnormal dorsolateral frontal and medial temporal functional imaging findings, while the presence of depressive symptoms is associated with anterior cingulate and superior temporal changes, as well as dorsolateral prefrontal cortex (DLPFC), right middle temporal, and right parietal hypo-metabolism. In addition, the presence of emotional lability was associated with abnormal functional imaging findings in the anterior cingulate and DLPFC and left basal ganglia, while the presence of apathy was related to basal ganglia, DLPFC, anterior cingulate and medial orbitofrontal cortex abnormalities. Finally, the presence of anxiety was associated with abnormal functional imaging findings in temporal-limbic structures, including entorhinal cortex, para-hippocampal gyrus and insula.

Although it is well known that cognitive decline is a hallmark of AD, growing research suggests that NPS is also highly prevalent in individuals with AD and may increase risk of diagnosis (Pietrzak et al., 2012). In fact, Dr. Alzheimer noted that his first patient presented more NPS than cognitive symptoms. Almost all people with AD develop at least one NPS throughout the course of their disease (Lyketsos et al., 2012). The most prevalent NPS in AD is apathy, with a prevalence of 49%, followed by aggression, sleep disorder, anxiety and depression (Zhao et al., 2016).

Not only are NPS seen frequently in AD, but NPS contribute significantly to the cost of AD. Evidence indicates that caregivers who tend to AD patients exhibiting moderate to severe NPS have the highest caregiver burden (Rocca et al., 2010). Increasing levels of caregiver burden often lead to earlier

institutionalization and increased cost to care for the AD patient (Rocca et al., 2010). Both cognitive deterioration and presence of NPS are important factors to assess in AD because they contribute to early institutionalization, increased caregiver burden, decreased quality of life in both patient and caregiver and many more detrimental outcomes (Andrieu et al., 2016; Garcia-Alberca et al., 2013, Raggi et al., 2015).

Cognitive Symptoms and NPS in Diverse Populations

Although both cognitive impairment and NPS may be present in some individuals with AD, some research suggests that cognitive symptoms and NPS may manifest differently in individuals from various racial/ethnic backgrounds. There are several reasons this might be the case, including both cultural and genetic contributions. With regard to genetic contributions, which alleles of the Apolipoprotein E (ApoE) gene are present predict the risk of AD, which may contribute to differences in rates of cognitive changes and dementia in various groups (Fillenbaum et al., 2001). With regard to cultural contributions, for example, evaluation of the severity of, and distress about, NPS exhibited could be confounded by cultural beliefs, leading them to be interpreted as signs of normal aging, while in other cultures, these symptoms could be viewed as abnormal (Stella et al., 2015). However, this area of research has been relatively unexplored; in fact, many studies lack enough racial/ethnic diversity to examine this issue or do not report inter-group diversity.

The purpose of the present study is to examine whether there are racial/ethnic differences in the severity of cognitive impairment and the severity of NPS in individuals with AD who were research participants in a large multi-site study of AD (Uniform Data Set; National Alzheimer's Coordinating Center; Alzheimer's Disease Center Program, 2017). Prior to presenting the study, a review of how cognitive changes and NPS are assessed will be presented. Then, the variability in cognitive impairment across different racial/ethnic groups and the genetic and sociocultural factors that influence it will be

reviewed. Lastly, the frequency and variability in NPS across different racial/ethnic groups and the potential genetic and sociocultural influences on NPS will be reviewed as well.

Measurement of Cognition and NPS

To see which racial/ethnic groups have the highest prevalence of severe cognitive impairment and NPS, the severity and frequency of cognitive impairment and NPS must be assessed. Existing studies vary in the way that these factors are assessed, with strengths and weaknesses to various methods.

To measure cognitive impairment, the most common tools in the literature are the Clinical Dementia Rating (CDR) and the Mini Mental State Exam (MMSE). The CDR is a 5-point scale that evaluates the six domains of Alzheimer's disease that affect cognition or the patients' ability to function independently. These domains include the personal care, orientation, judgement and problem solving, community affairs, memory, and home and hobbies (Morris et al., 1997). The clinician makes these evaluations by rating specific patient symptoms on a scale from very mild dementia to severe. This measure is the subjective determination of the clinician and is based on their clinical impression, not any formal testing. The MMSE, on the other hand, is a 30-point test that is used to document cognitive impairment by directly assessing different cognitive domains or functions (Tombaugh et al., 1996). Tombaugh et al. (1996) showed that the MMSE is highly sensitive to moderate to severe cognitive impairment but showed low levels of sensitivity for mild cognitive impairment. Since both the MMSE and CDR measures are not sensitive to the important cognitive changes in early dementia, these tests by themselves should not be used as a diagnostic tool for assessing and identifying dementia; however, in many large epidemiological studies, these are the only cognitive tests available. In addition, cognitive measures can also be affected by several socioeconomic factors, such as education. This may also be a

confound for any study of racial/ethnic differences, given that lower education rates may be related to racial/ethnic status (Evans et al., 1997).

The most common way to measure NPS is the Neuropsychiatric Inventory (NPI). The NPI is a 12-item questionnaire that can be used to assess changes in behavioral and psychological disturbances in an AD patient (Cummings 1997). The NPI score is calculated by multiplying the frequency score, which is how often each of the 12 symptoms occur, by the severity score, which is how severe the symptom is. The NPI is sometimes filled out by a clinician but usually filled out by a caregiver. Caregiver reports are susceptible to caregiver bias, in that their own psychological concerns may be strongly related to their ratings of the patients' NPS (Stella et al., 2015). However, clinician reports may also be biased in that the clinician does not have knowledge of the daily behaviors of the AD patient, and clinicians often use a caregiver's report as a basis for clinician ratings (Lyketsos et al., 2012). In a recent study, it was shown that the biggest inconsistency in NPI scores between caregivers and clinicians occurred when patient depression was being assessed. The caregivers' scores ranged from +22.5 higher to -4.5 lower than the clinicians' ratings (Stella et al., 2015). Common discrepancies also occur when assessing anxiety, agitation, irritability and aberrant motor behavior in patients with mild dementia due to AD, according to Stella et al. (2015). As mentioned, one reason for the discrepancies that arise could be the amount of time both clinicians and caregivers spend with the patient. Clinicians only interact with the patient at the time of the assessment, while caregivers may spend the majority of their time with the patient; however, in some studies, caregivers are not spending enough time assessing the patient (Lyketsos et al., 2012). Because of these issues, it is important to examine how knowledgeable the caregiver is about the AD patient when considering caregiver report of NPS.

Variability in Cognitive Impairment across Different Groups

An increasing number of studies have been done to explore the variability in cognitive decline across various racial/ethnic groups, although more studies are needed. Per the Health and Retirement Study, the prevalence of moderate to severe cognitive impairment in AD patients aged 65 and older was 10.5% in 2010. However, racial/ethnic differences in prevalence were noted; rates were 8.8% in Whites, 23.9% in African Americans, and 17.5% in Hispanic/Latinx. African Americans are two to three times more likely to develop more severe cognitive impairments over the course of their disease (Alzheimer's Association, 2010, Schwartz et al., 2003).

Several factors might be related to these cognitive differences. For example, one contributor might be genetic differences. Other potential contributors to racial/ethnic differences in cognitive impairment in AD are sociocultural differences such as in education level, differences in socioeconomic status (SES), access to health care, risk behaviors and preventative measures.

Apolipoprotein E

A genetic predictor of AD is the Apolipoprotein E gene (ApoE). The protein encoded by the ApoE gene combines with lipids to produce lipoproteins, whose role is to aid in the packaging and transport of cholesterol. Disruption of the ApoE in humans and transgenic mice leads to abnormal cholesterol levels, which may lead to cardiovascular diseases and thus may raise the risk of dementia (Liu et al., 2013). ApoE also seems to be directly involved in neural restoration and synaptogenesis (Mahley et al., 2012). Another study suggests that the ApoE gene may be involved in maintaining synapto-dendritic connections following brain injury (Mahley et al., 2006). Some ApoE is needed for these functions but the ApoE ε4 allele is associated with deficits in neurite outgrowth, disrupts neuronal cytoskeleton, magnifies amyloid beta accumulation, and progresses tau-mediated degeneration of nerve cells (Mahley et al., 2006).

Although the complete mechanism behind why ApoE ε4 increases risk of AD is not fully understood, there is a widely-known relationship between having even one ε4 allele and typical-age AD (Tang et al., 1998). Individuals who are homozygous for the ApoE ε4 allele have an even higher risk of being diagnosed with AD compared with individuals with the ApoE ε2 or ε3 allele. (Murrell et al., 2006). The ε2 allele is associated with lower risk of AD compared to the ε3 allele.

The ε4 allele, which increases one's risk to Alzheimer's disease, is more prevalent in some racial/ethnic groups than others. Researchers have found higher rates of ε4 in African Americans but equivalent rates of ε4 in Whites and Hispanic/Latinx (Tang et al., 1998). Logue et al. (2011) also showed a higher rate of ε4 alleles in African Americans versus White control samples in a very large study. If cognitive symptoms and NPS are related to ApoE status, then different rates of ε4 alleles could explain differences in cognitive performance and presence of NPS across different racial/ethnic groups.

However, there is some evidence that the risk of getting AD in people who have the ε4 allele differs by racial/ethnic group status. Although the ε4 allele has been shown to increase one's risk of AD in all ethnic groups (Murrell et al., 2006), some early studies suggested that the risk increases disproportionately across various ethnic groups (Green et al., 2002, Kalaria et al., 1997, Maestre et al., 1995, Sahota et al., 1997, Tang et al., 1998). For example, Tang et al. (1998) investigated the association of the ApoE ε4 allele and AD in older African American, Hispanic/Latinx, and White communities. Their results confirmed that ApoE genotypes influence the relative risk of AD in Whites and Hispanic/Latinx. However, the relative risk (RR) of developing AD was increased due to the ApoE ε4 allele for Whites (RR=2.5), but not for Hispanic/Latinx (RR=1.1) and African Americans (RR=1.0). The results obtained from this study led to the conclusion that the presence of the ε4 allele is an element of AD risk in Whites, but African Americans and Hispanic/Latinx have increased prevalence of AD

diagnosis regardless of their ApoE genotype. Other older studies have also shown that the presence of the ε4 allele only marginally increases the risk of AD diagnosis for African Americans and Hispanic/Latinx due to weaker association of the ε4 allele and incidence of AD (Green et al., 2002, Kalaria et al., 1997, Maestre et al., 1995, Sahota et al., 1997). However, other studies, including more recent ones, have shown that there is no difference in the increased risk of AD with ApoE ε4 genotype across different racial/ethnic groups (Fillenbaum et al., 2001, Graff-Radford et al., 2002, Jun et al., 2010, Sawyer et al., 2009). For example, Sawyer et al. (2009) had bigger samples and more accurate measures of cognitive functioning than most of the other studies examining this issue and they found similar association of ApoE ε4 and dementia in African Americans versus Whites. Overall, these findings are mixed, but some results suggest that other cofounding factors may play a role in the disproportionate frequency of AD in certain racial/ethnic groups, such as SES or other factors that impact health outcomes (Green et al., 2002).

Interestingly, the effects of NPS and ApoE genotype seem to increase the risk of AD diagnosis separately, but when these factors occur simultaneously, the risk of AD diagnosis multiplies. Burke et al. (2016) provided evidence that there is an increased risk of individuals developing AD if at least one symptom assessed by the NPI is present. It is important to note that the participants used in the Burke et al. (2016) study were from the NACC but from a sample that was cognitively intact, and they were studied over time. In other words, at baseline when the study was done, there were no observable signs of AD. The NPI was completed by caregivers as opposed to trained health professionals. The risk of AD in this sample increased by a multiple of 13 if the individual was an ε4 carrier with delusions. The risk of AD diagnosis was 11x higher for individuals who displayed apathy and disinhibition who were also ε4 carriers (Burke et al., 2016). However, their study did not examine whether the results varied

depending on ethnicity, even though ethnicity percentages were noted in their tables. Also, this study failed to study differences in NPS or ApoE genotype between the different racial/ethnic groups.

Sociocultural Factors affecting Cognitive Impairment

Studies have shown that individuals with lower SES and education are at increased risk of AD diagnosis (Chow et al., 2002, Evans et al., 1997, Sawyer et al., 2009). A study performed by Schwartz et al. (2003) found statistically significant differences in cognitive scores, with African Americans scoring lower than Whites in both men and women. However, when SES was accounted for, there was a 25.8% decline in the differences in scores between the racial/ethnic groups, suggesting that a large part of the differences in scores was due to SES. It is also important to note that in their study, the White group had higher overall educational attainment than the African American sample. Since low levels of educational attainment are related to increased risk of cognitive decline, this may also explain the differences observed in cognitive impairment across various racial/ethnic groups.

In addition, there are differences in health problems that may increase risk of AD in different racial/ethnic groups. For example, African American populations may be at higher risk of developing AD due to higher rates of hypertension, cardiovascular disease, diabetes and other health risks for AD (Barnes & Bennett, 2014). This suggests that diabetes, hypertension and cardiovascular disease potentially increases one's risk of AD as stated in Barnes & Bennett (2014). Barnes & Bennett (2014) also did not incorporate Hispanic/Latinx samples in their study. Finally, it is possible that there is bias in the measures of cognitive impairment that are commonly used in these studies. For example, it is possible that these measures are not reflecting the effects of cognitive impairments but instead are administered or scored differently by clinicians who are working with diverse individuals.

Frequency and Variability of NPS in Different Groups

The prevalence of NPS in AD patients has been suggested to be influenced by population of origin (See Tables 1 and 2). For example, in one recent study, it was found that Chinese caregivers reported higher rates of anxiety and delusions (58.1% and 58.1%) in the individuals they cared for than the caregivers of Whites (37.3% and 39.6% respectively), but there were otherwise no differences in rates of various NPS across their samples (Chow et al., 2002). However, they also noted that the White sample of patients had a higher educational level on average, which was correlated with milder CDR scores in the patients. This may imply that the White sample had higher cognitive functioning, which perhaps would be related to less severe NPS. This was the only study that actually examined differences within their own data with statistical tests. Although Burke et al. (2016) did not statistically test for differences within their samples, examination of their data suggests that there may be some differences in NPS across different racial/ethnic groups. For example, the trend observed is that Hispanic/Latinx had the highest rates of NPS, while African Americans had the lowest rates (per Table 2). Also, it is of importance to note that the patients were rated by their caregiver at time 1, when the patients did not have dementia yet; thus, the percentages overall are much lower than any other studies in Table 2. For example, in some studies, the participants are analyzed before the diagnosis of AD. In other studies, the analyzed participants were already diagnosed with AD. In the Garcia-Alberca et al. (2013) paper, which could be more appropriately compared to the Chow et al. (2002) samples because of the reports of other factors that may have influenced the ratings, apathy was reported as very highly prevalent (92%), while rates of euphoria seemed to be very low in comparison. Across all the studies, one thing that stayed consistent was that all studies included a limited number of minority patients, so that could have confounded the data comparisons.

Possible causes for potential racial/ethnic differences in NPS rates include differences in the ApoE ε4 allele frequency between the different races, as reviewed above, the likelihood of the differences

being related to brain changes, which may result in different symptom presentation, or even sociocultural differences. This might vary with ethnicity because it is possible that certain racial/ethnic groups are more susceptible to disease and neurodegeneration than others. However, further research is needed to explore these possibilities.

Sociocultural Influences on NPS

As noted above, NPS are typically rated by caregivers, and caregiver mental health factors could be related to the ratings they provide (Burke et al., 2016, Chow et al., 2002, Garcia-Alberca et al., 2013). Caregiver burden refers to the negative emotional responses associated with being a caregiver to a patient (Alzheimer's Association, 2010). Caregiver burden is usually measured by administering a questionnaire to the caregiver that asks them to assess the burden that is associated with certain caregiving tasks that they are obligated to perform (Macera et al., 1993). Caregiver burden is an important variable to consider in AD because it is strongly linked to instutionalization of the AD patient and need for interventions for the caregiver (Morycz et al., 1985, Pruchno et al., 1990).

There exist some evidence that environmental and cultural factors may be related to the caregiver's rating of NPS. Brown et al. (2013) suggests that some of the disparities in ratings might be related to the education level of the caregiver. For example, caregivers with higher educational attainment provided higher quality care as evaluated by a caregiver survey, suggesting that educational gradient properties also apply to the caregiver. It may be easier for people with higher education to have the cognitive resources to provide better caregiving and be less burdened by an AD patient's NPS. Another factor might be disparities in treatment of AD in minority groups. Kalkonde et al. (2009) described differences in treatment of AD in those from different racial/ethnic groups, which then could lead to increased burden if there was less appropriate treatment in minority patients with dementia. For example, a patient experiencing fewer NPS due to taking appropriate medications may lead to lesser burden in caregivers.

Hernandez et al. (2010) came to a similar conclusion as the previous papers, which is that African Americans are less likely to receive the right medication to treat AD and that participants with higher educational attainment and MMSE scores had higher usage of the prescribed medicine. This suggests that African Americans are not receiving proper medication, perhaps as a function of their lower education and SES. Thus, patients and their caregivers who have lower education, lower SES, or come from minority groups may not have the appropriate resources needed to access information pertaining to AD or even facilities and/or institutions that specialize in treating this disease. This may increase patient cognitive symptoms and NPS and thus lead to higher caregiver burden.

As mentioned earlier in the thesis, caregiver distress may also be related to perceiving more symptoms in the patients they care for. For example, if the caregivers report higher rates of burden, then they may also rate severity of NPS higher. This may account for the differences seen in NPS scores between different racial/ethnic groups, because if caregivers from a certain racial/ethnic are more likely to be burdened and stressed, then that may affect their ratings of those symptoms. In addition, cultural factors may play a role in the caregiver report of symptoms and caregiver ratings of burden. For example, research suggests caregiver burden varied between different cultures, as some cultures deemed the symptoms due to AD as a part of 'normal aging' (Schwartz et al., 2003). Another study suggested that NPS may be viewed as signs of normal aging while other cultures view them as abnormal, which results in differences in ratings across various racial/ethnic groups (Stella et al., 2015). An example from the literature of cultural context would include how in Brazil, women, specifically daughters and spouses, are required to carry out care for patients with dementia. Individuals from cultures who view NPS as abnormal are more likely to rate the symptoms more harshly as opposed to individuals from cultures who think the NPS present is normal for that age.

In summary, the reviewed literature suggests that NPS and rate of cognitive decline in AD manifest differently across different racial/ethnic groups. However, racial/ethnic differences may be related to genetic factors, such as ApoE ε4 status, environmental factors, such as SES and fewer years of education, cultural factors, or bias factors, such as differences in treatment.

Existing literature is limited by a significant lack of diversity along racial/ethnic lines in many studies, making it difficult to examine potential differences. Further, extremely diverse SES and education levels may contribute to the differences in results between racial/ethnic groups. Further research needs to be conducted to examine whether there are differences in cognitive impairment and NPS in different racial/ethnic groups with consideration for education or SES differences. In addition to this, greater incorporation of African Americans and Hispanics/Latinx in studies is essential in hopes of examining the many factors of Alzheimer's disease so that these groups can be better represented.

The Present Study

The primary aim of this thesis was to examine whether the severity of cognitive impairment and NPS in AD patients varies by racial/ethnic status. As noted above, only a few studies have examined this issue, some suggest there may be differences, but that those differences may be influenced by other factors such as the education level of both the patient and the caregiver, ApoE status of the patient and other socioeconomic factors.

A secondary aim was to examine whether the relationship between cognition and NPS differs by race/ethnicity. While studies show that cognitive impairment is related to presence of NPS, it is not clear that this relationship holds true across different racial/ethnic groups.

The third aim was to examine whether the relationship of ApoE status to cognition and NPS varies by race/ethnicity. As reviewed above, there has been mixed evidence about whether the relationship between ApoE status and cognition/NPS differs in different racial/ethnic groups.

Method

Participants

Participants used in the study were collected from the Uniform Data Set (UDS) of the Alzheimer's Disease Centers (ADC) program of the National Institute on Aging (UDS (2017); National Alzheimer's Coordinating Center; Alzheimer's Disease Center Program), which is a publicly available dataset of a prospective, standardized, and longitudinal clinical evaluation of patients with AD in the National Institute on Aging's ADC Program. The data was obtained between the years of 2005 and 2017. For this thesis, access was requested for data from the first visit for all participants diagnosed with AD, if their data included patient demographics, caregiver demographics, performance on the MMSE and CDR, scores on the NPI, patient medical history, dementia diagnostic history, and ApoE status. These are the measures that were specifically used and analyzed in the thesis.

UDS originally provided a dataset of 13,036 participants. The final sample for this thesis consisted of 10,014 participants. Figure 1 shows the criteria for exclusion of the 3,022 participants from the study. Participants were excluded if they had a paid caregiver rather than an informal caregiver, if the caregiver had been coded as providing unreliable data, if the patient or caregiver reported more than one racial/ethnic identity, if the patients' or their caregivers' Hispanic/Latinx identity was unknown, if the participants' or their caregivers' racial/ethnic identity was not reported as African-American, White or Hispanic/Latinx, or if important demographic factors such as age or education level were unknown.

Of the final sample of participants, 80.27% identified as White, 11.64% identified as African-American and 8.09% identified as Hispanic/Latinx. Caregiver racial/ethnic distribution was very similar, with Whites making up 80.18% of the sample, African-Americans making up 11.38%, and Hispanics/Latinx making up 8.44% of the sample. Overall, participant and caregiver reported racial/ethnic status was almost always congruent; 98.7% of participants who identified as White had a

caregiver who identified as White, 96.5% of participants who identified as African-American had a caregiver who identified as African-American, and 91.9% of participants who identified as Hispanic/Latinx also had a caregiver who identified as Hispanic/Latinx. The overall mean age for all participants was 75.0 years old and participants' overall mean education level was 12.58 years. The overall mean age for all caregivers was 60.00 years and caregivers' overall mean education level was 14.57 years. The study participants were 45.8% male and 54.2% female. The study caregivers were 32.7% male and 67.3% female.

Among the caregivers, 59.2% were the spouse, partner, companion, significant others, common-law partners, life partners, boyfriends, girlfriends, live-in partner or fiancés of the participants. Another 30.04% were children of the participants, and 2.89% were siblings of the participants. Other relatives, stepparents, adopted family, in-laws, grandchildren, legal guardians and parents were 3.88% of the caregivers, and 3.9% were friends, neighbors, god-children, pastors, religious sisters, house keepers, exes, separated partners, and colleagues of the participants.

There were some patient demographic differences by racial/ethnic status. See Table 3. Age differed among the groups, $F(2,10011) = 15.089$, $p<.001$, with the White sample younger than the African-American sample, $p<.001$, and the African-American sample older than the Hispanic/Latinx sample, $p<.001$. Participant age did not differ significantly between the Hispanic/Latinx and White samples, $p=1.000$. Education also varied among the groups, $F(2,10011) = 1121.73$, $p<.001$, with the White sample having significantly more education than the African-American sample, $p<.001$, and the Hispanic/Latinx sample having significantly less education than the White sample, $p<.001$, and the African-American sample, $p<.001$. There were gender differences by participant racial/ethnic status, $\chi^2(2,10014)=180.571$, $p<.001$. Males made up 49.12% of the White participants, 30.52% of the African-American participants, and 35.27% of the Hispanic/Latinx participants. These differences reflect the

male to female ratio in the elderly for the different racial/ethnic groups. Note that a study done by Van Den Eeden et al. (2003) on Parkinson's disease showed that the Hispanic/Latinx sample had the highest age- and gender-adjusted incidence rates, followed by Whites, and African Americans. They also found that amongst those three racial/ethnic groups, incidence of the disease was approximately twofold higher in men than the incidence among women.

There were also caregiver demographic differences by racial/ethnic status. Caregiver age differed among the groups, $F(2,10011) = 317.165$, $p<.001$, with the White caregivers older than the African-American caregivers, $p< .001$ and the Hispanic/Latinx caregivers, $p<.001$. The African-American caregivers were older than the Hispanic/Latinx caregivers, $p<.001$. Caregiver age did not differ significantly between the Hispanic/Latinx and White caregivers, $p=1.000$. Caregiver education also varied among the groups, $F(2,10011)=310.693$, $p<.001$, with the White caregivers having significantly more education than the African-American caregivers, $p<.001$and the Hispanic/Latinx caregivers having significantly less education than the White caregivers, $p<.001$, and the African-American caregivers, $p<.001$. There were also gender differences in caregivers by their racial/ethnic status, $\chi^2(2,10014)=58.529$, $p<.001$. Males made up 34.46% of the White caregivers, 24.65% of the African-American caregivers, and 26.75% of the Hispanic/Latinx caregivers.

Measures

The CDR is a 5-point scale that evaluates the six domains of Alzheimer's disease that affect cognition or the patients' ability to functionally perform. These domains include the personal care, orientation, judgement and problem solving, community affairs, memory, and home and hobbies (Morris et al., 1997). Higher scores on the CDR means there is a greater severity of dementia. The CDR score was used as one measure of cognitive impairment in this thesis.

The MMSE is a 30-point test that is used to document cognitive impairment by directly assessing different cognitive domains or functions (Tombaugh et al., 1996). Higher scores on the MMSE are generally related to better performance on cognitive tests. The total score on the MMSE, in which participants can receive a maximum score of 30, was used as a second measure of cognitive impairment in this thesis.

NPI is a 12-item questionnaire that can be used to assess behavioral and psychological disturbances in an AD patient (Cummings 1997). In the UDS dataset, the NPI was rated by a caregiver. In regard to this particular thesis, only informal caregivers were used as opposed to paid caregivers. Subscales of the NPI include agitation, anxiety, apathy, appetite, delusions, depression, disinhibition, elation, hallucination, irritability, motor disturbance and nighttime behaviors. Higher scores on these subscales indicate greater severity of the specific symptom. In this thesis, total scores and subscale scores were used to indicate severity of neuropsychiatric symptoms in the patients.

ApoE is a known genetic risk factor for developing AD. Individuals with ApoE ε4 status in particular are at a disproportionate risk for developing AD (Graff-Radford et al., 2002). For this thesis, ApoE status was coded as positive for individuals who had either one or two ε4 alleles and coded as negative for individuals with absence of the ε4 allele.

Analyses

For all analyses, only $p<.001$ findings will be interpreted, due to the size of the sample and the number of analyses conducted.

The first study aim was to examine whether the severity of cognitive impairment and NPS in AD patients varies by racial/ethnic status. Cognitive impairment was assessed with the MMSE and the CDR scores. This aim was analyzed with Analysis of Covariance tests, with covariates being participant age and education and the independent variable being race/ethnicity. Age and education were used as

covariates due to the significant differences in study groups on these variables, and existing research shows that age and education can significantly impact the result when trying to evaluate cognition of the patients. For example, studies have shown how individuals with lower SES and education are at increased risk of AD diagnosis (Chow et al., 2002, Evans et al., 1997, Sawyer et al., 2009). Significant F tests were followed by Bonferroni-corrected t tests.

For NPS, the dependent variables were total score, agitation, anxiety, apathy, appetite, delusions, depression, disinhibition, elation, hallucination, irritability, motor disturbance and nighttime behaviors. Analysis of Covariance tests were performed, with covariates being caregiver age and education and patient cognition (CDR). Caregiver age and education were covariates in the analyses because of the research reviewed above showing that ratings of NPS can be influenced by caregiver variables, and the study groups were significantly different on these variables. The patient's cognitive ability was also included as a covariate because, as reviewed above, cognitive status is related to NPS in AD patients.

The second study aim was to examine the relationships between cognition and NPS and whether their relationship differs by race/ethnicity. To address this aim, correlations among cognitive scores and NPS scores were calculated separately by race/ethnicity groups.

The third study aim was to examine whether the relationship of ApoE status to cognition and NPS varies by race/ethnicity. For this aim, Analysis of Covariance models similar to those for Study Aim 1 were conducted, but in addition to the independent variable being race/ethnic status, ApoE status of the participants was included as another independent variable. A significant interaction term would suggest that the relationship of ApoE status to cognition varied in the different race/ethnicity groups.

Results

Study Aim 1

Scores on the MMSE significantly differed between the groups, $F(2,8877)=14.483$, $p<.001$, with the White sample scoring higher, signifying less cognitive impairment, than both the African-American sample, $p<.001$, and the Hispanic/Latinx sample, $p<.001$ (See Figure 2). There were no significant differences in scores between the African-American and Hispanic/Latinx sample, $p= .748$. The covariates used when performing cognitive analyses were participant age and education. Participant age was not significant, $F(1,8877)=.535$, $p=.465$, but participant education was significant, $F(1,8877)=379.871$, $p<.001$.

Scores on the CDR also differed between the groups, $F(2,10009)=14.485$, $p<.001$, with the Hispanic/Latinx sample scoring higher, signifying greater cognitive impairment, than the White sample, $p<.001$, and the African-American sample, $p<.001$ (See Figure 3). The White and African-American samples were not significantly different from one another, $p=.205$. Participant education was significant, $F(1,10009)=145.347$, $p<0001$, as was participant age, $F(1,10009)=81.572$, $p<.001$. See Table 4.

Figure 4 shows the individual NPS scores across the different racial/ethnic groups. Out of the 12 NPS subscales, 3 of the subscale scores showed no racial/ethnic differences when covariates such as caregiver age and education and CDR scores were accounted for. Those symptoms were apathy, $F(2,9774)=3.390$, $p=.034$, disinhibition, $F(2,9773)=.677$, $p=.508$, and elation, $F(2,9774)=.807$, $p=.446$. With regard to covariates, CDR scores were related to apathy, $F(1,9774)=882.074$, $p<.001$, disinhibition, $F(1,9773)=284.911$, $p<.001$, and elation, $F(1,9774)=21.018$, $p<.001$, while caregiver age was related to disinhibition, $F(1,9773)=58.490$, $p<.001$, and elation, $F(1,9774)=33.119$, $p<.001$, but not apathy, $F(1,9773)=.411$, $p=.521$. Finally, caregiver education was not related to in apathy, $F(1,9774)=3.072$, $p=.080$, disinhibition, $F(1,9773)=.118$, $p=.732$, or elation, $F(1,9774)=.005$, $p=.942$.

For three of the other subscales, there were significant differences amongst racial/ethnic groups, with follow-up tests showing that the White sample scored lower than the African-American sample and

the Hispanic/Latinx sample and the African-American sample scored lower than the Hispanic/Latinx sample. These subcategories were delusions, $F(2,9773)=90.961$, $p<.001$, hallucinations, $F(2,9772)=62.127$, $p<.001$, and nighttime behaviors, $F(2,9767)=26.681$, $p<.001$. For delusions, covariates that were significant were caregiver age, $F(1,9773)=47.637$, $p<.001$, and CDR scores, $F(1,9773)=500.103$, $p<.001$. For hallucinations, the covariates that were significant were CDR scores, $F(1,9772)=703.141$, $p<.001$, and caregiver education, $F(1,9772)=21.482$, $p<.001$. For nighttime behaviors, the only covariate that was significant was CDR scores, $F(1,9767)=199.531$, $p<.001$.

For three of the other subcategories, the overall test showed significant group differences, with the follow-up tests showing that the White sample was lower than the African-American sample but with no significant differences between the African-American and Hispanic/Latinx sample. These subcategories were irritation, $F(2,9772)=7.224$, $p<.001$, appetite changes, $F(2,9770)=7.656$, $p<.001$, and motor disturbances, $F(2, 9774)=19.729$, $p<.001$. For irritation, the covariates that were significant were caregiver age, $F(1,9772)=25.530$, $p<.001$, CDR scores, $F(1,9772)=82.677$, $p<.001$, and caregiver education, $F(1,9772)=14.739$, $p<.001$. For appetite changes, the only covariate that was significant was CDR scores, $F(1,9770)=179.514$, $p<.001$. For motor disturbance, the covariates that were significant were caregiver age, $F(1,9774)=63.963$, $p<.001$, and CDR scores $F(1,9774)=907.378$, $p<.001$.

For the anxiety subcategory, while overall differences between racial/ethnic groups were noted, $F(2,9773)=11.084$, $p<.001$, the pattern among the groups was different. The African-American sample was significantly lower than both the White and the Hispanic/Latinx samples, but the White and Hispanic/Latinx samples were not significantly different. Furthermore, for the depression subscale, there were differences among racial/ethnic groups, $F(2,9770)=10.886$, $p<.001$, but the pattern among the groups was different. The White sample showed the least severity of symptoms, while the Hispanic/Latinx sample showed significantly more, and the African-American sample showed

significantly more than both other groups. For agitation, there were differences among racial/ethnic groups, $F(2,9774)=25.812$, $p<.001$, but the pattern among the groups were different with the White group scoring lower than the African American but the Hispanic/Latinx group fell in the middle and was not significantly different from both the White and African American groups. For anxiety, the covariates that were significant were caregiver age, $F(1,9773)=44.288$, $p<.001$ and CDR scores, $F(1,9773)=208.875$, $p<.001$. For depression, significant covariates were also caregiver age, $F(1,9770)=141.407$, $p<.001$ and CDR scores, $F(1,9770)=14.089$, $p<.001$. For agitation, covariates that were significant were caregiver age, $F(1,9774)=22.562$, $p<.001$, and CDR scores, $F(1,9774)=471.934$, $p<.001$.

In addition to individual NPI subscales scores, total NPI scores were also calculated by adding up all of the scores from each NPI subscale and then analyzed. (See Table 5). Total NPI scores showed differences between groups of different racial/ethnic identities, $F(2,9754)=30.899$, $p<.001$, with the White sample being significantly lower than the African-American sample, $p<.001$, and the Hispanic/Latinx sample, $p<.001$ (See Figure 5). There were no significant differences between the African-American sample and the Hispanic/Latinx sample, $p=.224$. Covariates that showed significant racial/ethnic differences in total NPI scores were CDR scores, $F(1,9754)=1070.136$, $p<.001$ and caregiver age, $F(1,9754)=102.976$, $p<.001$. Caregiver education was not significant covariate when analyzing total NPI scores, $p=.004$.

Study Aim 2

Table 6 shows the correlations of NPS scores to cognitive ability separately in the three racial/ethnic groups. The general pattern was that worse cognition is related to worse NPS scores, but that the relationship of NPS to cognitive scores did not seem to differ by racial/ethnic group (See Table

6). The general trend that emerged was that higher total NPI scores were correlated with worse cognition (higher CDR scores and lower MMSE scores).

Study Aim 3

For this study aim, another 23% of participants did not have ApoE status coded, N=2354, and thus they were not included in the analyses.

Table 7 shows the percent in each racial/ethnic group that are ApoE ε4 positive, which was significantly different amongst the groups. Between the African-American and Hispanic/Latinx groups, significant differences were noted, $\chi^2(1,1278)=33.064$, $p<.001$, but not between the White and African-American groups, $\chi^2(1,7091)=8.111$ $p=.004$. Of the participants, 56% of the White sample, 61% of the African-American sample and 44% of the Hispanic/Latinx sample had at least one ε4 allele.

When analyzing the MMSE scores, the covariate age was not significant, $F(1,7119)=1.151$, $p=.283$. The covariate education was significant, $F(1,7119)=316.926$, $p<.001$ (See Figure 6). Consistent with Study Aim 1, collapsed across ApoE status, there were differences in racial/ethnic status in the MMSE scores, $F(2,7119)=7.184$, $p<.001$. Collapsed across racial/ethnic groups, there was a significant difference in ApoE groups, $F(1,7119)=16.521$, $p<.001$, with the ApoE ε4 group showing more impairment. The interaction between ApoE status and racial/ethnic groups was not significant, $F(2,7119)=1.301$, $p=.272$.

A two-by-two ANCOVA statistical model was used to analyze CDR scores. When analyzing the CDR scores, the covariate age was significant, $F(1,7652)=61.283$, $p<.001$ (See Figure 7). The covariate education was significant as well, $F(1,7652)=125.742$, $p<.001$. Consistent with Study Aim 1, collapsed across ApoE status, there were differences in racial/ethnic status in the CDR scores, $F(2,7652)=7.824$, $p<.001$. Collapsed across racial/ethnic groups, there was a significant difference in ApoE groups, $F(1,7652)=22.089$, $p<.001$, with the ε4 group showing more cognitive impairment. The interaction

between ApoE status and racial/ethnic groups was not significant, $F(2,7652)=2.920$, $p=.054$. See Table 8.

When analyzing the relationship of total NPI scores, the covariate caregiver age was significant, $F(1,9754)=102.976$, $p<.001$, along with the covariate CDR score, $F(1,9754)=1070.136$, $p<.001$. Covariate education showed no significant differences, $F(1,9754)=8.406$, $p=.004$ (See Figure 8). Consistent with Study 1 findings, collapsed across ApoE status, there were differences in racial/ethnic status in the total NPI scores, $F(2,7493)=17.185$, $p<.001$. Collapsed across racial/ethnic groups, there were not significant differences in ApoE groups, $F(1,7493)=7.353$, $p=.007$. The interaction between ApoE status and racial/ethnic groups was not significant, $F(2,7493)=5.932$, $p=.003$. The White group showed a decrease in NPS impairment if they were ε4 positive, while the African American and Hispanic/Latinx groups showed an increase in NPS impairment if they were ε4 positive. (See Table 9). For the White and Hispanic/Latinx samples, the interaction of race/ethnicity to ApoE status was not significant. The only group that was actually significant was the African American sample, where the ε4 was related to worse NPI total. Even though the means of total NPI were in that direction for Hispanic/Latinx sample, it was not significant. In addition, even though the White sample looked like the opposite direction, it was not significant All of the sample sizes was quite large, so the lack of significance suggests that these trends are not meaningful.

Discussion

The results showed that there are some racial/ethnic differences in cognitive impairment and NPS across the three racial/ethnic groups, although their relationship to one another and to a risk factor for AD (ApoE status) did not differ by racial/ethnic groups.

Results for Study Aim 1 showed that on both of the cognition measures, the White sample generally performed the best, while the Hispanic/Latinx sample generally either scored the worst or the

same as the African-American sample, even accounting for participant age and education. A similar trend also appeared when looking and comparing the severity of NPS, both individual subscale scores and total NPI scores, across racial/ethnic groups. Even when caregiver age and education and patient cognitive ability was accounted for with covariates, significant racial/ethnic differences were still present in many NPS, with the most typical pattern being less NPS in the White sample relative to the other groups. This is consistent with the data from Table 5 that suggested that the White sample generally had showed less psychological disturbances as opposed to the African American and Hispanic/Latinx groups, as represented by their lower scores on the NPI.

The results for Study Aim 1 suggest cognitive and NPS differences across different racial/ethnic groups. There could be a plethora of reasons for these differences, however. Although prior studies suggest that education could explain these differences, and there were education differences in the racial/ethnic groups, education level was accounted for in Study Aim 1 analyses and thus cannot explain the findings. Another explanation for why these differences occurred may be due to a possible language barrier, especially in the Hispanic/Latinx sample. For example, many individuals of Hispanic/Latinx descent also speak Spanish and for many of them, it is their primary language. It is possible that the Hispanic/Latinx participants and their Hispanic/Latinx caregivers were not fully able to comprehend or assess the cognition questionnaire. This suggests the possibilities of some biases that may occur during cognitive measures, which might lead to Hispanic/Latinx samples scoring lower on these measures. However, to the degree possible, measures were administered to participants in their native language, suggesting that was not likely a reason for the results in the present study. It is also possible that patients and caregivers from minority groups are less likely to receive proper treatment and referrals for cognitive decline, which may result in participants not coming in for assessment until they are already more impaired (Hernandez et al., 2010). Research shows that minority groups are less likely to receive

the proper medication at appropriate timing, due to their lower education scores and SES and individuals with higher educational attainment are more likely to receiver higher quality care (Brown et al., 2013, Hernandez et al., 2010). This reflects one of the many health disparities that America is currently dealing with and the present study did not account for that. Evidence that suggests this might have been true in the present study is that African Americans and Hispanic/Latinx were already at an older age at their initial visit. This speaks to the need to provide more education about age-related diseases and their symptoms and more health literacy programs to individuals from underrepresented groups, so that individuals, along with their caregivers, are more likely to seek medical care at an earlier stage of the disease.

Finally, it may be that the differences in cognitive ability and NPS seen in our study reflect other biases against racial/ethnic groups. In other words, it may be that the measures of cognitive ability and NPS are not as accurate or valid to use in individuals from diverse groups. Another way to look at whether the differences reflect any bias, however, is to see whether the relationships between cognition and NPS vary in the 3 groups, as reflected in Study Aim 2 or whether the relationship of ApoE status to cognition and NPS varies in the 3 groups, reflected in Study Aim 3. If these relationships are different in different groups, this would reflect that the measures do not behave in the same way for different groups, which is a potential indicator of bias.

Results for Study Aim 2 showed that across all racial/ethnic groups, higher NPS severity was correlated with higher CDR scores and lower MMSE scores, which represent higher severity of cognitive decline. The effect sizes for NPS in relation to cognitive ability were generally small, with some medium effect sizes, but generally did not vary across the different racial/ethnic groups. These findings suggest that bias in either the measures of cognition, such as the MMSE and CDR, or the

measure of NPS, via the NPI, is not likely, given that they related to each other in similar ways in the different racial/ethnic groups.

Results for Study Aim 3 did not suggest that ApoE interacted with racial/ethnic groups in its relationship to either cognition scores or NPI scores. The findings for this study aim are consistent with existing studies that found no difference in the relation of ApoE status to risk of AD among different racial/ethnic groups (Fillenbaum et al., 2001, Graff-Radford et al., 2002, Jun et al., 2010, Sawyer et al., 2009) but were not consistent with findings from other studies (Green et al., 2002, Kalaria et al., 1997, Maestre et al., 1995, Sahota et al., 1997, Tang et al., 1998). Due to the fact that the relationships between ApoE status and racial/ethnic status were similar amongst the different groups, it also does not suggest that there in bias in the measures of cognition or of NPS that could explain the findings.

Study Limitations

While the present study controlled for participant education, it did not control for SES, which other studies have shown to be related to cognition in AD and also varies by racial/ethnic status. Thus, it may be that SES differences could contribute to racial differences in the cognitive and neuropsychiatric measures.

Another limitation that this thesis did not control for was the relationship of caregiver to participant as well as the frequency of encounters between the two. According to a recent study, the level of caregiver burden is not only generally related to severity and the type of NPS present and the degree of cognitive impairment, but also how dependent the patient is on the caregiver and how much time the caregiver spends with the patient (Hirao et al., 2015). For example, children of Alzheimer's disease individuals may be viewing severity of symptoms differently than a spouse or even an ex-partner. Frequency of encounters between participants and caregivers may also contribute to the differences in the NPS rating because a caregiver who encounters their patients five times a week may

feel more burdened, which increases stress levels, as opposed to a caregiver who encounters their patients one day a week.

Another potential limitation may be due to that fact that correlating a caregiver's ratings of presence of NPS with caregiver's ratings of burden may be confounded by general caregiver distress biasing report on both measures, since both measures are taken simultaneously. The study could not control for caregiver stressors or distress, which other studies have suggested might be related to how caregivers view the symptoms of the patients they care for (Stella et al., 2015).

Additionally, another possible limitation is that there was no control for the duration of the dementia prior to the participants coming into the study. If there is disproportionate access to health facilities across the different racial/ethnic groups, individuals from minority groups may not have the opportunity to be assessed until they are older in age and have more advanced symptoms. This reflects a major disparity in the health care system that was not studied. We did not have access to data on current medications or on other health factors for the participants in the study, and these factors may be related to the differences in cognitive impairment and NPS that we found.

Another limitation, which is true in most diversity research, is that racial/ethnic status is self-reported, which may not always be entirely accurate. This may be related to the fact that race/ethnicity are not strict biological categories. In other words, "African Americans" have a wide range of genotypes of origin, including the percentage on "European" and "African" genetic origin. The same is true of "Hispanic/Latinx". Also, just because an individual self-reported a certain racial/ethnic category, that does not implicate that those individuals strongly identify with the culture associated with that racial/ethnic identity. For example, it is possible that individuals who are genetically biracial choose to identify more strongly with one racial/ethnic group than the other.

Implications and Future Directions

In future studies, greater number of minorities should be incorporated into cognition and psychological studies so that they could be equally represented with their White counterparts. Recent research shows that minority groups are not being represented in scientific studies proportional to their population in the United States. The specific data pool used in this thesis was similar in diversity to previous studies, since the White group made up more than half of the entire population sample, but the sample size allowed for a large number of diverse individuals to be included to test the hypotheses. Additionally, some researchers fail to report racial/ethnic identities in their study. In addition, more focus should be given to whether it is something about racial/ethnic identity or background that can explain the differences. One way to address this is better measurement of racial/ethnic status. Specific terms should be modified or invented when describing the different racial/ethnic groups so that the results are specific to that particular group. For example, throughout the paper, I abstained from using the term 'Caucasian' because it is derogatory towards minority groups and it also can refer to White individuals from American, Europe, Arabia, and Central and Northern Asia. The term African American is also non-specific, for it can be used to describe Africans, Afro-Latinx, Afro-Caribbean and more. This non-specification of racial/ethnic groups could possibly confound data and results. In addition, future studies should measure identification with a group to better explore potential cultural issues. Future studies should also consider measuring cultural beliefs about aging to better explore how culture might contribute to observed differences.

Future studies should also measure SES and include it in analyses to account for its effects on cognition and NPS. In addition, other health disparities that can be related to racial/ethnic status and to SES, including the presence of other medical factors and use of medications, may explain the differences in cognitive and NPS scores and should be measured in future studies.

Another focus for future study is to examine these differences in individuals who are at the earliest signs of the disease. Longitudinal studies of individuals who tested positive for the ε4 allele may help in early detection and better preventive measures of the disease. Longitudinal studies may also better address concerns about accessing participants at different stages of disease severity. In addition, future studies could include more measures of cognition that are also able to detect less severe cognitive impairment.

Finally, future studies that examine NPS in patients with AD should examine caregiver factors (how they are related, frequency of contact) and how they may relate to ratings of NPS in patients with AD. As aforementioned, some of the disparities in ratings might be related to the education level of the caregiver and this should be measured in future studies (Brown et al., 2013). Future studies should also account for age and financial stability of the caregiver, as it is possible that these factors may affect ratings. Further, future studies should account for caregiver distress and burden when examining ratings they make about NPS in patients.

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Tables

Table 1

Sample characteristics of prior studies examining differences in NPS

Authors (years)	Chow et al., (2002)	Burke et al., (2016)	García-Alberca et al., (2013)
Sample of Study	430 patients with their caregivers (144 from Koahsiung, 86 from Taipei, 31 from Hong Kong and 169 from USA)	11,453 cognitively intact patients at visit 1 (620 converters to AD, 947 non-converters)	114 patients and their primary caregivers
Origin of Sample (Country)	Hong Kong, USA, Taipei, Koahsiung	USA	Spain
Distribution of Various Racial Ethnic Groups in Sample	Kaohsiung-33.49% Taipei- 20.0% Hong Kong-7.21% Los Angeles-39.30%	White- 80.7% African American-13.2% Hispanic- 6% Other- 5.9%	Not specified
How NPS was measured	NPI	NPI-Q	NPI
Who Measured NPS	Caregivers	Caregiver	Caregiver
• **Age, Gender, Education Level**	Patients: Kaohsiung • 73.1 yrs ± 8.7 • 55% female • 6 yrs ±5 Patients: Taipei • 74.8 yrs ± 6.9 • 55% female • 10 yrs ± 5 Patients: Hong Kong • 78.0 ± 8 • 87% female • 2 yrs ± 3 Patients: Los Angeles • 77.4 yrs ± 7.5 • 72% female • 13 yrs ± 3	Patients • 71.18 yrs ± 10.87 • 65.2% female • Not specified	Patients • 77.34 yrs ± 5.74 • 62.5% female • 6.56 ± 2.62 Caregivers • 62.15 yrs ± 10.37 • 77.5% female • 6.56 ± 2.62
Relation to Patient	Not specified	Not Specified	43.8% son/daughter 38.8% husband/wife 7.4% brother/sister 10% other relatives

Note. NPS – Neuropsychiatric symptoms. NPI – Neuropsychiatric Inventory

Table 2

Percentage of patients with various NPS in prior studies across different settings

Authors (years)	**Chow et al., (2002)**				**Burke et al., (2016)**				**García-Alberca et al., (2013)**
	Koahsiung	**Taipei**	**Hong Kong**	**Los Angeles**	**White**	**African American**	**Hispanic/Latinx**	**Other**	**Spain**
Aberrant Motor Behavior	40.6%	37.1%	61.3%	43.8%					49%
Agitation	40.3%	46.1%	61.3%	49.1%	5.47%	4.19%	7.48%	5.66%	50%
Anxiety	37.8%	39.3%	58.1%*	37.3%	8.42%	4.92%	15.25%	8.49%	40%
Apathy	38.9%	47.2%	35.5%	59.2%*	4.24%	4.19%	7.48%	3.73%	92%
Appetite Changes	29.2%*	29.2%*	53.6%	47.3%					26%
Delusions	40.3%	31.5%	58.1%**	39.6%	0.71%	0.73%	1.87%	1.19%	24%
Depression	43.7%	49.4%	46.7%	56.2%	13.23%	8.38%	21.44%	14.00%	58%
Disinhibition	35.4%	19.1%	25.8%	29.6%	2.33%	1.80%	3.50%	2.38%	26%
Euphoria	11.8%	7.8%	19.4%	15.4%	0.82%	0.73%	1.29%	0.30%	5%
Hallucination	19.3%	24.7%	22.6%	13.6%	0.26%	0.13%	0.72%	0.60%	18%
Irritability	44.4%	51.7%	63.3%	43.2%	10.87%	7.91%	14.39%	10.13%	63%
Sleep Disturbance	34.7%	36%	53.6%	39.6%	10.24%	6.65%	15.54%	10.58%	46%

Note. χ^2: * = p<0.05; ** = p<0.01

Table 3

Participant and Caregiver Demographics

	Participant Age[1]		**Participant Education**[2]		**Caregiver Age**[3]		**Caregiver Education**[4]	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
White (N=8038)	74.61	9.64	15.17	3.077	65.39	12.70	15.67	2.625
African-American (N=1166)	76.19	8.81	12.86	3.530	59.53	13.23	14.72	2.723
Hispanic/ Latinx (N=810)	74.27	10.09	9.71	5.266	55.07	14.17	13.33	3.838

Note. 1 for participant age, White and Hispanic/Latinx sample younger than African-American sample, White and Hispanic/Latinx sample are not significantly different. 2 for participant education, Hispanic/Latinx sample lower than African-American and White sample, African-American sample lower than White sample. 3 for caregiver age, Hispanic/Latinx sample lower than African-American and White sample, African-American sample lower than White sample. 4 for caregiver education, Hispanic/Latinx sample lower than African-American and White sample, African-American sample lower than White sample.

Table 4

Cognition Scores Across Racial/Ethnic Groups

	MMSE[1]		**CDR**[2]	
	Mean	Standard Deviation	Mean	Standard Deviation
White (N=7140) - MMSE (N=8038) – CDR	21.78	6.47	0.97	0.68
African-American **(N=1049) -MMSE (N=1166) – CDR**	19.81	6.60	1.07	0.72
Hispanic/Latinx (N=693) -MMSE (N=810) –CDR	18.75	6.96	1.26	0.81

Note: MMSE=Mini Mental State Examination, CDR= Clinical Dementia Rating. 1 for MMSE scores, White sample scored higher than African-American sample, no significant differences between White and Hispanic samples or African-American and Hispanic samples. 2 for CDR scores, Hispanic/Latinx sample scored higher than African-American and White samples, no differences between White and African-American sample.

Table 5
Neuropsychiatric Symptom Scores Across the Racial/Ethnic Groups

	White		**African-American**		**Hispanic/Latinx**	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Agitation[3]	0.44	0.760	0.66	0.909	0.65	0.956
Anxiety[4]	0.56	0.815	0.51	0.828	0.73	0.996
Apathy[3]	0.61	0.879	0.59	0.896	0.73	1.015
Appetite[3]	0.35	0.704	0.46	0.800	0.48	0.837
Delusions[2]	0.18	0.541	0.44	0.816	0.48	0.880
Depression[5]	0.53	0.770	0.59	0.853	0.78	0.953
Disinhibition[1]	0.27	0.636	0.33	0.728	0.37	0.771
Elation[1]	0.06	0.303	0.08	0.354	0.07	0.338
Hallucination[2]	0.08	0.365	0.21	0.592	0.29	0.720
Irritability[3]	0.53	0.784	0.66	0.887	0.69	0.956
Motor Disturbance[3]	0.26	0.639	0.45	0.842	0.46	0.885
Nighttime Behaviors[2]	0.40	0.762	0.58	0.931	0.65	1.009
Total Score[2]	4.28	4.26	5.56	5.55	6.38	6.10

Note. 1 for all groups equal. 2 for White group lower than African American and Hispanic/Latinx groups while African American and Hispanic/Latinx groups are equal. 3 for White group lower than African American group while Hispanic/Latinx group equal to African American and White group. 4 for African American group lower than White and Hispanic/Latinx groups while White and Hispanic/Latinx groups are equal. 5 for Hispanic higher than White and African American groups while White and African American groups are equal.

Table 6

Correlations of Cognitive scores with Neuropsychiatric Symptoms (NPS) separately for Racial/Ethnic Groups

	White (N=7040) -MMSE (N=7857) – CDR		**African-American (N=1033) – MMSE (N=1140) – CDR**		**Hispanic/Latinx (N=680) – MMSE (N=783) – CDR**	
	MMSE	CDR	MMSE	CDR	MMSE	CDR
Agitation	-0.126[1]	0.201[1]	-0.244[1]	0.292[1]	-0.23[1]	0.234[1]
Anxiety	-0.131[1]	0.134[1]	-0.174[1]	0.176[1]	-0.254[1]	0.203[1]
Apathy	-0.211[1]	0.283[1]	-0.219[1]	0.295[1]	-0.292[1]	0.326[1]
Appetite	-0.083[1]	0.132[1]	-0.069[3]	0.163[1]	-0.099[2]	0.123[2]
Delusions	-0.198[1]	0.215[1]	-0.223[1]	0.220[1]	-0.271[1]	0.291[1]
Depression	-0.026[3]	0.037[2]	-0.035	0.045	-0.144[1]	0.082[3]
Disinhibition	-0.102[1]	0.163[1]	-0.225[1]	0.232[1]	-0.143[1]	0.151[1]
Elation	-0.030[3]	0.049[1]	-0.086[2]	0.069[3]	-0.013	0.014
Hallucination	-0.197[1]	0.242[1]	-0.269[1]	0.302[1]	-0.357[1]	0.340[1]
Irritability	-0.023[3]	0.079[1]	-0.174[1]	0.173[1]	-0.122[2]	0.111[2]
Motor Disturbance	-0.231[1]	0.270[1]	-0.351[1]	0.369[1]	-0.357[1]	0.359[1]
Nighttime Behaviors	-0.060[1]	0.114[1]	-0.162	0.229[1]	-0.178[1]	0.229[1]
Total NPI	0.300	-0.219	0.374	-0.321	0.364	-0.369

Note. 1 for $p<.001$, 2 for $p<.01$, 3 for $p<.05$.

Table 7

Presence of ApoE ε4 Allele Across Racial/Ethnic Groups

ApoE Status	**White**	**African-American**	**Hispanic/Latinx**	**Total**
No ε4 alleles	2803 (43.9%)	283 (38.8%)	301 (55.8%)	3387 (44.2%)
At least 1 ε4 allele	3589 (56.1%)	446 (61.2%)	238 (44.2%)	4273 (55.8%)
Total	6392	729	539	7660

Note. ApoE=Apolipoprotein E.

Table 8

ApoE Status and Cognition Scores Across Racial/Ethnic Groups

	White (N=6392) – CDR (N=5966) – MMSE		**African-American (N=729) – CDR (N=680) – MMSE**		**Hispanic/Latinx (N=539) – CDR (N=481) – MMSE**	
	ε**4-**	ε**4+**	ε**4-**	ε**4+**	ε**4-**	ε**4+**
	Mean/SD	Mean/SD	Mean/SD	Mean/SD	Mean/SD	Mean/SD
CDR	0.92/0.647	0.98/0.681	0.92/0.667	1.09/0.717	1.18/0.728	1.25/0.782
MMSE	22.48/6.239	21.59/6.451	21.33/5.875	19.89/6.656	18.96/6.606	18.72/6.867

Note. CDR=Clinical Dementia Rating, MMSE=Mini Mental State Exam.

Table 9

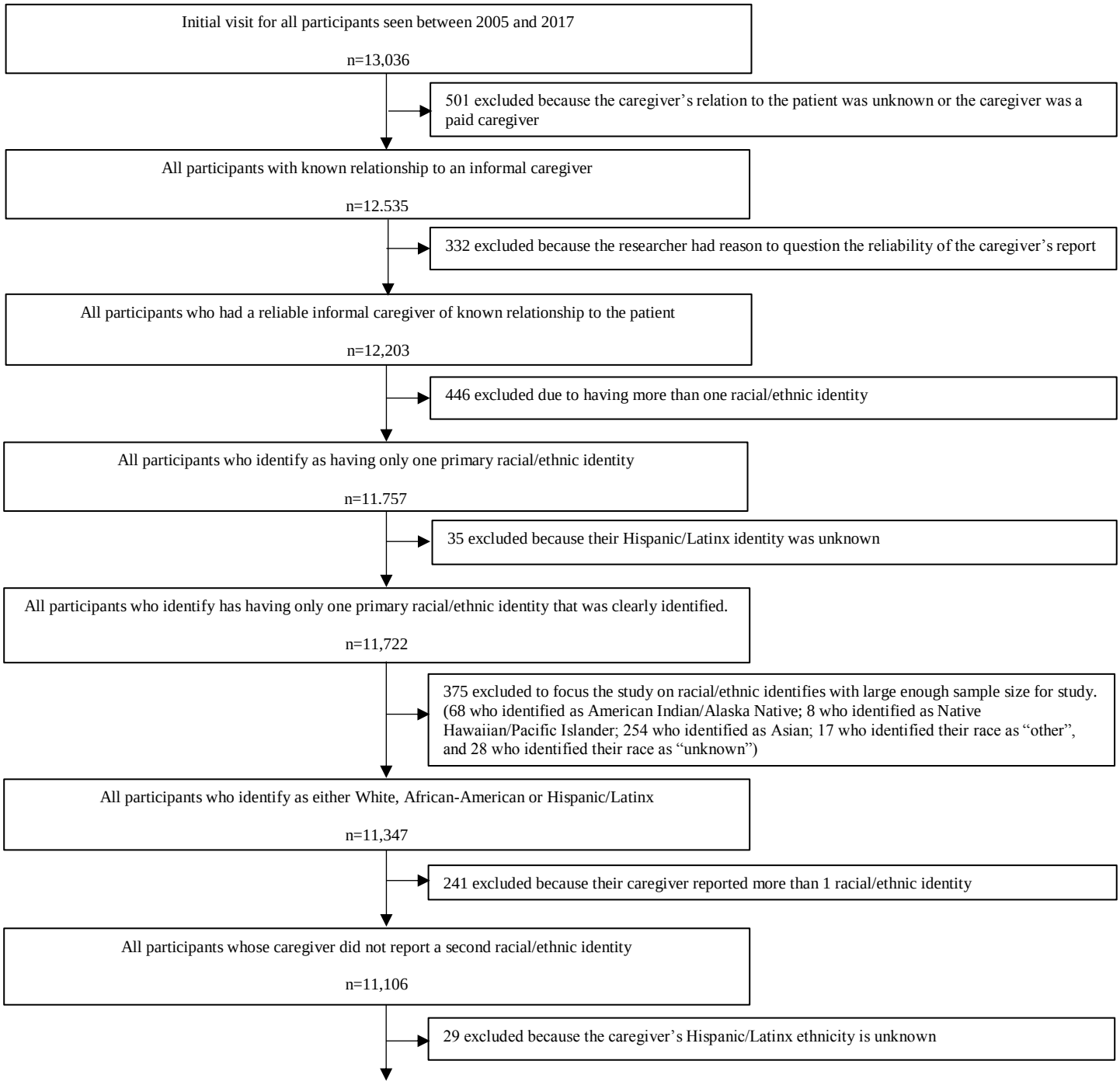
ApoE Status and Neuropsychiatric Symptoms Across Racial/Ethnic Groups

	White (N=6266)		**African-American (N=716)**		**Hispanic/Latinx (N=526)**	
	ε4-	**ε4+**	**ε4-**	**ε4+**	**ε4-**	**ε4+**
	Mean/SD	Mean/SD	Mean/SD	Mean/SD	Mean/SD	Mean/SD
Agitation	0.43/0.751	0.44/0.752	0.58/0.885	0.71/0.933	0.59/0.93	0.68/0.995
Anxiety	0.52/0.793	0.58/0.808	0.36/0.731	0.53/0.845	0.67/0.968	0.79/1.025
Apathy	0.62/0.887	0.60/0.856	0.47/0.817	0.64/0.933	0.67/1.017	0.75/1.042
Appetite	0.36/0.718	0.33/0.674	0.38/0.792	0.50/0.817	0.46/0.824	0.51/0.863
Delusions	0.15/0.509	0.19/0.559	0.39/0.801	0.46/0.816	0.46/0.884	0.52/0.907
Depression	0.52/0.768	0.53/0.755	0.52/0.843	0.62/0.857	0.69/0.950	0.78/0.931
Disinhibition	0.28/0.652	0.26/0.615	0.24/0.648	0.35/0.744	0.33/0.795	0.44/0.771
Elation	0.07/0.321	0.06/0.285	0.02/0.168	0.08/0.389	0.07/0.354	0.06/0.311
Hallucination	0.06/0.324	0.07/0.364	0.14/0.486	0.22/0.598	0.25/0.653	0.26/0.693
Irritability	0.55/0.787	0.52/0.768	0.62/0.880	0.67/0.876	0.62/0.948	0.76/0.997
Motor Disturbance	0.25/0.636	0.26/0.625	0.27/0.666	0.44/0.832	0.42/0.850	0.49/0.916
Nighttime Behaviors	0.42/0.769	0.37/0.733	0.58/0.937	0.54/0.902	0.70/1.035	0.65/1.012
Total NPI	4.23/4.36	4.19/4.04	4.58/5.21	5.76/5.53	5.93/6.13	6.69/6.09

Note: ε4- for absence of the ApoE ε4 allele. ε4+ for presence of the ApoE ε4 allele.

Figures

Figure 1: Participant Exclusion Criteria



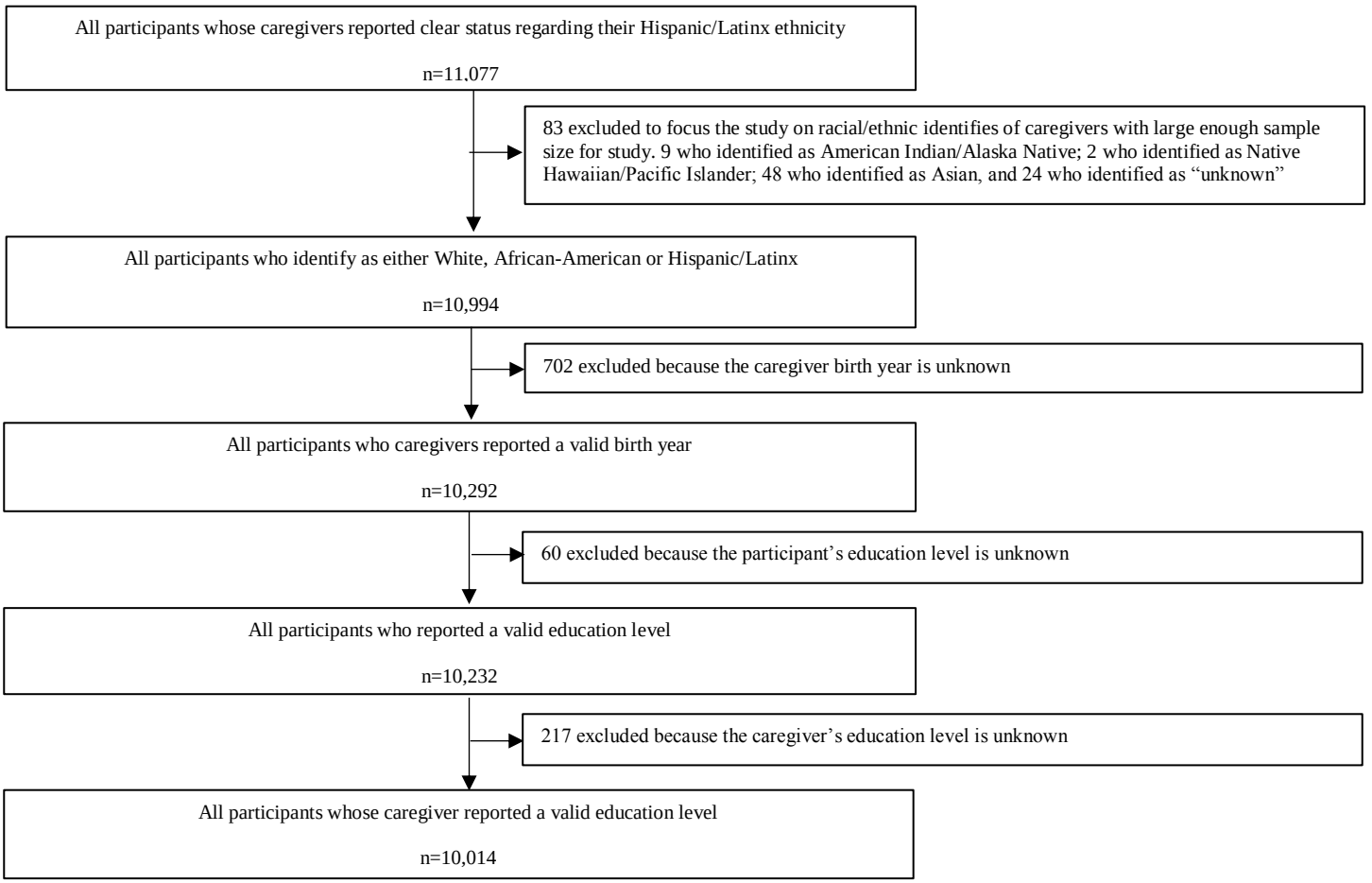

All participants whose caregivers reported clear status regarding their Hispanic/Latinx ethnicity
n=11,077
83 excluded to focus the study on racial/ethnic identifies of caregivers with large enough sample size for study. 9 who identified as American Indian/Alaska Native; 2 who identified as Native Hawaiian/Pacific Islander; 48 who identified as Asian, and 24 who identified as "unknown"
All participants who identify as either White, African-American or Hispanic/Latinx
n=10,994
702 excluded because the caregiver birth year is unknown
All participants who caregivers reported a valid birth year
n=10,292
60 excluded because the participant's education level is unknown
All participants who reported a valid education level
n=10,232
217 excluded because the caregiver's education level is unknown
All participants whose caregiver reported a valid education level
n=10,014

Figure 2: MMSE Scores Across Racial/Ethnic Groups

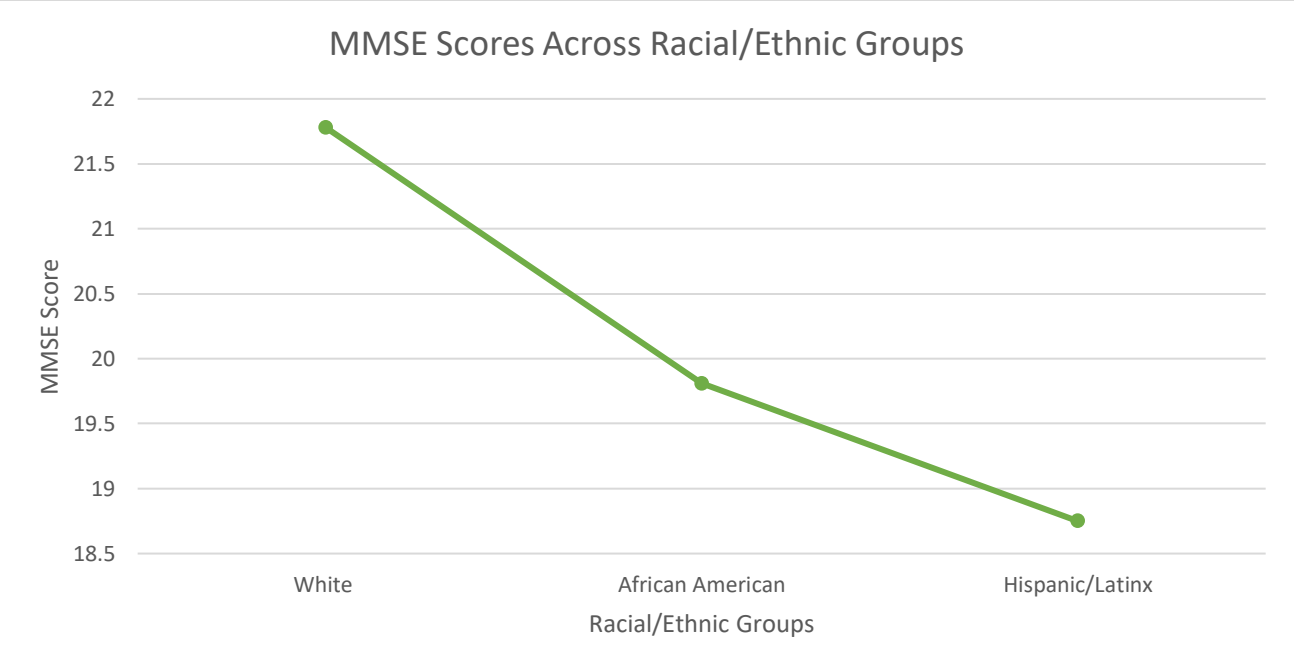


Figure 3: CDR Scores Across Racial/Ethnic Groups

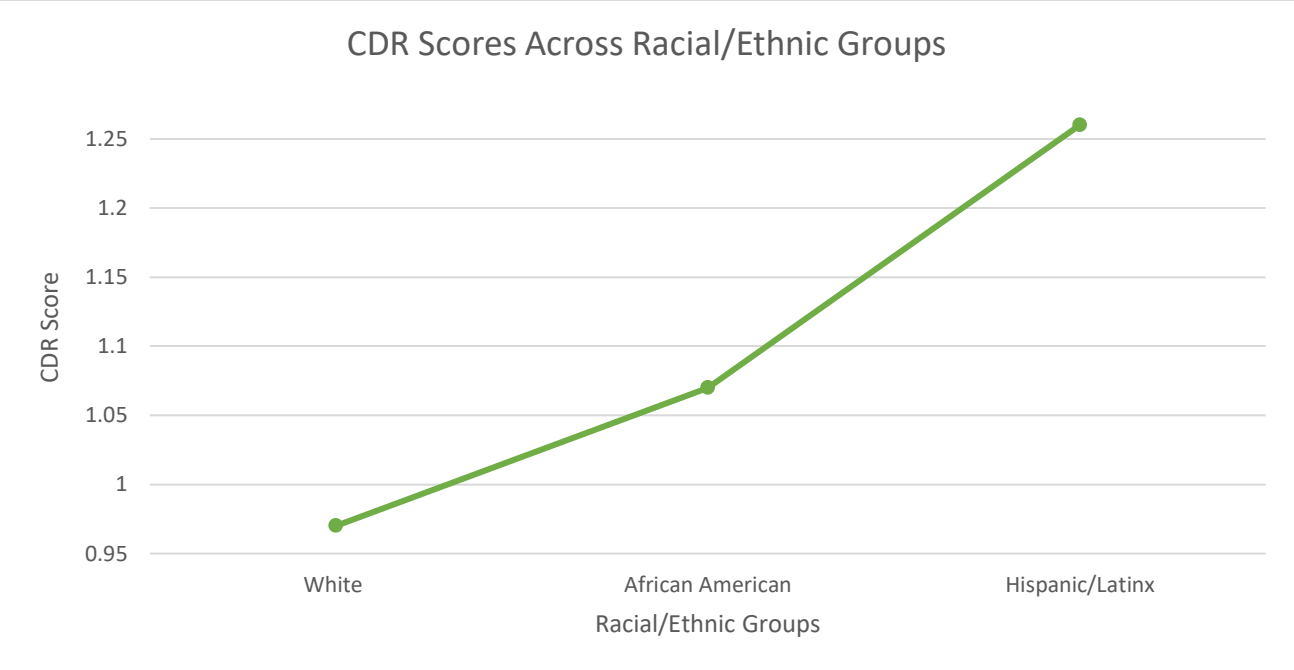


Figure 4: Individual Neuropsychiatric Symptoms Scores Across Racial/Ethnic Groups

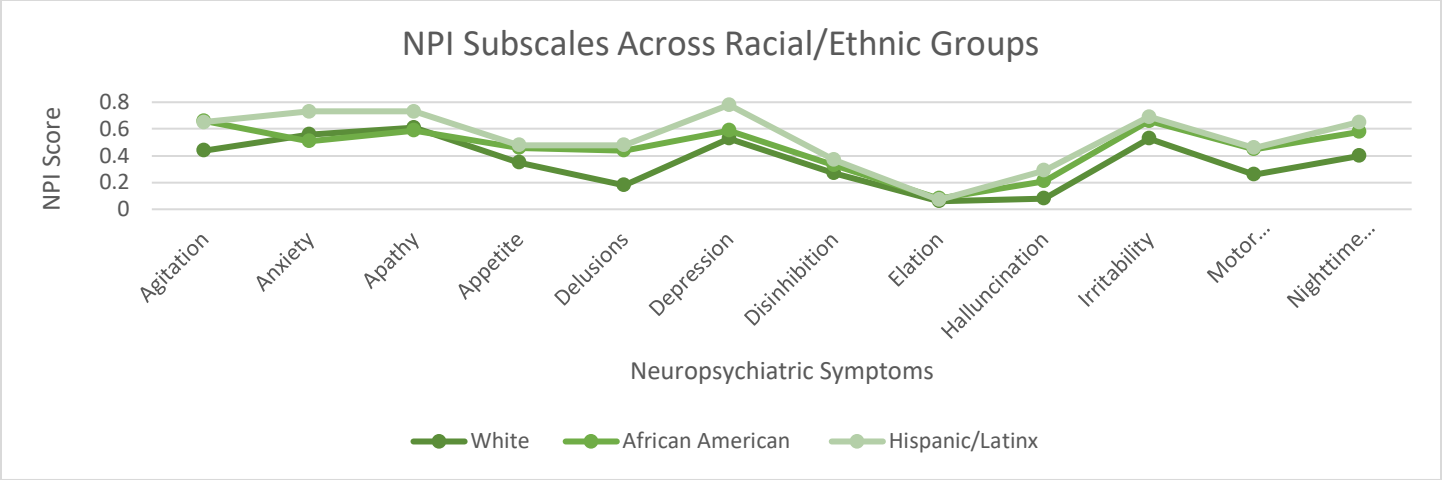


Figure 5: Total Neuropsychiatric Symptoms Scores Across Racial/Ethnic Groups

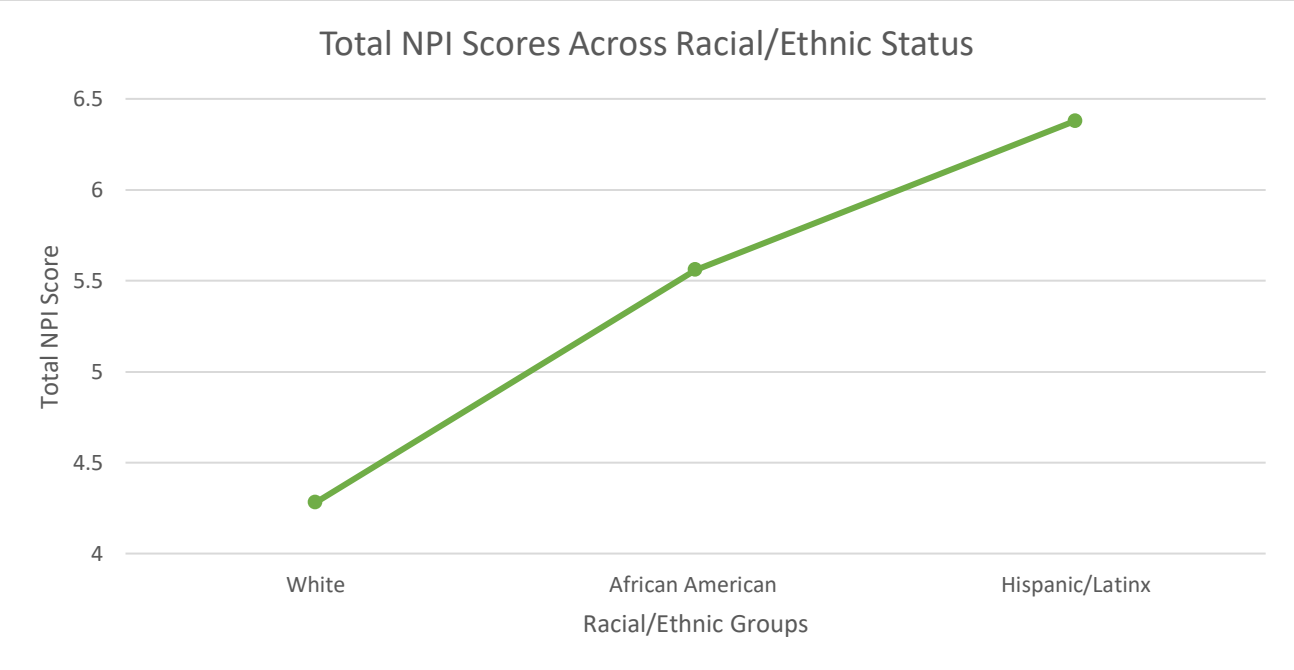


Figure 6: ApoE Status and MMSE Scores Across Racial/Ethnic Groups

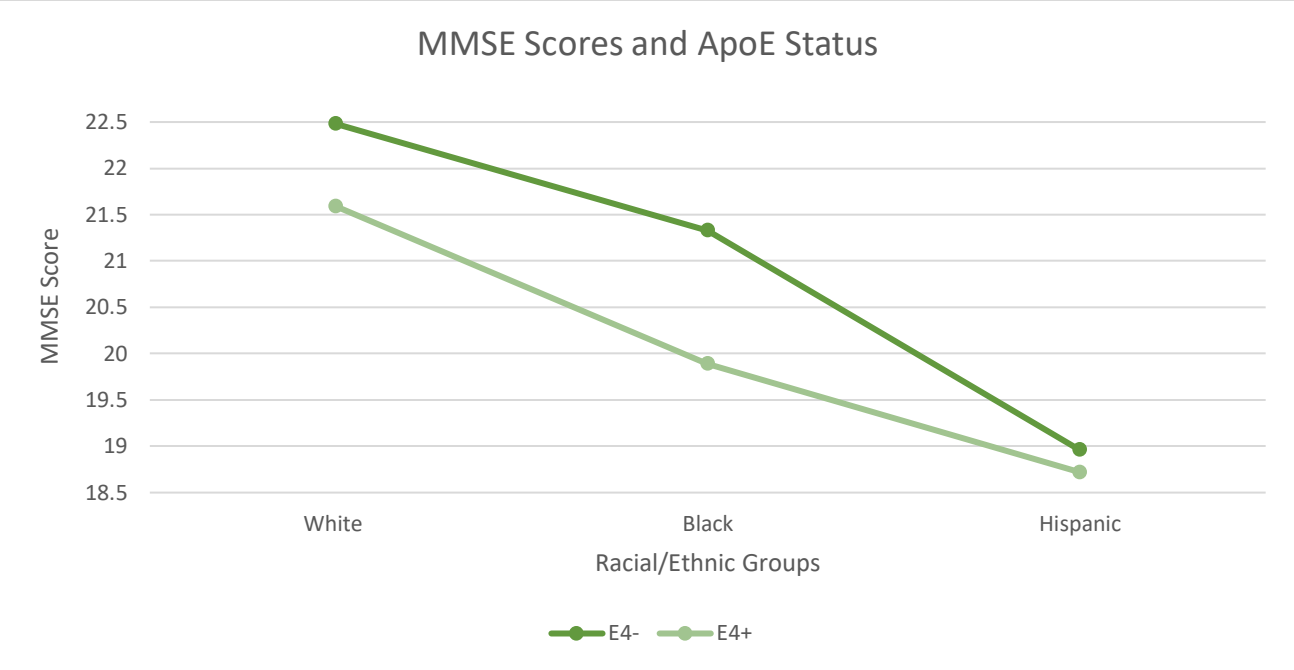


Figure 7: ApoE Status and CDR Scores Across Racial/Ethnic Groups

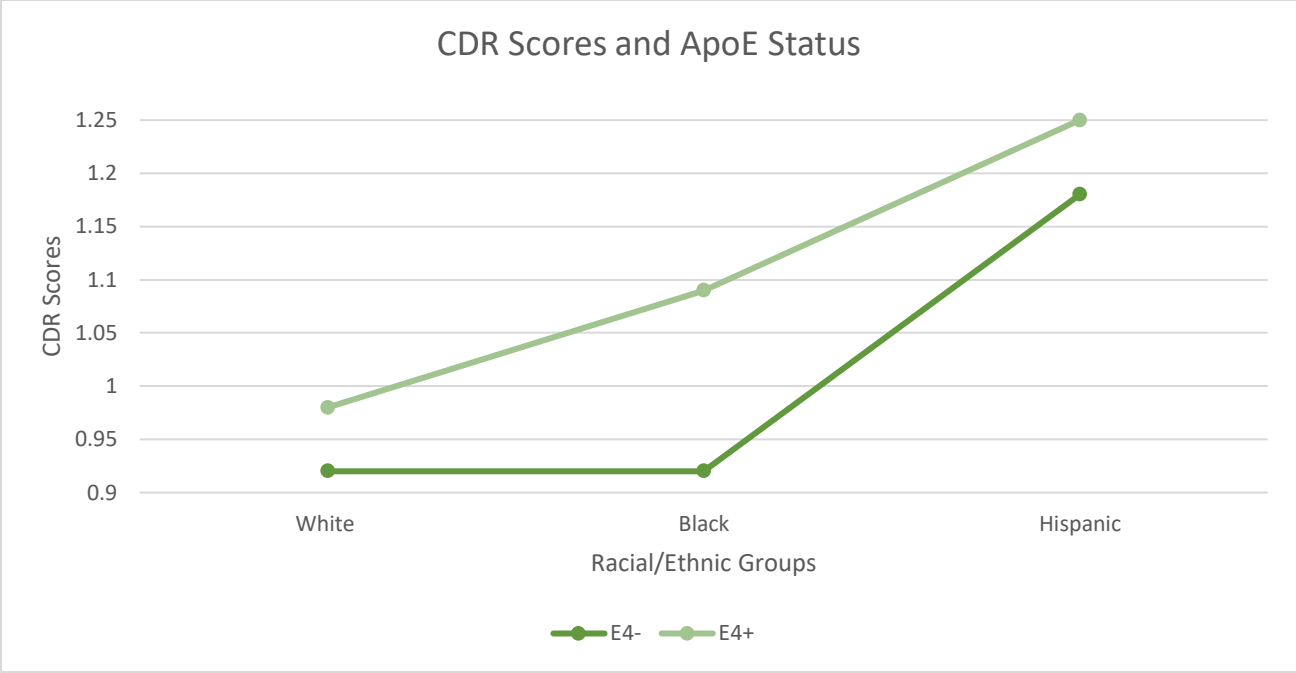


Figure 8: ApoE Status and Total Neuropsychiatric Symptoms Scores Across Racial/Ethnic Groups