Building Cognitive Resilience Against Alzheimer's Disease Through Multilingualism

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background: Globally, there are 9.9 million new cases of dementia each year, meaning one new case is diagnosed every 3.2 seconds (Prince et al., 2015). The risk of Alzheimer's disease (AD) increases with increasing age, and so with the rising aging population, the prevalence of AD is projected to increase in the years to come. Cognitive resilience has been a focus of preventative strategies against AD/dementia as cognitive resilience is hypothesized to delay or prevent the onset of clinical symptoms of dementia despite the presence of Alzheimer neuropathology (see review by Stern, 2002). Cognitive resilience has two components: cognitive reserve refers to an 'active' process of using neural networks efficiently to compensate for brain damage, and brain reserve relies on structural advantages within the brain that increase the capacity to tolerate brain damage. Multilingualism (i.e., speaking more than one language) may contribute to cognitive resilience against dementia/AD, as it can improve cognitive flexibility and executive function through constant switching between languages and the use of inhibition and attention control.

Objectives: The first two objectives of this study were to investigate whether there was an association of cognitive resilience with (1) multilingualism or (2) type of language. The second two objectives of this study were to explore whether (3) cortical atrophy (an indicator of brain reserve) or (4) education (an indicator of cognitive reserve) modified the association of cognitive resilience with multilingualism or type of language.

Methods: Data were used from the Nun Study, a longitudinal study on aging with religious sisters, aged 75+ at baseline. Multilingualism was determined through convent archival records. Neuropathological diagnosis of AD was based on both Consortium to Establish a

Registry for Alzheimer's Disease (CERAD) and the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NIA-RI) criteria. Dementia status was assessed by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria at the last cognitive assessment before death. Analyses included logistic regression models adjusted for the presence of apolipoprotein E-ε4 allele, age at death, education, primary language, and immigration status. Firth regression was used to test for interactions between the exposure variables and cognitive resilience and for any subsequent stratified models.

Results: Speaking four or more languages (versus speaking fewer languages) was significantly associated with cognitive resilience based on NIA-RI criteria only, and remained so after adjusting for all of the covariates (OR=5.00, 95% CI=1.08-27.56). Speaking German significantly reduced the likelihood of cognitive resilience based on CERAD criteria only, even after adjusting for all covariates (OR=0.50, 95% CI=0.27-0.94). With respect to ceiling and floor effects, adjusting for education or atrophy in multivariable models did not cause any substantial changes to the association between multilingualism and cognitive resilience. When using type of language as an exposure variable, adjusting for education did not substantially change the association between type of language and cognitive resilience; however, when adjusted for atrophy the statistically significant association observed between speaking German and cognitive resilience became nonsignificant (OR=0.55, 95% CI=0.27-1.09). Lastly, no statistically significant associations

were observed between multilingualism or type of language and cognitive resilience when stratified by education or the presence of atrophy.

Discussion: Overall, speaking four or more languages significantly increased the likelihood of cognitive resilience. However, no evidence of a benefit of bilingualism on cognitive resilience was observed in this study. Previous research indicates that only the studies that were cross-sectional and had used a clinic-based sample observed a bilingual benefit, while studies that were longitudinal and had used a population-based sample found a protective effect against dementia, only when higher number of languages were spoken. Since this current study was longitudinal and had used a population-based sample, the findings were consistent with the previous studies that did not observe a bilingual benefit against dementia. Other than the methodological differences, this current study perhaps did not observe a bilingual protective effect because of the measure of multilingualism used, which was less stringent than in some previous studies. For example, the participants in this study only had to self-report the number and the type of languages they were proficient in and thus, this study could not incorporate other important aspects of multilingualism, such as reading ability, language comprehension, frequency and intensity of language use, and age at language acquisition, in the assessment of multilingualism. However, this current study did use a stringent measure of the outcome, cognitive resilience, based on both the dementia status at the last cognitive assessment and the presence of Alzheimer neuropathology. Moreover, after controlling for various confounders, such as the presence of apolipoprotein

E-ε4 allele, age at death, education, primary language, and occupation, a significant benefit from speaking four or more languages on cognitive resilience was still observed.

Secondly, previous research has shown mixed findings on the cognitive benefits of linguistically similar or linguistically dissimilar languages, where there have been studies that observed cognitive benefits from speaking either similar or dissimilar languages or no significant cognitive benefits at all. Because the outcomes of most previous studies were on cognitive benefits rather than on dementia/AD/cognitive resilience, the findings from previous studies cannot be extrapolated fully to the findings from the current study. Although speaking similar languages has been found to benefit cognition presumably because of greater levels of cross-linguistic interference experienced while speaking, in this current study, speaking similar languages such as German and English did not significantly contribute to cognitive resilience. While speaking German and English was initially shown to significantly reduce the likelihood of cognitive resilience, since German speakers in this study had higher levels of atrophy present than those who spoke other type of languages, it is likely that the presence of atrophy instead of speaking the German language itself was responsible for reducing the likelihood of cognitive resilience.

Finally, when the models were adjusted for atrophy or education to explore the floor and ceiling effects, respectively, no substantial changes were observed between multilingualism and cognitive resilience. Between the type of language spoken and cognitive resilience, only the significant association between speaking German and cognitive resilience became nonsignificant, as a higher number of German speakers had atrophy present. As there

were no significant interactions between the exposure variables and atrophy or education and no significant trends supporting a ceiling or floor effect were observed in the stratified analyses, this current study did not provide supportive evidence for the presence of a ceiling or floor effect for cognitive resilience.

Overall, speaking four or more languages was shown to increase the likelihood of cognitive resilience, whereas there was no evidence of benefit of speaking two or three languages on cognitive resilience. Since those who spoke four or more languages were likely to have experienced higher levels of intellectual stimulation than those who spoke fewer languages, the results may indicate that a higher degree of intellectual stimulation is the underlying factor that is required to significantly build up cognitive resilience. It is also possible that those who spoke four or more languages were different in the sense that they had higher levels of intelligence or had a greater tendency to engage in intellectually stimulating activities than those who spoke fewer languages. Moreover, the context within which the languages were spoken might have influenced the results. In addition, this research project did not find any evidence on type of language being important for contributing to cognitive resilience; this topic has not often been studied and warrants further investigation. Finally, multilingualism can be considered as one modifiable way to enhance cognitive stimulation in order to build up cognitive resilience and thus reduce the impact of AD, thereby improving the quality of life of aging populations.

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Dedication

To my loving mom, dad, and brother.

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List of Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ADL	Activities of daily living
ANOVA	Analysis of variance
APOE	Apolipoprotein E
APP	Amyloid precursor protein
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CIND	Cognitive impairment no dementia
CSF	Cerebrospinal fluid
DSM	Diagnostic and Statistical Manual
HR	Hazard ratio
IQ	Intelligence quotient
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangles
NIA-RI	National Institute on Aging-Reagan Institute
NINCDS-ADRDA	National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NMDA	N-methyl-D-aspartate
NP	Neuritic plaques
PET	Positron emission tomography
PSEN	Presenilin
rCBF	Regional cerebral blood flow

1.0 Introduction

Currently, over 900 million people worldwide are over the age of 60 (Prince et al., 2015), and the global life expectancy at age 60 has increased between 1990 and 2012 from 16.6 to 18.5 years for men and from 19.7 to 21.5 years for women (World Health Organization, 2014). As the risk of dementia increases exponentially with increasing age, this rise in the aging population causes major concern and is a focus for extensive research. At present, 46.8 million people suffer from dementia worldwide, and this number is projected to double over the next 20 years (Prince et al., 2015). Globally, there are 9.9 million new cases of dementia each year, meaning one new case is diagnosed every 3.2 seconds (Prince et al., 2015). The estimated 2015 global cost of dementia was 818 billion US dollars, and by 2030, this cost will rise to 2 trillion US dollars (Prince et al., 2015). In Canada, the cumulative monetary burden from both direct and indirect costs is also high, about 570 billion Canadian dollars (World Health Organization, 2014). Because those with dementia experience deterioration of cognitive competence in, for instance, language and problem-solving skills and memory, as well as challenges in performing activities of daily living, their quality of life is reduced due to the loss of their independence and social connectedness (Alzheimer's Association, 2015). Thus, dementia is an increasing concern for seniors, family caregivers, health professionals and society as a whole.

Dementia comprises both reversible and irreversible conditions, and Alzheimer's disease (AD) is the most common irreversible form (Alzheimer Society of Canada, 2010). Although there have been some advances in the development of pharmaceutical drugs that can alleviate symptoms of AD, no cure is yet available (Alzheimer's Association, 2015). AD is a neurodegenerative disorder associated with both Alzheimer neuropathology, such as neuritic

plaques (NPs) and neurofibrillary tangles (NFTs), as well as clinical symptoms of dementia. Thus, the gold-standard diagnosis of AD requires both the presence of Alzheimer neuropathology and the clinical symptoms of dementia. However, depending on the individual, the presence of Alzheimer neuropathology may not always directly lead to the onset of clinical symptoms of dementia (SantaCruz et al., 2011). For example, some individuals are able to delay the onset of dementia despite the presence of Alzheimer neuropathology, until a critical threshold of brain damage is reached (see review by Stern, 2002). The time it takes to reach this threshold depends on the amount of reserve present. Brain reserve relies on structural advantages, such as greater synaptic connections between neurons, which can increase the capacity to tolerate relatively more brain damage without reaching the threshold that marks the onset of symptoms (Stern, 2002). On the other hand, cognitive reserve refers to an 'active' process of using neural networks efficiently to compensate for brain damage. The level of cognitive reserve is thought to depend on intellectual factors, such as education and occupation (Stern, 2002). The combination of both cognitive and brain reserve can be termed cognitive resilience.

Multilingualism (i.e., speaking more than one language) has been suggested as a contributor to cognitive resilience because it requires higher levels of cognitive flexibility involving task switching, inhibition, attention control, and improved executive functioning compared to monolingualism (see review by Guzman-Velez & Tranel, 2015). However, evidence for such an association has yet to be explored. To date, research has studied the relationship between multilingualism and AD, but the results for this relationship have been mixed. For example, studies that used clinic-based samples have found evidence of an association between multilingualism and AD (Alladi et al., 2013; Bialystok, Craik, & Freedman, 2007; Craik, Bialystok, & Freedman, 2010), whereas population-based samples have found no

association (Yeung, St. John, Menec, & Tyas, 2014; Zahodne, Schofield, Farrell, Stern, & Manly, 2014). Also, the benefits from multilingualism have been found to vary depending on the characteristics of language use, such as the number of languages spoken (see review by Freedman et al., 2014; Hack, Tyas, Dubin, Fernandes, & Riley, 2012) and the frequency of using more than one language (Alladi et al., 2013). In one study, multilingualism was found to be associated with AD only when the educational level was low (Gollan, Salmon, Montoya, & Galasko, 2011). Therefore, given the possible relationship between multilingualism and AD, the objective of this study was to determine whether multilingualism plays a significant role in increasing cognitive resilience.

This research project focused on using secondary data from the Nun Study, which is a longitudinal study of 678 Roman Catholic sisters from the School Sisters of Notre Dame congregation, who were 75 years of age or older at baseline (Snowdon, 2002). The first two objectives of this study were to investigate whether there was an association of cognitive resilience with (1) multilingualism or (2) type of language. The second two objectives of this study were to explore whether (3) cortical atrophy (an indicator of brain reserve) or (4) education (an indicator of cognitive reserve) modified the association of cognitive resilience with multilingualism or type of language.

2.0 Literature Review

2.1 Dementia

The prevalence of dementia is projected to double every 20 years, meaning that there will be approximately 66 million cases of dementia by 2030 and an estimated 115 million cases by 2050 (Prince et al., 2015). Globally, there are 9.9 million new cases of dementia each year (Prince et al., 2015). Dementia is a collective term that encompasses decline in cognitive abilities that can lead to memory loss and deterioration in thinking, language processing, judgement and reasoning skills, as well as behavioral changes in mood and personality, and difficulty with performing activities of daily living (ADL) (i.e., eating, dressing, bathing) (Alzheimer Society of Canada, 2010). Since those with dementia experience deterioration of physical and mental abilities, their quality of life becomes reduced due to the loss of their independence and social connectedness (Alladi et al., 2013). The challenges of dementia can impose a painful experience on caregivers as well. In addition, the estimated 2015 global cost of dementia was 818 billion US dollars, and by 2030, this cost will rise to 2 trillion US dollars (Prince et al., 2015). In Canada, the financial burden of dementia is also high—approximately 570 billion Canadian dollars (World Health Organization, 2014). Thus, dementia impacts not only persons with dementia, but also family caregivers, health professionals and society as a whole.

While there are many types of dementia, AD is the most common (Alzheimer Society of Canada, 2010). AD is characterized by brain damage resulting from two types of brain lesions: NPs and NFTs (*see section 2.2.1*). Vascular dementia, the second most common form of dementia, is caused by disruptions in the vascular system that carries blood to the brain (Alzheimer Society of Canada, 2010). Other forms of dementia include frontotemporal dementia, dementia with Lewy bodies, and Creutzfeldt-Jakob disease, all of which have symptoms

associated with other chronic conditions such as Parkinson's disease and Huntington's disease. However, dementia does not result only from degenerative diseases, but also from other conditions such as infection, depression, traumatic events and some medications (see review by Tyas & Gutmanis, 2015). AD, vascular dementia, frontotemporal dementia, Lewy Body dementia, and Creutzfeldt-Jakob disease are categorized as "irreversible dementias," (i.e., not curable with treatment), whereas dementias that result from diseases such as thyroid or kidney diseases are deemed "reversible" (i.e., curable with treatment) (Alzheimer Society of Canada, 2010).

2.2 Alzheimer's Disease

2.2.1 Etiology

In 1906, Alois Alzheimer discovered two types of brain lesions in a severely demented patient (see reviews by Herrup, 2012; Tyas & Gutmanis, 2015). He concluded that these brain lesions, NPs and NFTs, were responsible for the symptoms of AD. Many mechanisms for Alzheimer pathology have been suggested: the amyloid cascade hypothesis, inflammation, oxidative stress, mitochondrial dysfunction, excitotoxicity, calcium dysregulation, and autophagy (Tyas & Gutmanis, 2015). The amyloid cascade hypothesis is the most commonly proposed mechanism for both early- and late-onset AD (Herrup, 2012). In 1984, Glenner and Wong first characterized NP as short (~ 40 amino acids) β-amyloid (Aβ) peptides, a component of a type I transmembrane protein called the amyloid precursor protein (APP) (Herrup, 2012). When the APP is metabolized, the concentration of Aβ peptides may increase depending on the types of enzymes used to break down the protein. When the Aβ load reaches a certain threshold, the amyloid cascade becomes activated, which leads to the formation of microscopically visible plaques/aggregates that cause neuronal damage (see review by Paula, Guimarães, Diniz, &

Forlenza, 2009). The other main type of brain lesion related to AD is NFTs. NFTs are associated with tau protein—a microtubule-associated protein that maintains neuronal structure and transport. When the tau proteins are phosphorylated, the structure of microtubules destabilizes and leads to the formation of paired helical filaments called NFTs (Herrup, 2012). Currently, NPs and NFTs are the most commonly known biomarkers of AD. These pathological changes of AD seem to emerge in a sequential manner (see reviews by Jack et al., 2010; Jack et al., 2013). Initially, Aβ plaques form in the brain, as indicated by reductions in $A\beta_{42}$ in the cerebrospinal fluid (CSF) and an increase in amyloid concentration in positron emission tomography (PET) amyloid imaging (Jack et al., 2010; Jack et al., 2013). Following a lag period, the individual may experience tau-mediated neuronal dysfunction and neurodegeneration, as indicated by tau in the CSF or by fluorodeoxyglucose PET (Jack et al., 2013). Next, magnetic resonance imaging reflects changes in brain structure, which gradually leads to the onset of cognitive impairment, depending on the individual's level of cognitive resilience. Therefore, NPs and NFTs do not develop simultaneously in AD, but occur in a gradual sequential process followed by symptoms of cognitive impairment.

2.2.2 Diagnosis and Treatment

One of the challenges experienced in diagnosing AD is the risk of misclassifying memory loss and other cognitive deficits as part of the “normal” aging process (see review by Khachaturian, 1985). The standard diagnosis of AD relies upon clinical evaluation (during life—only providing a presumptive diagnosis of AD), and neuropathological assessment (following death), which confirms this diagnosis.

2.2.2.1 Clinical Diagnostic Criteria for Alzheimer's Disease

Clinical diagnosis of AD is generally determined using specific sets of criteria. These criteria include the National Institute of Neurological Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984; updated in McKhann et al., 2011), the Consortium to Establish a Registry for AD (CERAD) *clinical* criteria (Morris et al., 1989), and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) criteria (American Psychiatric Association, 2013).

The NINCDS-ADRDA criterion diagnoses AD into three categories called "possible AD," "probable AD," and "definite AD" (McKhann et al., 2011). Subjects are diagnosed with "possible AD" if they have an atypical onset of dementia, and if AD is the "most plausible" cause for their observed cognitive impairments. If the subjects have a typical onset of dementia, and if AD is the only fitting cause (i.e., no other conditions can explain the symptoms) for their observed cognitive impairments, they are diagnosed as "probable AD." Lastly, when "probable AD" becomes confirmed by neuropathologic evidence (based on post-mortem examination), the diagnosis will shift to "definite AD" (McKhann et al., 2011).

Cognitive function is assessed through the CERAD neuropsychological battery (Morris et al., 1989). The CERAD clinical criteria diagnose AD if subjects have cognitive impairments in any of the cognitive domains, such as language, memory, praxis and general intellectual status, that can impact ADL (Morris et al., 1989). To diagnose AD as either "possible" or "probable," the CERAD criteria make use of demographic, clinical, neurological and neuropsychological information (Fillenbaum et al., 2008).

The DSM clinical criteria diagnose dementia based on whether subjects experience cognitive impairments in both memory and in one or more other cognitive domains that can

interfere with ADL (American Psychiatric Association, 2013). Some examples of the cognitive domains include short-term memory, abstract thinking, judgment, aphasia, apraxia, and agnosia (Tyas & Gutmanis, 2015). Some of the notable changes of the latest version of the DSM manual (fifth edition) include using the new term "neurocognitive disorder" as an alternative to using the term "dementia," with a further classification of the observed cognitive impairment based on the level of severity (from mild to major) (Tyas & Gutmanis, 2015).

In all three criteria, the investigators first have to obtain information on subjects' medical history and medication use, and then perform a clinical evaluation with laboratory tests to confirm whether other health issues, such as Parkinson's disease, depression, or schizophrenia, could have caused the dementia-like symptoms (Tyas & Gutmanis, 2015). Regular follow-ups have to be done to ensure that the rate of cognitive decline is indicative of AD instead of normal aging (Tyas & Gutmanis, 2015).

2.2.2.2 Neuropathologic Diagnostic Criteria for Alzheimer's Disease

As discussed in section 2.2.1, the presence of NPs and NFTs are currently known biomarkers of AD. There are two main types of neuropathologic diagnostic criteria for AD: CERAD (Mirra et al., 1991) and the National Institute on Aging-Reagan Institute (NIA-RI) neuropathologic criteria (NIA-RI Working Group, 1997; revised in Hyman et al., 2012). The Braak staging assessment is included as part of the NIA-RI diagnostic criteria (Braak & Braak, 1991).

In the CERAD *neuropathologic* criteria, a neuropathologist first examines tissues from brain regions, and determines the frequency of NPs present in the neocortex (Mirra et al., 1991). Each score is based on the degree of NPs present in the brain tissue: "no neuritic plaques," "CERAD score sparse," "CERAD score moderate," or "CERAD score frequent" (Mirra et al.,

1991). Secondly, the neuropathologist integrates information on the age at death and the NP scores to create an "age-related plaque score" (Mirra et al., 1991). Lastly, these age-related plaque scores are evaluated alongside clinical information to confirm whether the diagnosis of AD is definite, probable or possible (Mirra et al., 1991). One limitation of the CERAD criteria is that they use only the NP counts, and ignore NFTs in the diagnostic process.

Braak staging observes the pattern of AD progression in various regions of the brain based on NFTs only (Braak & Braak, 1991). In total, there are seven Braak stages, all classified based on the location of NFTs: Braak stage 0 (if no NFTs are present), Braak stages I-II (if NFTs are found in the entorhinal cortex and closely related areas), Braak stages III-IV (if NFTs are found in the hippocampus and amygdala), and Braak stages V-VI (if NFTs are found throughout the neocortex) (Hyman et al., 2012). The stages (I through VI) in the Braak staging criteria are often condensed into three groups (I-II, III-IV, and V-VI) (Braak & Braak, 1991). One limitation with Braak staging is that it uses only NFT counts in the diagnostic process.

For the NIA-Reagan criteria, the original publication in 1997 was revised in 2012 by incorporating new information on the preclinical phase of AD and the characterization of neuropathology based on amyloid plaques, NFTs, and NPs (NIA-RI Working Group, 1997; Hyman et al., 2012). In the NIA-Reagan criteria, the NP scores from CERAD are combined with NFT scores from Braak staging to create an AD diagnostic criteria with four possible classifications: "not likely AD," "low likelihood of AD," "intermediate likelihood of AD," or "high likelihood of AD" (Hyman et al., 2012). Since the NIA-Reagan criteria take into account both the presence of NPs and NFTs, these criteria may become a better measure of the degree of Alzheimer neuropathology than the CERAD criteria. The NIA-Reagan criteria do assume that the number of NPs and NFTs are correlated; however, this is not always the case (NIA-RI

Working Group, 1997). Neuropathologic assessments have shown that in some deceased subjects the NP and NFT scores do not correlate (i.e., some deceased subjects have a higher score for NP and a lower score for NFT, and vice versa) (NIA-RI Working Group, 1997). The diagnostic classification of AD for such deceased subjects is not yet established, and so the NIA-Reagan criteria are unable to include these "unclassified subjects" in the diagnosis (NIA-RI Working Group, 1997).

2.2.2.3 Treatment

Although some advancement has been made in the design of pharmaceutical drugs that can alleviate symptoms (e.g., memory loss, issues with language production, and motor skills), no cure is yet available for AD (Alzheimer Society of Canada, 2010). The two classes of pharmaceutical drugs that are currently available are cholinesterase inhibitors and glutamate reabsorption inhibitors (see review by Campos et al., 2016). The majority of cholinergic neurons are found in the basal forebrain, and cholinergic neurotransmission occurs in the neocortex and hippocampus of the brain. In AD, the accumulation of amyloid plaques in the basal forebrain affects cholinergic neurotransmission to the hippocampus, thereby causing adverse effects on cognitive function (Campos et al., 2016). Acetylcholine is a neurotransmitter that carries out neural transmission signaling to cholinergic neurons, and acetylcholinesterase is the enzyme that degrades acetylcholine. As a treatment option, taking cholinesterase inhibitors (such as donepezil, galantamine, and rivastigmine) will prevent breakdown (i.e., hydrolysis) of acetylcholine by acetylcholinesterase, and will increase the concentration of acetylcholine for signal transmission between neurons (Campos et al., 2016).

Glutamate is another neurotransmitter that could contribute to the clinical symptoms of AD. People with AD accumulate high concentrations of glutamate in the synaptic cleft between

neurons, which can cause an overstimulation of the N-methyl-D-aspartate (NMDA) receptors (see review by Danysz & Parsons, 2012). The NMDA receptors have high permeability to calcium ions and a voltage-dependent block by magnesium ions (Danysz & Parsons, 2012). When the receptors are overstimulated, the block by magnesium ions is removed and calcium ions are allowed to freely enter cells (Danysz & Parsons, 2012). As a result, when the NMDA receptors undergo chronic and mild activation by glutamate, neurodegeneration from excitotoxicity and cell death can occur (Campos et al., 2016; Danysz & Parsons, 2012). Memantine is a medication that acts as an NMDA-receptor antagonist that can prevent an influx of calcium ions into the neurons, which is responsible for causing oxidative stress and neuronal excitotoxicity and death (Campos et al., 2016). Thus, Memantine can inhibit the adverse effects of high levels of glutamate on post-synaptic neurons, and is prescribed to patients with moderate to advanced AD (Campos et al., 2016).

2.2.3 Risk Factors

To date, research has shown that AD is caused by various modifiable and non-modifiable risk factors. Some common examples of non-modifiable risk factors are age, family history of dementia, genetics, and gender; examples of modifiable risk factors include cardiovascular risk factors, tobacco use, alcohol consumption, and low levels of education (see reviews by Tyas & Gutmanis, 2015; Graves 2004).

2.2.3.1 Non-modifiable Risk Factors

Age is the most established risk factor for AD. The risk of AD is shown to double every five years among individuals who are older than 65 years of age (see review by Carrillo, Thies, & Bain, 2012). Moreover, among individuals who live up to 100 or more years, the risk of AD increases to 41% (Carrillo et al., 2012). Thus, older adults have an increased risk of AD.

Family history of dementia is one of the most robust risk factors for AD (Graves, 2004). Autosomal dominant, single gene mutations on chromosomes 1, 14, and 21 affect gene coding for APP, presenilin 1 (PSEN1) and presenilin 2 (PSEN2), respectively, and can lead to the onset of familial or early-onset AD by producing greater levels of amyloid beta aggregates (Graves, 2004; Tyas & Gutmanis, 2015). Familial AD increases the risk of AD by the number of relatives affected (Graves, 2004). However, the risk of familial AD declines with increasing age (Graves, 2004). In the general population, the prevalence of familial AD accounts for less than 1% of all AD cases (see review by Schu, Sherva, Farrer, & Green, 2012).

Genetics also play a role in late-onset (sporadic) AD. The *APOE* gene codes for apolipoprotein E, which is a cholesterol and lipid-delivering glycoprotein, made up of 299 amino acids that is highly expressed in the liver and in the central nervous system (see review by Holtzman, Herz, & Bu, 2012). Apolipoprotein E is responsible for maintaining cholesterol homeostasis. In the central nervous system, *APOE* is expressed by astrocytes and microglia (Holtzman et al., 2012). The *APOE* gene has three types of alleles: *APOE*-ε2, *APOE*-ε3 and *APOE*-ε4 (see review by Meyer et al., 1998). The *APOE*-ε2 allele is thought to be protective against AD, while the *APOE*-ε4 allele is a strong and well-established risk factor for AD. The effects of the *APOE*-ε4 allele follow a dose-response relationship where having two copies of the *APOE*-ε4 allele (i.e., homozygous dominant) significantly increases the risk of AD more than having just one copy of the *APOE*-ε4 allele (i.e., heterozygous dominant) (see review by Roses, 1996). For example, in one study, individuals with two copies (homozygous) of the *APOE*-ε4 allele increased their risk of AD from 20% to 90% and had an earlier mean age of onset, decreasing from 84 to 68 years (Corder et al., 1993). Lastly, the presence of the *APOE*-ε4 allele is not a sufficient cause of AD, but rather a risk factor that can interact with other

external/environmental factors to increase an individual's susceptibility to developing sporadic AD.

Gender is a possible risk factor for AD, but findings have varied. Some incidence studies found that women had a higher risk of developing AD than men (Bachman et al., 1993; see review by Janicki & Schupf, 2010; Letenneur, Commenges, Dartigues, & Barberger-Gateau, 1994), while other studies found no association (Hebert et al., 1992; Rocca, Cha, Waring, & Kokmen, 1998). Moreover, women in the oldest age groups may be at a higher risk of developing AD than men (Fratiglioni et al., 1997; Letenneur et al., 1999; Ruitenberg, Ott, van Swieten, Hofman, & Breteler, 2001). Women's tendency to smaller head circumferences and their lower levels of estrogen and other hormonal changes in the blood following menopause (Janicki & Schupf, 2010) have been cited as contributing to their higher incidence of clinical symptoms of AD. However, both men and women may have an equal likelihood of developing Alzheimer neuropathology (Graves, 2004). A recent meta-analysis has indicated that the difference in the incidence and prevalence of dementia due to AD between men and women was statistically non-significant, and that any differences observed between these two sexes may have been caused by several possibilities, such as methodological issues, environmental risk factors having different impacts on the sexes, or biological differences between men and women (see review by Fiest et al., 2016). Therefore, the impact of gender on AD is not yet clear and warrants further investigation.

2.2.3.2 Modifiable Risk Factors

The risk of developing AD in later life increases in relation to many behaviors associated with modifiable risk factors, such as diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, tobacco use, and low levels of education (Norton, Matthews, Barnes,

Yaffe, & Brayne, 2014). The combined risk of these seven modifiable factors is equivalent to 9.6 million cases of AD globally (Norton et al., 2014). Moreover, if the prevalence of these risk factors is reduced by 10% per decade, the global prevalence of AD could decline by 8.3% by 2050 (Norton et al., 2014). In addition to the above-mentioned factors, alcohol consumption and vascular factors, such as stroke and plasma homocysteine levels, are also considered to be modifiable risk factors of AD (see review by Graves, 2004; Roher et al., 2011; Seshadri et al., 2002). These risk factors are discussed in detail below.

Diabetes is known to be a risk factor for AD (Botero et al., 2012). For example, type II diabetes has been associated with dementia and late onset AD, after adjusting for age, sex, education, *APOE,* and ethnicity (Cheng et al., 2011). Moreover, diabetic individuals who take insulin treatment have shown an increased risk of AD compared to diabetics who take oral hypoglycemic agents as treatment (Leibson et al., 1997; Luchsinger, Tang, Stern, Shea, & Mayeux, 2001; Ott et al., 1999). Further, in the Honolulu-Asia Aging Study, diabetes and the *APOE*-ε4 allele acted synergistically to increase the risk of AD by five-fold in *APOE*-ε4 carriers who were diabetic compared to those without both diabetes and the *APOE*-ε4 allele (Peila, Rodriguez, Launer, & Honolulu-Asia Aging Study, 2002). A significant association was also observed between diabetes and the number of NPs and NFTs in the hippocampus and NFTs in the cortex among individuals with the *APOE*-ε4 allele, compared to those who either had the *APOE*-ε4 allele or diabetes only (Peila et al., 2002).

High blood pressure may cause poor cognitive function in later life through increased brain atrophy and Alzheimer neuropathology, and decreased brain weight (Launer, Masaki, Petrovitch, Foley, & Havlik, 1995). A significant association has been observed between hypertension and the risk of AD (Meng et al., 2014; see review by Tolppanen, Solomon,

Soininen, & Kivipelto, 2012) and dementia (Skoog et al., 1996); however, some studies have not found an association (Posner et al., 2002). The reasons for not finding any significant association between hypertension and AD/dementia could be due to survivor bias (see review by Luchsinger, Tang, Shea, & Mayeux, 2004). Since the majority of studies related to AD/dementia are conducted in populations that are over the age of 65, those with an onset of hypertension in middle age may die from other causes and would not survive long enough to get dementia/AD (Luchsinger et al., 2004).

Overall, both diabetes and hypertension may affect AD through cerebrovascular disease (Luchsinger et al., 2004). Approximately 60-90% of people with AD show evidence of cerebrovascular pathology, with about 30% showing cerebral infarction (see review by Kalaria, 2002). Older populations in general have an increased risk of cerebrovascular disease as they are more prone to be affected by various vascular risk factors such as hypertension, diabetes and high homocysteine levels (see review by de Toledo Ferraz Alves, Tania Correa, Ferreira, Wajngarten, & Busatto, 2010). Vascular mechanisms, such as impairment in cerebral blood flow, have been shown to be associated with clinical diagnosis of AD (Roher et al., 2011), similar to the presence of vascular lesions (Heyman et al., 1998; Snowdon et al., 1997). The presence of both vascular lesions and Alzheimer neuropathology can lead to an earlier onset of dementia. Some studies have found that vascular risk factors and cerebrovascular disease could induce pathological effects of AD (Luchsinger et al., 2004). For example, cardiovascular risk factors could affect β-amyloid deposition and increase the risk of AD (Luchsinger et al., 2004). Thus, vascular risk factors increase the risk of both cerebrovascular disease as well as AD, and therefore, minimizing the prevalence of vascular risk factors can significantly reduce the incidence of AD.

In addition, high plasma homocysteine levels (a major vascular risk factor) can affect AD risk (de Toledo Ferraz Alves, Tania Correa et al., 2010). For example, when plasma homocysteine levels were >14 μmol per liter, the risk of AD doubled (Seshadri et al., 2002). Moreover, a meta-analysis has shown that the association between plasma homocysteine levels and AD is not influenced by age (see review by Shen & Ji, 2015). However, not all studies have found an association. For example, a study of 1249 elderly participants showed no correlation between plasma homocysteine levels and the onset of dementia or mild cognitive impairment (MCI) (Arioğul, Cankurtaran, Dağli, Khalil, & Yavuz, 2005). The findings from different studies may vary depending on confounders, such as nutritional habits and genetic differences in populations being studied (Arioğul et al., 2005). Therefore, further research is needed to address the effects of these confounders on the association between plasma homocysteine levels and AD/dementia.

Midlife increased body mass index (BMI) has been shown to be a strong risk factor of dementia (see review by Emmerzaal, Kiliaan, & Gustafson, 2015). While the majority of studies have shown an association between increased body mass index (BMI) in midlife and the risk of dementia (Hassing et al., 2009; Whitmer et al., 2008; Xu et al., 2011), some studies have not found an association (Fitzpatrick et al., 2009; Ravona-Springer, Schnaider-Beeri, & Goldbourt, 2013). Small sample size was a limitation in these studies. Conversely, a recent retrospective cohort study performed on a very large sample (approximately two million participants) also showed contradictory results compared to most previous studies, where an increased BMI in midlife reduced the risk of dementia (Qizilbash et al., 2015). For example, people who were obese had a 29% lower risk of dementia than people with a healthy weight (Qizilbash et al., 2015). Since this study could not adjust for covariates such as blood pressure, physical activity

level, socioeconomic status, and ethnic origin, all of which can affect the association between BMI and dementia, it is possible that the findings were affected by these confounding factors (Qizilbash et al., 2015). Moreover, people who were underweight had a 34% higher risk of dementia than people with a healthy weight (Qizilbash et al., 2015). Being underweight in late life has been shown to elevate the risk of dementia (Emmerzaal et al., 2015; Fitzpatrick et al., 2009; Qizilbash et al., 2015). On the other hand, having an increased BMI in late life has been shown to reduce the risk of dementia (Barnes et al., 2009; Fitzpatrick et al., 2009; see review by Gustafson & Luchsinger, 2013). Factors, such as late-life low blood pressure; low cholesterol levels; high leptin levels; and age-related changes in the metabolism of carbohydrates, lipids and proteins, may be responsible for the reduced risk of dementia in late life among individuals with high BMI values (Qizilbash et al., 2015). In summary, most studies show that increased BMI is a risk factor for dementia in midlife and not a risk factor in late life; however, being underweight has also been shown to be a risk factor in late life. Thus, maintaining a healthy weight instead of being either over- or underweight would be the most suitable strategy for minimizing the risk of dementia.

Depression is another risk factor that can cause dementia (see reviews by Diniz, Butters, Albert, Dew, & Reynolds, 2013; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). In a meta-analysis of 23 studies, depression in late life significantly increased the risk of all-cause dementia (OR=1.85, 95% CI=1.67-2.04), AD (OR=1.65, 95% CI=1.42-1.92) and vascular dementia (OR=2.52, 95% CI=1.77-3.59) (Diniz et al., 2013). Another population-based cohort study found that older adults with depressive symptoms were more likely to be diagnosed with dementia over a five-year follow-up period (Gatz, Tyas, St. John, & Montgomery, 2005). Although a stronger association has been shown between depression and vascular dementia in

some studies, this study found all types of dementia to have a similar strength of association with depression (Gatz et al., 2005). A recent study has found that individuals with depressive symptoms were more likely to experience a higher rate of cognitive decline (Wilson et al., 2014). However, it is not yet clear whether reverse causality can influence these results. For example, it is unclear whether the depressive symptoms led to dementia, or if the dementia-related brain changes resulted in depressive symptoms, or both. Thus, further investigation will be required to clarify the direction of the association between depression and dementia.

Tobacco use has been shown to increase the risk of AD. Smokers with dementia had a higher likelihood of death (3.4 times) than non-demented smokers over a three-year period (Wang, Fratiglioni, Frisoni, Viitanen, & Winblad, 1999). Moreover, tobacco use had a dose-response effect on the risk of AD, with moderate to heavy-level smokers having a greater risk of AD than non-smokers (Tyas et al., 2003). However, this dose-response effect was not observed among very heavy smokers, perhaps due to survival bias (i.e., heavy smokers may have had a shorter survival than non-smokers with or without an AD diagnosis) (Tyas et al., 2003). Level of smoking was associated with the presence of Alzheimer-type neuropathology: the number of NPs increased with the intensity of smoking, with heavy smokers having the highest number of NPs (Tyas et al., 2003). The adverse effect from smoking was also observed in another study where smokers with the *APOE*-ε4 allele had a higher risk of AD than those without the allele (Merchant et al., 1999). Lastly, 13.9% of AD worldwide cases have been found to be attributable to smoking; therefore, reducing the rates of smoking could significantly impact the prevalence of AD (Norton et al., 2014).

Alcohol consumption is known to be associated with dementia, termed alcoholic dementia; however, the association between alcohol consumption and AD is less clear. Similar to

tobacco use, alcohol consumption may have a dose-response effect (Graves, 2004). In one study, individuals with heavy alcohol consumption experienced adverse effects on cognitive function and an increased risk of dementia (Orgogozo et al., 1997). However, in another study, low to moderate alcohol consumption showed protective effects against AD, with one to six alcohol drinks per week shown to decrease the risk of AD (Mukamal et al., 2003). Other studies have found a protective effect against AD with the consumption of wine only and no other alcoholic beverages (Lindsay et al., 2002; Truelsen, Thudium, Gronbaek, & Copenhagen City Heart Study, 2002). Although some studies show a dose-response effect on AD from the consumption of alcohol, other studies have found no association (Tyas, Manfreda, Strain, & Montgomery, 2001). Tobacco use can also influence alcohol-consumption effects on AD, because both tobacco and alcohol are often consumed together, and the nicotine present in tobacco can interact with the adverse effects of alcohol (Tyas, Koval, & Pederson, 2000). The reasons for the inconsistent findings can include methodological issues present in the studies. For example, using case-control studies to determine the effects of alcohol on the risk of AD is problematic, because the researchers use proxy reports from caregivers (since all cases are diagnosed with AD) and self-reports from the controls (Tyas et al., 2000). Because the alcohol consumption (exposure) information is not collected using the same type of sources, the results may show a spurious association between alcohol consumption and the risk of AD. On the other hand, cohort studies can avoid using proxy reports since the participants are not diagnosed with AD at baseline (Tyas et al., 2000). Furthermore, when cohort studies are used, no association has been observed between alcohol consumption and AD, except when the participants' type of residence (community or institution) was taken into account (Tyas et al., 2000). Moreover, in both cohort and case-control studies, researchers have found another challenge, that is, distinguishing

between AD and alcoholic dementia (a type of dementia not consistently diagnosed in epidemiologic studies). Therefore, the methodological issues related to these studies should be addressed in order to confirm whether alcohol consumption affects the risk of AD.

Physical activity is a factor that can protect against AD and dementia. Studies have shown that physical activity, including mild physical activity such as walking, can improve cognition and decrease the risk of cognitive impairment (see reviews by Ahlskog, Geda, Graff-Radford, & Petersen, 2011; Baumgart et al., 2015; Beydoun et al., 2014; Rolland, van Kan, & Vellas, 2008; Sofi et al., 2011). More importantly, older adults participating in exercise programs as well as regularly performing vigorous exercises can greatly enhance their cognitive function (Barnes et al., 2013). However, to date, research has yet to discover the optimal duration of exercise and at what period of life an individual must begin exercising to experience the maximum benefits on cognition (Baumgart et al., 2015).

Intellectual factors such as educational attainment and multilingualism that promote cognitive stimulation can also protect against AD. The highest number of worldwide AD cases (19.1%) were attributable to low educational attainment, out of other modifiable risk factors for AD (Norton et al., 2014). Studies have shown that individuals with high levels of education have a decreased risk of AD and dementia, while individuals with low levels of education have an increased risk (Evans et al., 1997; Fratiglioni et al., 1997; Launer et al., 1999; Letenneur et al., 1999; Stern et al., 1994). Moreover, another prospective cohort study demonstrated that each additional year of education enhances cognitive function, even though post-mortem examinations on deceased subjects revealed a higher level of Alzheimer neuropathology (Bennett et al., 2003). However, not all studies have access to post-mortem examinations and as a result, researchers often use alternate measures, such as resting regional cerebral blood flow

(rCBF) as a surrogate measure for the presence of Alzheimer neuropathology (see review by Stern, 2012). The rCBF and Alzheimer neuropathology have an inverse relationship, where low rates of rCBF indicate higher levels of Alzheimer neuropathology and vice versa (Stern, 2012). Higher levels of education were associated with a depleted flow of rCBF in the parietotemporal area, indicating the presence of Alzheimer neuropathology (Stern, Alexander, Prohovnik, & Mayeux, 1992). Recent studies have shown that low academic performance increases the risk of dementia as well (Bezerra et al., 2012; Dekhtyar et al., 2015; Dekhtyar, Wang, Fratiglioni, & Herlitz, 2016; Mehta et al., 2009; Tyas, Iraniparast, MacKinley, Costa, & Fearon, 2016). For example, after controlling for age and educational attainment, "below average" school performance was associated with the risk of AD (OR: 4.8, 95% CI:1.5-1.6) (Mehta et al., 2009). A more recent longitudinal study has also found similar findings, where low school grades were associated with an increased risk of dementia, after adjusting for educational attainment and occupational complexity (HR: 1.54, 95% CI: 1.03-2.29) (Dekhtyar et al., 2016). Therefore, intellectual factors such as higher educational attainment and academic performance can reduce the risk of AD, presumably by enhancing higher levels of cognitive stimulation from early life.

The mechanisms for the observed associations of educational attainment and academic performance on AD remain unclear. One plausible explanation is that advanced and active learning from higher educational attainment promotes greater levels of cognitive stimulation, which, in turn, help to develop more synaptic connections between neurons that build up neural reserve (Stern et al., 1994). The higher the capacity of neural reserve, the greater the brain's ability to compensate for damage and delay the onset of AD symptoms (Stern et al., 1994; Stern, 2002). Conversely, if the levels of education are low, the neural reserve capacity may be insufficient to compensate for brain damage. In addition, the level of education can be influenced

by various external factors such as available opportunities, socioeconomic status, and poor nutrition (Markesbery, 1998). Therefore, research based on studying the effects of low educational attainment on AD have to take these external factors into account as well.

Occupation is also a promoter of cognitive reserve. Those with lower occupational attainment (based on the United States census categories: unskilled, semiskilled, skilled trade/craft, and clerical) were at more than twice the risk of developing dementia, compared to those with higher occupational attainment (based on the United States census categories: manager, business/government, and professional/technical) (Stern, 2012). Lastly, leisure activities can enhance cognitive reserve too (Abutalebi et al., 2015; Stern, 2012). The risk of developing dementia was 38% less among participants who were involved in more than six leisure activities compared to participants who were not (Abutalebi et al., 2015; Stern, 2012). Therefore, cognitive reserve can be increased by education, occupation and leisure activities. Lastly, multilingualism can improve cognitive flexibility, thereby enhancing neural reserve to protect against AD as well. The cognitive benefits and the protective effects of multilingualism on AD will be discussed in *sections 2.3 and 2.5.*

2.3 Multilingualism

2.3.1 Cognitive Advantages of Multilingualism

Multilingualism can improve executive function. Because factors that enhance higher levels of cognitive stimulation, such as education, physical activity, and leisure activities, can improve executive function and help protect against dementia (see review by Stern, 2009), multilingualism, which is known to enhance cognitive flexibility, could exhibit similar benefits. Executive function is known as a domain-general system that includes a wide variety of

functions, such as managing, integrating, regulating, coordinating, attention control and visual perceptions (see reviews by Bialystok, 2011; Valian, 2015). Executive function can be broken down into three core components: inhibition, updating (working memory), and shifting (Miyake et al., 2000). The level of executive function with respect to these three components is assessed through performance-based tests (Valian, 2015). For example, to study the effects of multilingualism on executive function, various performance tasks are available: Simon, Stroop or Flanker tasks (testing for conflict resolution/attention) and day-night task (testing for inhibition) (Bialystok, 2011). Therefore, the performance in these assessments can be used as an indirect measure of the effects of multilingualism on executive function.

Multilinguals have efficient conflict-resolution skills, because when they are speaking a particular language, they have to be able to inhibit speaking other languages to avoid mixing languages (Abutalebi et al., 2015; Bialystok, 2011). When bilinguals participated in performance tests where inhibitory control was assessed, they performed better than monolinguals (Abutalebi et al., 2015; Clare et al., 2014). Conflict resolution capacities increase with age: older bilinguals had a larger bilingual advantage (i.e., less interference shown in tests) than older monolinguals (Bialystok, Poarch, Luo, & Craik, 2014). Moreover, older bilinguals performed better on performance-based tasks than young bilinguals, because of their ability to more efficiently use various brain mechanisms than young bilinguals, or perhaps because young bilinguals showed a ceiling effect on the assessments (see review by Bialystok, Abutalebi, Bak, Burke, & Kroll, 2016). Inhibitory control involves functions associated with attention such as interference suppression (i.e., the ability to control attention and avoid irrelevant cues) and response inhibition (i.e., the ability to control inappropriate habitual responses) (Martin-Rhee & Bialystok, 2008). Bilinguals have been shown to exhibit inhibitory control through interference suppression

and not through response inhibition (Martin-Rhee & Bialystok, 2008). However, one study that compared the ability to encode (i.e., to view a set of words and store them in memory) and retrieve (i.e., to recall the viewed words) in older monolinguals versus older bilinguals showed that the older monolinguals recalled more words than the older bilinguals, when participants completed the tasks with full attention (without the presence of distractors) (Fernandes, Craik, Bialystok, & Kreuger, 2007). Further, when the attention was divided by the use of distractors, bilinguals and monolinguals had similar recall abilities in most conditions, except during the encoding phase with an unrelated distractor (Fernandes et al., 2007). Bilinguals had a disadvantage in recalling words compared to monolinguals in the simplest task (with full attention condition), but their recall ability was similar to monolinguals in most of the difficult tasks (with distractors). These findings could imply that bilinguals did have an advantage in resisting further reductions in recalling words while performing tasks with increasing difficulty (Fernandes et al., 2007). However, in comparison to other studies, bilinguals in this study failed to exhibit a clear bilingual advantage in maintaining attention control in the midst of interference (Fernandes et al., 2007). Further, multilinguals tend to have smaller vocabularies and lower levels of lexical access compared to monolinguals, which may have caused challenges in verbal recall, and thus led to inconsistent findings (Fernandes et al., 2007). Overall, the conflict-resolution capacity difference between bilinguals and monolinguals was more evident when performance tests included complex non-verbal tasks (Bialystok, Craik, Binns, Ossher, & Freedman, 2014).

Other cognitive processes such as working memory, task switching, inductive reasoning, speech segmentation, rule learning and semantic memory, all appear to be improved with second language learning (Jafari, Esmaili, Toufan, & Aghamollaei, 2015). Bilinguals' performance in

working memory tasks improves only if the tasks themselves are related to the executive control system (see review by Bialystok, 2009). For example, if the memory tasks were associated with verbal recall, the bilinguals performed poorly (Bialystok, 2009). Moreover, bilinguals have better task-switching abilities than monolinguals, since they are constantly switching between languages (Gold, Johnson, & Powell, 2013). The brain areas responsible for language switching, such as the left lateral frontal cortex and the anterior cingulate cortex, have developed increased efficiency in bilinguals (Gold et al., 2013). Moreover, bilinguals are able to apply these efficient language-switching skills in their everyday non-linguistic settings and for perceptual switching skills as well (Gold et al., 2013). Thus, the process of learning a second language itself provides bilinguals with a useful set of cognitive skills.

Neuroimaging studies have also shown that bilinguals have high levels of activation and functional connectivity in brain regions that are associated with the executive control system, such as the left prefrontal cortex, inferior parietal lobule, and temporal poles (Bialystok et al., 2016; Grady, Luk, Craik, & Bialystok, 2015). Executive function, particularly selective attention, is usually developed in the prefrontal cortex (see review by Diamond, 2010), and therefore, the brain activation that occurs in the prefrontal cortex in bilinguals indicates higher levels of executive function.

Although studies show that bilingualism benefits the executive control system, other studies have not found such an association. For example, bilinguals did not significantly differ from monolinguals on assessments related to executive function (Clare et al., 2014). The reason for the mixed findings may have been the dominant language of the environment. For example, if a bilingual lives in a highly bilingual environment, the amount of effort required for conflict resolution/inhibition is much less than that for individuals living in a second-language dominant

environment (Clare et al., 2014). Small sample sizes of recruited bilinguals in studies can further influence results in regards to any associations between multilingualism and executive function, because of insufficient power (Clare et al., 2014). Moreover, young bilinguals did not have a better performance than monolinguals completing the Stroop task for interference (Kousaie & Phillips, 2012). Similarly, older bilinguals also did not show any beneficial effects of bilingualism in this study (Kousaie & Phillips, 2012). Some possible explanations for the inconsistent findings are presented by Valian (2015): (i) even with cognitive flexibility that occurs with multilingualism, individuals may perform differently from one task to another, depending on the nature of their experience, such as their frequency of using multiple languages; (ii) minor changes in performance-based tasks can cause variations in the performance of participants; and (iii) the results from performance-based tasks can vary, as no single assessment can measure the effects of all possible cognitively stimulating experiences on executive function. Moreover, another challenge with predicting multilingualism's effects on executive function is the possibility of reverse causality influencing this association. For instance, it is difficult to determine whether multilinguals are capable of learning multiple languages because they were born with superior executive function, or if the multilinguals developed a higher level of executive function after they learned multiple languages (Valian, 2015). As a result, the cause and effect relationship between multilingualism and executive function is not always clear.

2.3.2 Cognitive Disadvantages of Multilingualism

Multilingualism can also cause various disadvantages to cognitive abilities. For example, multilinguals perform poorly on verbal fluency tasks and experience difficulty with tip-of-the-tongue word retrieval (Bialystok, 2009). Monolinguals can outperform bilinguals on cognitive assessments that include features such as timing and retrieving low frequency words (measured

by speed and naming accuracy) (see review by Gasquoine, 2016). Moreover, among Spanish-English bilinguals, monolinguals performed better on the Stroop test than bilinguals; in particular, naming with the color-word condition was poorly performed by bilinguals (Rosselli et al., 2002). To measure the lexical access of bilinguals, three types of cognitive tests were used: the Peabody Picture Vocabulary Test III (Form B), Boston naming task, and the category and letter fluency test (Bialystok, Craik, & Luk, 2008). The results showed that monolinguals had higher scores than bilinguals on the vocabulary test, but no difference was observed among different age groups. For the Boston naming task, monolinguals outperformed bilinguals for both the picture naming and definition versions of the test. Monolinguals also had higher letter and category fluency scores than bilinguals, and for this test, younger participants performed better than older participants. However, no interaction was observed between age and language for all three tests (Bialystok et al., 2008). The poor vocabulary and letter fluency scores for bilinguals may perhaps have been due to cross-language interference from the two spoken languages, or to bilinguals less frequently using words that are distinct to specific languages (Gollan, Montoya, & Werner, 2002). Therefore, individuals that speak more than one language may experience certain cognitive disadvantages as well.

2.3.3 Challenges Associated with Multilingualism Research

2.3.3.1 Using Subjective Versus Objective Measures

When measuring multilingualism (as an exposure), studies have to focus on language history, which includes the level of proficiency, frequency and intensity of use of multiple languages, and the age of second-language acquisition. The size of bilingual or multilingual samples and the language used in the cognitive assessments must also be considered. The level of language proficiency can be measured objectively or subjectively. Studies that use subjective

measures usually rely on self-reporting by participants, or on caregivers' reports regarding participant's language history (Alladi et al., 2013; Bialystok et al., 2014; Yeung et al., 2014). However, using self-reports or caregiver interviews to determine language proficiency may lead to inaccurate estimations, since the caregivers and the participant could over- or under-estimate the levels of language proficiency, based on how they subjectively perceive fluency in a language. To address this issue, some studies include objective measures to ensure that the results are more accurate and to help minimize bias. For instance, the reading level in a spoken language can be measured as an indirect objective measure of the proficiency in that language (Zahodne et al., 2014). Generally, studies use objective measures as a way to validate subjective measures. These challenges may be addressed through standardization of both subjective and objective measures of bilingualism across studies for effective comparisons (Zahodne et al., 2014). Sample size also poses challenges in studies related to bilingualism, because of difficulty in obtaining a sufficient sample of bilinguals (Yeung et al., 2014). Lastly, the language used in cognitive assessments can influence a participant's performance too. For example, participants who speak English as their primary language may perform better on the highly language-based cognitive assessments that are in English, compared to those who speak English as a second language (Yeung et al., 2014).

2.3.3.2 Frequency and Intensity of Language Use

Collecting data on the frequency and intensity of use of multiple languages is important because these factors can influence results. The higher the frequency of use of both languages by bilinguals, the greater the practice of inhibition would be, and in turn, the greater benefit to executive function: when bilinguals actively used both languages on a daily basis, the protective effects of bilingualism on aging increased (Emmorey, Luk, Pyers, & Bialystok, 2008). The

beneficial effects experienced by active bilinguals were further demonstrated in another study where older adults who were all Persian-English bilinguals from an early age, with a high intensity of bilingualism (i.e., speaking more than one language daily), were able to perform well on lexical memory tasks (Jafari et al., 2015). Moreover, speaking three or more languages on a regular basis was significantly associated with better cognitive performance, particularly in verbal abilities and processing speed (Ihle, Oris, Fagot, & Kliegel, 2016). Therefore, both frequency and intensity of language use can be assessed to determine the protective effects of multilingualism against AD and dementia.

2.3.3.3 Age of Second Language Acquisition

Age of second language acquisition is also important when collecting data on multilingualism. However, the results for the effects of age of second language acquisition on bilingual advantage have varied. Those with an early exposure to a second language have demonstrated a higher performance on visual episodic memory (Schroeder & Marian, 2012). Other studies have indicated that early-life versus late-life acquisition of a second language can have different effects on cognition and the frontal executive functions (Bak, Nissan, Allerhand, & Deary, 2014; Jafari et al., 2015; Jasinska & Petitto, 2013). For example, bilinguals who learned a second language before the age of six showed strong lateral hemispheric connections in the brain, whereas bilinguals who acquired a second language after the age of six showed left hemispheric dominance while speaking both languages (Jafari et al., 2015). Both early- and late-life learning of second language can benefit cognition; however, earlier exposure to a second language has greater benefits if the individuals have higher levels of intelligence (Bak et al., 2014). Moreover, learning a new language at a later age could still have beneficial effects on cognition through frequent use of interference control while speaking two languages (Ansaldo,

Ghazi-Saidi, & Adrover-Roig, 2015). Further, a later age of second language acquisition can result in cognitive benefits, but only among immigrants that migrate to a second-language-dominant country in young adulthood (Woumans et al., 2015). Since immigrants have to put forth more cognitive effort to learn a new language, higher levels of cognitive effort will, in turn, boost the level of cognitive resilience. Another study stated that those who learn a second language at a later age are able to recruit more networks in the prefrontal cortex than bilinguals exposed to an earlier second language learning or monolinguals (Jasinska & Petitto, 2013). However, a significant association was not found between the age of second language acquisition and the clinical manifestation and diagnosis of AD, perhaps because the oldest participants in the sample were only 25 years old when they learned a second language (Woumans et al., 2015). In summary, current research shows inconsistent findings of a cognitive benefit from earlier exposure to a second language; this topic warrants further investigation.

2.3.3.4 Typological Similarity Between Languages

The cognitive benefits associated with speaking multiple languages can be influenced by the typological similarity between spoken languages. When two linguistically similar languages are spoken by an individual, he/she will experience greater levels of cross-linguistic interference (Serratrice, Sorace, Filiaci & Baldo, 2009). English is a Germanic language and is thus linguistically more similar to German than romance languages (e.g., French, Spanish, and Italian) (Serratrice et al., 2009). Because of the similarities between English and German, English-German bilinguals tend to selectively choose word orders that are common to both languages instead of those unique to each language (Dopke, 1998). To date, studies have provided evidence of cognitive benefits from speaking either typologically similar or dissimilar languages. For example, a study conducted on Spanish-Catalan bilinguals reported they had

enhanced executive function compared to Spanish monolinguals (Costa, Hernández, & Sebastián-Gallés, 2008). In a study conducted in Hong Kong, those speaking dissimilar languages (Cantonese-English) and similar languages (Cantonese-Mandarin) were separately analyzed (Abutalebi, Canini, Della Rosa, Green, & Weekes, 2015). The results showed that both groups had a significant association between second language exposure and increased gray matter in the right inferior parietal lobule. However, the association between naming performance and increased gray matter volume trended toward significance in those who were Cantonese-English bilinguals only. Thus, it was hypothesized that speaking similar languages created more cognitive demand than speaking dissimilar languages, as bilinguals have to minimize overlaps of both languages from causing interference while speaking (Abutalebi et al., 2015). Conversely, speaking two typologically dissimilar languages has also been shown to have cognitive benefits. For example, a study found that those who spoke two dissimilar languages such as Korean-English had more cognitive benefits than the Korean monolinguals (Yang & Yang, 2016). Because Korean belongs to the Altaic language group and English belongs to the Indo-European language group, there are orthographic differences between English and Korean. The findings indicated that during Korean word reading the posterior region of the right dorsolateral prefrontal cortex (involved in visual processing) became activated, in addition to the brain regions that were activated during alphabetical word reading. Because there are additional brain activations when speaking dissimilar languages, it is possible that Korean-English bilinguals have enhanced executive function, as they utilize visuospatial processing as well as give careful attention to the phonemic and semantic differences while speaking (Yang & Yang, 2016). Similarly, another study found that those who spoke Chinese-English outperformed the monolinguals in cognitive benefits (Tao, Marzecova, Taft, Asanowicz, & Wodniecka, 2011).

With respect to bidialectical languages, results from studies that had used participants who spoke two bidialectical languages have shown no differences in cognitive benefits compared to monolinguals. For example, those who spoke Italian-Venetian bi-dialectics had similar performances in cognitive tests compared to the Italian monolinguals (Scaltritti, Peressotti, & Miozzo, 2015). However, the study mentioned that the participants who spoke Italian-Venetian bi-dialectics had less opportunity to switch frequently between languages, and this may have influenced the findings (Scaltritti et al., 2015). Similarly, another study conducted on individuals speaking Mandarin-Min bi-dialectics did not have any significant advantages in conflict resolution skills compared to monolinguals (Wu, Zhang, & Guo, 2016). Since studies conducted on bilinguals who spoke bidialectical languages did not show any cognitive advantageous over monolinguals, it may be possible that speaking bi-dialectics does not provide additional cognitive benefits. Bidialectical languages only differ in pronunciation, and the language rules and syntax are comparable between the two dialects (Wu et al., 2016). As a result, there may be less cognitive demand and cross-linguistic interference involved in those who speak bidialectical languages compared to those who speak languages that have lexical, syntactic, and phonologic dissimilarities (Wu et al., 2016). In summary, speaking either two typologically similar or dissimilar languages has been shown to benefit cognition, and this area of research warrants further investigation.

2.3.3.5 Measuring Outcome

Measuring the outcome is a challenge in these studies. Often, studies have focused on the age of onset of dementia symptoms, or the age of clinical diagnosis of dementia/AD as their outcome (Lawton, Gasquoine, & Weimer, 2015). Study findings vary depending on how the outcome was measured. For example, if the onset of dementia was diagnosed through a clinical

diagnosis, including neuropsychological testing and standard diagnostic criteria for dementia (completed by neurologists and clinicians), there was no delay in the onset of dementia symptoms among bilinguals (Lawton et al., 2015). However, when measuring the onset of dementia symptoms through subjective reports, the results did show a delayed onset among bilinguals compared to monolinguals (Bialystok et al., 2007; Woumans et al., 2015). Retrospective reports on the onset of dementia symptoms are usually completed by asking patients and family caregivers to report on the time point at which they first became aware of the symptoms (Bialystok et al., 2007). Using self-reports/proxy reports can lead to inaccurate estimations of the age at which the symptoms began to occur; however, if the means of collecting the data was equivalent across all participants, the results will not be affected by a systematic bias (Bialystok et al., 2007). Further, measuring the age at diagnosis of dementia/AD can be subjective since some patients may decide to seek medical help at a later stage of AD than others (Bialystok et al., 2007). Therefore, measuring the outcome using objective measures helps minimize the potential for the reporting of inaccurate data, in comparison to using subjective measures.

2.3.3.6 Study Population and Study Design

The nature of the study sample and the study design can influence the findings as well (Lawton et al., 2015). For instance, studies that use community-based samples versus samples from specialist memory clinics differed in their findings: samples from memory clinics showed a delayed onset of symptoms (Bialystok et al., 2007; Bialystok et al., 2014; Craik et al., 2010; Woumans et al., 2015), whereas community-based samples did not show such a relationship (Crane et al., 2010; Lawton et al., 2015; Ljungberg, Hansson, Adolfsson, & Nilsson, 2016; Sanders, Hall, Katz, & Lipton, 2012; Yeung et al., 2014; Zahodne et al., 2014). The reasons for

the inconsistent findings may be that clinic-based samples include selective participants. For instance, clinic-based samples only include participants who are willing to seek medical help or have access to healthcare services. Moreover, the participants in the clinic-based samples, or their family members or health care providers, think they may have cognitive impairments and thus care at a memory clinic is sought. On the other hand, community-based samples include participants with memory impairments who have and have not sought healthcare services. Consequently, community-based (or population-based) samples are more representative of the general population, increasing the generalizability of study findings.

The study design can also influence findings. For example, cross-sectional studies have found an association between multilingualism and AD/dementia (Bialystok et al., 2007; Craik et al., 2010; Woumans et al., 2015), while prospective cohort studies have found none (Crane et al., 2010; Ljungberg et al., 2016; Sanders et al., 2012; Yeung et al., 2014). In cross-sectional studies, the participants/family caregivers are asked to recall the onset of dementia symptoms in participants. However, in prospective cohort studies, because the participants are free of dementia at baseline, the incidence of dementia/AD is assessed as it develops during the study, which helps to preserve temporality and avoid recall bias and subjective reporting of information. Thus, given the limitations present in cross-sectional studies, further research should be done based on prospective studies to confirm the findings.

2.3.3.7 External and Environmental Influences

Many external and environmental factors, such as immigrant status, occupation, and education can influence the protective effects of multilingualism on cognition. For example, immigrant status can enhance bilingual benefits, particularly in young immigrants who migrate to a second language-dominant community environment (Woumans et al., 2015). When

individuals have been forced by circumstances to learn a second language with a high level of proficiency, they demonstrate comparatively higher levels of performance on assessments than those who learned another language only for interest (in addition to their mother tongue) (Kavé et al., 2008). In a like manner, immigrants who learn a second language out of necessity may have a stronger bilingual benefit against the risk of dementia (Yeung et al., 2014). Further, those whose best language spoken was a language other than the mother tongue, had a higher cognitive performance (based on Katzman cognitive screening test and Folstein MMSE scores) than those whose best spoken language was the mother tongue (Kave et al., 2008). Similarly, education can interact with multilingualism, as highly educated people become more interested in language learning than people with low levels of education (Yeung et al., 2014). That is, intellectual curiosity among highly educated individuals is thought to be a driver of additional language acquisition. Thus, the effect of education on bilingualism may depend on the nature of language learning. Furthermore, occupation, as a proxy measure for socioeconomic status, has been shown to influence the association between bilingualism and the onset of AD (Woumans et al., 2015). Occupations with high demands and stress load modified the protective effects of bilingualism, and led to earlier diagnoses of AD (Woumans et al., 2015). Lastly, socio-linguistic context can play a role as well. If bilinguals live in a community where both languages learned are spoken frequently in the environment, then these bilinguals may experience a lower cognitive demand to switch between languages than bilinguals who speak languages different from what is being frequently spoken in the community (Clare et al., 2014). When bilinguals have a low cognitive demand to switch between languages, they may not experience *significant* cognitive benefits, although they could still have more cognitive demand than monolinguals. For example, in studies where bilinguals were recruited from highly bilingual environments, such as in Montreal

(Chertkow et al., 2010) and Wales (Clare et al., 2014), no significant bilingual benefit was observed among bilinguals who spoke the main languages of the community. Thus, there may be an optimal level of cognitive demand required to speak multiple languages, in order for significant cognitive benefits to emerge and to reduce the risk of dementia. In summary, immigration status, education, occupation and the socio-linguistic context can influence the protective effects of multilingualism on AD and dementia.

2.4 Cognitive Resilience

The diagnosis of AD requires both the presence of Alzheimer neuropathology and the clinical symptoms of dementia. However, the relationship between Alzheimer neuropathology and the clinical symptoms of dementia is not always direct, and can vary between individuals (SantaCruz et al., 2011). For example, some individuals are able to withstand Alzheimer neuropathology without exhibiting any clinical symptoms of dementia until a critical threshold of brain damage is reached (Stern, 2002). The time it takes to reach the threshold depends on the amount of reserve present. Reserve has two components: brain reserve and cognitive reserve (Stern, 2002), and *cognitive resilience* is a term that encompasses both. Although conceptual differences exist between brain and cognitive reserve, and they both make independent contributions to reserve, it may be possible that they interact together in some instances.

2.4.1 Brain Reserve

Brain reserve is a "passive" model referring to "brain reserve capacity" that buffers the potential adverse effects of brain damage on cognitive function (see reviews by Stern, 2002; Valenzuela & Sachdev, 2006). Brain reserve, also called the "hardware" of the brain, relies on biological structures such as the number of synapses and brain weight (Stern, 2002; Stern, 2012).

According to the brain reserve model, individuals with larger brain weights and with a greater number of synapses have more brain reserve capacity and are able to better tolerate brain damage (Stern, 2002). Thus, individuals with higher brain reserve are able to delay the onset of AD, despite significant brain damage caused by Alzheimer neuropathology (Stern, 2002). However, individuals with higher brain reserve cannot tolerate brain damage indefinitely; a critical threshold for brain damage is present, beyond which the clinical symptoms of AD start to occur (Stern, 2002; Stern, 2012). Because not every individual has the same level of brain reserve capacity, not every individual will exhibit symptoms of AD at the same rate (Stern, 2002; Stern, 2012). Initially, the brain reserve model was considered to be quantitative, and reserve to have a fixed capacity (Stern, 2002; Stern, 2012). However, recent research has found that stimulating environments can induce the production of new neurons (neurogenesis) as well as the brain-derived neurotrophic factor (BDNF), a protein that promotes neural plasticity in the brain (Stern, 2002; Stern, 2012). Therefore, brain reserve capacity is not fixed and can possibly be increased through ongoing neurogenesis.

2.4.2 Cognitive Reserve

Unlike brain reserve, cognitive reserve relies on an efficient use of available or alternate brain networks to compensate for brain damage and to maintain cognitive functioning to the best level possible (Stern, 2002). Cognitive reserve is called the "software" of the brain, and helps individuals to compensate for brain damage, even after the total level of brain reserve has become depleted (Stern, 2002; Stern, 2012). Unlike brain reserve, cognitive reserve capacity varies between individuals, depending on the presence of intellectual factors that enhance cognitive stimulation (Stern, 2002; Stern, 2012). Some examples of such factors are multilingualism, education, occupation, premorbid IQ, mental activities and exercise (Abutalebi

et al., 2015; Stern, 2012; Valenzuela & Sachdev, 2006). Since multilingualism involves using certain cognitive processes such as inhibition, attention control and task switching skills, it can improve cognitive flexibility. Cognitive stimulation can decrease the incidence of dementia by 46%, and can induce a positive effect on normal aging as well, with evidence of reduced rates of hippocampal atrophy from high levels of cognitive stimulation (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008). In summary, cognitive reserve acts through an efficient use of brain networks, and can be enhanced through cognitively stimulating activities.

Similar to brain reserve, cognitive reserve also has a critical threshold, which marks the onset of dementia or cognitive decline (Stern, 2002; Stern, 2012). The higher the level of cognitive reserve, the greater the ability to compensate for brain damage (Stern, 2002; Stern, 2012). Thus, individuals with high cognitive reserve can have a delayed onset of dementia, which in turn, leads to less burden and suffering for both the persons with dementia and their caregivers. However, once the level of cognitive reserve is depleted, the individuals will begin to show clinical symptoms of dementia. According to the cognitive reserve hypothesis, those with higher levels of cognitive reserve will have a faster rate of cognitive decline and shorter survival (i.e., shorter time to death) following the onset of dementia. Evidence supporting this hypothesis is seen in individuals with high levels of education (i.e., those with higher levels of cognitive reserve), who have shown a delayed onset of dementia coupled with shorter survival post-onset (Stern, 1998).

2.4.3 Ceiling and Floor Effects of Cognitive Resilience

While it is possible that there is no maximum level of cognitive resilience, researchers speculate that there may be an upper limit to how much cognitive resilience can be increased. The various factors, such as education, multilingualism, and occupation that may contribute to

cognitive reserve may work in different ways to attain the maximum level (ceiling) of cognitive resilience. If these factors have varying degrees of strength to increase cognitive resilience, the stronger factors would likely outcompete the weaker factors. Subsequently, the weakly contributing factors may no longer have room to contribute to cognitive resilience as the maximum level of resilience may already have been reached. However, if no strong contributing factors are present, the weakly contributing factors may combine with other weakly contributing factors to increase cognitive resilience. Since various factors can promote cognitive resilience, how all these factors interact is not yet clear. For example, the Nun Study found that a larger brain size (measured from head circumference) was significantly associated with a lower risk of dementia, but only among the religious sisters who had lower levels of education (Mortimer, Snowdon, & Markesbery, 2003). Because larger brain size did not significantly reduce the risk of dementia when the education level was high, this finding may reflect a ceiling effect by showing the presence of a stronger factor (education) outcompeting the weaker factor (brain size). A similar finding was demonstrated in another study where bilingualism was able to delay the diagnosis of AD only when the education level was low (Gollan et al., 2011). Education is a strong established promoter of cognitive resilience, and therefore multilingualism may be a weaker factor in comparison to education. Moreover, in studies that did show a bilingual benefit against the age of dementia diagnosis, the participants had low levels of education (Bialystok et al., 2007; Craik et al., 2010). Therefore, cognitively resilient individuals may experience a ceiling effect, depending on the contributors of cognitive resilience that are present.

Cognitive resilience can also be reduced by factors that cause brain damage, such as cortical atrophy. A recent study showed that bilinguals were able to better maintain intact cognition following a stroke than monolinguals, even though a stroke event causes significant

brain damage and increases the likelihood of dementia/AD (Alladi et al., 2016). Similarly, in one study bilinguals had more severe cerebral atrophy than monolinguals, even though both groups had the same level of cognition, disease severity, and education (Schweizer, Ware, Fischer, Craik, & Bialystok, 2012). Thus, bilinguals may have had more cognitive resilience than monolinguals to compensate for greater severity of cerebral atrophy. However, if bilinguals had severe levels of brain damage, their cognitive resilience may be completely used up, thereby making them unable to tolerate any more brain damage (i.e., floor effect). Thus, the balance between the effects of building and reducing factors of cognitive resilience will determine the net amount of resilience present to compensate for brain damage and to delay the onset of dementia.

2.4.4 Plausible Mechanisms of Cognitive Resilience

To date, two plausible mechanisms have been proposed for cognitive reserve: neural reserve and neural compensation (Stern, 2012). Neural reserve refers to the anatomical differences in using brain networks (Stern, 2012). Some individuals may possess greater levels of neural reserve than others, depending on different life experiences (Abutalebi et al., 2015). On the other hand, neural compensation refers to when individuals are capable of using alternate brain networks, if there is brain damage to an underlying major network (Stern, 2012). Often, neural compensation would be able to maintain cognitive function only at a sub-optimal level, since the alternate networks may not work as well as the normal brain network (Stern, 2012). Evidence for neural compensation has been shown through functional neuroimaging studies where high levels of activation have been observed among individuals with AD on task-related brain activation analyses (Stern, 2012). Thus, neural compensation usually takes effect when individuals are experiencing some level of brain damage (Stern, 2012). In short, both neural

reserve and neural compensation are plausible mechanisms that can explain the theory behind cognitive resilience.

2.4.5 Multilingualism and Cognitive Resilience

Given the cognitive benefits of speaking more than one language, multilingualism may be associated with cognitive resilience. Currently, neural reserve, neural compensation and a general cognitive reserve network have been proposed as plausible mechanisms by which multilingualism contributes to cognitive resilience. The following sections will discuss these mechanisms in relation to multilingualism.

2.4.5.1 Neural Reserve

Neural reserve can influence the brain physiologically (through selective activation of neural networks) and anatomically (through increased gray and white matter volumes in old age) (see review by Guzman-Velez & Tranel, 2015). At a physiological level, neural reserve refers to using an "optimal task-specific network" that increases efficiency at using the available networks in the presence of neuropathology (Guzman-Velez & Tranel, 2015). As a result, when individuals with a higher level of neural reserve perform a task-specific activity, they will show less brain activation, since they are using a more efficient neural network than individuals with lower levels of neural reserve (Guzman-Velez & Tranel, 2015). For example, when bilinguals spoke more than two languages before the age of ten, their performance on a task-switching activity was high, and showed less brain activation in the left dorsolateral prefrontal cortex, the left ventrolateral prefrontal cortex and the anterior cingulate cortex, compared to monolinguals (Gold, Kim, Johnson, Kryscio, & Smith, 2013). Bilingualism may induce neural reserve by improving stimulation of the executive control system, such as the left prefrontal cortex, inferior

parietal lobule and the temporal poles (Bialystok et al., 2014). In addition, older monolinguals seem to rely on controlled processing such as that which occurs in the right dorsolateral prefrontal cortex, which is associated with cognitive control, whereas bilinguals seem to rely more on automatic processing (Abutalebi et al., 2015). In summary, bilinguals have increased neural reserve by having different and more efficient neural networks than monolinguals.

At the anatomical level, neural reserve can affect gray and white matter volumes in the brain (Bialystok et al., 2016). Aging is a process that leads to a gradual cognitive decline accompanied by decreasing white matter integrity (Woumans et al., 2015) and gray matter volume (Abutalebi et al., 2015). Bilinguals had a higher integrity of white and gray matter in the following regions, which would otherwise decrease with age: left inferior frontal gyrus, left inferior parietal lobe, anterior cingulate cortex (the brain region responsible for language), and subcortical structures, such as the left caudate and putamen (Abutalebi et al., 2014; Bialystok et al., 2016; Grady et al., 2015). Older monolinguals show a higher rate of gray matter volume decline than older bilinguals (Abutalebi et al., 2014). In addition, bilinguals better maintain white and gray matter integrity as well as neural efficiency with age compared to monolinguals (Abutalebi et al., 2014). For instance, performances on the Flanker task (i.e., an attentional control task) have shown that bilinguals had higher levels of gray matter volume in specific regions of the brain (e.g., the anterior cingulate cortex) than monolinguals (Abutalebi et al., 2015). However, some studies did not find a significant difference in gray matter volume between bilinguals and monolinguals, but found white matter integrity to be greater among bilinguals than monolinguals, particularly in the frontal lobe (Gold et al., 2013; Olsen et al., 2015). Moreover, the amount of gray matter in the dorsolateral prefrontal cortex tends to decrease with age, but because bilinguals have greater amounts of neural reserve than

monolinguals, the age-related effects on the dorsolateral prefrontal cortex of bilinguals were not significant (Abutalebi et al., 2015). In summary, bilinguals have higher levels of neural reserve by maintaining both white and gray matter integrity and volume with age.

2.4.5.2 Neural Compensation

Neural compensation refers to the usage of alternate neural networks or brain structures to compensate for brain damage when the "optimal task-specific network" becomes disrupted (Guzman-Velez & Tranel, 2015). Two types of brain networks, called the frontoparietal control network and the salience network, are activated by the executive control system (Grady et al., 2015). The default mode network (also called the default network) becomes activated when individuals focus on internal brain functions/tasks such as retrieving memories, developing perceptions, and imagining future events (see review by Buckner, Andrews-Hanna, & Schacter, 2008). The default network is known as a set of "multiple interacting subsystems" where the medial temporal lobe and medial prefrontal subsystem, as well as the posterior cingulate cortex, all coordinate to carry out internal tasks in the brain (Buckner et al., 2008). Among bilinguals, stronger functional connectivity with the frontoparietal control network and the default network has been observed in comparison to monolinguals (Grady et al., 2015). In brief, the resting functional connectivity between frontal and posterior regions of the brain has been found to be stronger among bilinguals than monolinguals (Grady et al., 2015). Schweizer et al. (2012) found supportive evidence of bilingualism contributing to cognitive reserve through neural compensation. For example, when bilinguals and monolinguals diagnosed with AD had similar cognitive performance and education, bilinguals revealed greater levels of atrophy than monolinguals, particularly in the temporal horn and the temporal horn ratio—regions traditionally used to diagnose AD patients (Schweizer et al., 2012). Thus, Schweizer et al. (2012)

reasoned that even though bilinguals had greater amounts of atrophy than monolinguals, both bilinguals and monolinguals maintained a similar level of cognitive function, perhaps because of bilinguals' highly efficient neural compensatory ability. Moreover, bilinguals were able to perform the same cognitive task as monolinguals, even with significant levels of cerebral atrophy in their brains (Woumans et al., 2015). Interestingly, white matter in the brain seems to be preserved when individuals are subjected to high levels of cognitive stimulation and, as a result, researchers hypothesize that in neural compensation, white matter could compensate for gray matter damage among bilinguals (see review by Luk, Bialystok, Craik, & Grady, 2011; Schweizer et al., 2012). In summary, bilinguals have stronger functional connectivity between brain networks, can maintain cognitive function even in the presence of cerebral atrophy, and have a higher volume of white matter in the brain than monolinguals, all of which provides supportive evidence for bilinguals using neural compensation to enhance cognitive resilience.

2.4.5.3 General Cognitive Reserve Network

Some researchers also have suggested that bilingualism can act through a general cognitive reserve network, which is not associated with a task-specific function (Guzman-Velez & Tranel, 2015). An example of a general cognitive reserve network would be the upregulation of the noradrenergic system (Guzman-Velez & Tranel, 2015). The noradrenergic system is a neuronal system that is responsible for the synthesis, storage, and production of noradrenaline (also called norepinephrine), a neurotransmitter (Mynlieff, Charney, Breier, & Southwick, 2014). In the central nervous system, the noradrenergic system is associated with brain functions such as memory and learning (Mynlieff et al., 2014). Factors that promote cognitive reserve, such as education; social engagement; intelligence; and cognitive stimulating activities, including multilingualism, can upregulate the noradrenergic system (Guzman-Velez & Tranel, 2015). As a

result, noradrenaline release will activate neural compensatory mechanisms that can increase cortical volume and cortical connectivity, neurogenesis, and synaptogenesis, as well as increase disease modification mechanisms (anti-inflammatory processes) (Guzman-Velez & Tranel, 2015). The optimal noradrenergic system may thus increase cognitive resilience by enhancing both neural reserve and neural compensation in the brain when neuropathology is present (Guzman-Velez & Tranel, 2015). Thus, multilingualism may contribute to cognitive resilience through an upregulation of the adrenergic system in the brain.

2.5 Association of Multilingualism with Alzheimer's Disease/Dementia

2.5.1 Sample

2.5.1.1 Clinic-based Studies

One of the earlier studies on the association of multilingualism and AD was conducted by Bialystok and colleagues (2007), who found a four-year delay in the onset of dementia among bilinguals compared to monolinguals at a memory clinic in Toronto, Canada (Bialystok et al., 2007). Bilinguals were classified as those having the ability to fluently speak two languages since early adulthood (Bialystok et al., 2007). Using a specific definition may have controlled to some extent any over- or under-estimations made by participants self-reporting their level of language proficiency. Onset of dementia symptoms was measured retrospectively through an interview between a neurologist and patients or family caregivers (Bialystok et al., 2007). Since the patients or family caregivers may not have accurately recalled the onset of symptoms, this could lead to inaccurate outcome data. A similar study with a sample from the same memory clinic in Toronto, Canada subsequently found bilinguals to have a 4.3-year delay in the diagnosis of AD and a 5.1-year delay in the onset of symptoms in comparison to monolinguals (Craik et

al., 2010). Furthermore, a study conducted in India discovered a similar 4.5-year delay in the development of dementia among bilinguals compared to monolinguals (Alladi et al., 2013). Another study conducted in Belgium also found findings consistent with the previous studies, where a 4.6-year delay in manifestation of AD symptoms and a 4.8-year delay in diagnosis of AD were observed (Woumans et al., 2015). In a more recent study, bilinguals with mild cognitive impairment or AD had an onset of symptoms 4.7 years and 7.3 years later, respectively (Bialystok et al., 2014). Additionally, an interaction has been observed between bilinguals and the onset of MCI where bilinguals had a delayed diagnosis of single-domain amnestic MCI, which is the type that most commonly leads to dementia of the Alzheimer type (Ossher, Bialystok, Craik, Murphy, & Troyer, 2013). In summary, bilingual benefits were observed in studies of clinic populations performed in Canada, the United States, Belgium and India, with on average a four to five-year delay in the onset of dementia symptoms (see reviews by Bialystok et al., 2016; Bialystok, 2017) in clinic populations.

2.5.1.2 Population-based Studies

In contrast to clinic-based studies, population-based studies have typically shown no significant association between multilingualism and AD/dementia. For example, a community-based sample of older adults from the Manitoba Study of Health and Aging showed no significant association between being bilingual and the onset of dementia (Yeung et al., 2014). Similarly, Sanders et al. (2012) recruited participants from the Einstein Aging Study—a community-based, longitudinal study on aging and dementia—and showed no protective effects against the onset of dementia and AD among non-native English speakers compared to native English speakers. Further, Lawton et al. (2015) used a community-dwelling sample from the Sacramento Area Latino Study on Aging (SALSA) in Hispanic Americans (half of the sample

were immigrants), and showed no significant association between bilingualism and the age of dementia onset (Lawton et al., 2015). Lastly, a study that had used data from the Betula prospective cohort study in Sweden, where the participants were chosen from the population registry of Umea municipality, also did not show a significant association between bilingualism and the onset of dementia (Ljungberg et al., 2016).

In conclusion, unlike the clinic-based studies, population-based studies have not shown an association between bilingualism and dementia. The findings from clinic-based and population-based studies may have been inconsistent because of differences in their samples. Clinic-based studies are less representative of the general population than population-based studies (Valian, 2015), as samples from memory/specialist clinics are restricted to participants that already had, or were suspected to have, cognitive impairment. In addition, clinic-based studies cannot study the risk of developing MCI, dementia or AD, as no participants had normal cognition.

2.5.2 Study Design

The findings on the association between multilingualism and AD/dementia depend on the study design as well. For example, cross-sectional studies have found an association between multilingualism and the age of AD/dementia diagnosis (Bialystok et al., 2007; Craik et al., 2010; Woumans et al., 2015; Alladi et al., 2013). In these studies, data on the outcome were obtained from memory clinics, and the participants' language history was collected through retrospective reports from interviews with the patient and family caregivers. Using subjective and retrospective reports from patients and family caregivers may lead to unreliable data and recall bias (see review by Calvo, García, Manoiloff, & Ibáñez, 2015). Since cross-sectional studies

gather data on exposure and outcome at one point in time, temporality is not clear between the exposure and outcome.

On the other hand, when the studies were prospective in nature, no significant association between multilingualism and dementia/AD was observed. Prospective study designs minimize the potential for recall bias in reporting exposures because the participants are classified at baseline based on the exposure information (multilingualism), and the incidence of the outcome (onset of dementia or AD) is collected longitudinally. Therefore, temporality between the exposure and outcome is preserved. For example, Zahodne et al. (2014) conducted a prospective, community-based cohort study of 1067 Hispanic immigrants living in a Spanish-dominant environment. During the study, 282 participants developed dementia, but no significant associations were found between bilingualism and cognitive decline or dementia. Moreover, another longitudinal study had used data from the Betula prospective cohort study on memory, health, and aging in Sweden and had assessed 818 non-demented participants (736 monolinguals and 82 bilinguals), aged 60 years or older at baseline, for incidence of dementia over a 10-year follow-up period (Ljungberg et al., 2016). The participants' proficiency and frequency of second language use were recorded by self-report. The study findings showed that bilinguals did not have a delayed onset of dementia compared to monolinguals, even when the analyses were adjusted for age, sex and *APOE*-ε4 status (Ljungberg et al., 2016). The study proposed several reasons to account for these findings. One reason was that based on the results, there were 102 monolinguals and only 10 bilinguals had developed dementia in the study. Thus, the analyses conducted using this smaller sample of bilinguals would be inadequate to make conclusions. The other reason was that the bilinguals in this study had a low frequency of second language use, as 60% of the bilinguals reported using the second language only while travelling and 23% during

work (Ljungberg et al., 2016). As a result, the protective effect from bilingualism against the onset of dementia might not have been apparent because of insufficient levels of language switching by the bilinguals. However, given the longitudinal nature of this study design these study findings were consistent with the other longitudinal studies that had been done on the association between bilingualism and dementia. Furthermore, one study used 2087 participants from the Australian Longitudinal Study of Ageing to investigate whether bilingualism has an effect on cognitive function (based on the MMSE and executive function test scores) over time (Mukadam, Jichi, Green, & Livingston, 2017). The study showed that no significant differences were observed between bilinguals and monolinguals in the decline of MMSE scores or in baseline tests of executive function over time. However, because these cognitive tests were assessed in English, the performance in these cognitive tests might have been influenced by the participant's proficiency in English (Mukadam et al., 2017). Other studies with cohort study designs found no significant differences between speaking more than one language and the onset of dementia (Yeung et al., 2014) and AD (Clare et al., 2014). However, Yeung et al. (2014) had both cross-sectional (analyzed at time 1) and prospective cohort (with a follow-up assessment conducted at time 2) study designs. The findings of this study showed that not only in the prospective analyses but also in the cross-sectional analyses, there was no association observed between bilingualism and dementia among those who were English bilinguals or spoke English as a second language, compared to monolinguals (Yeung et al., 2014). In the prospective analyses, the findings of this study were consistent with other prospective studies. However, in the cross-sectional analyses the study findings contradicted most other cross-sectional studies, which have found an association between bilingualism and AD/dementia. This may be due to several reasons. First, the study by Yeung et al. (2014) used a population-based sample instead of

a clinic-based sample. Second, this study did not use detailed measures of the outcome in comparison to some other studies and perhaps had unadjusted potential confounders, such as the presence of *APOE*, vascular risk factors, and occupation. Thus, this contradictory finding demonstrates that the study design alone does not influence the results, but rather a combination of other influential factors such as the study sample, confounders, and measurement will play a role in the final results.

Lastly, an ecologic study of 93 countries demonstrated an association between decreasing incidence rates of AD and increasing number of people speaking two languages instead of one (Klein, Christie, & Parkvall, 2016). Countries with low life expectancy had a weakened association between multilingualism and AD, as the majority of people did not survive long enough to develop AD (Klein et al., 2016). Conversely, countries with a high life expectancy had a stronger association between multilingualism and AD (Klein et al., 2016). However, the limitation with ecologic studies is that the analyses are done at the population level (i.e., based on averages) instead of individual level. Ecologic fallacy can occur when inferences from the population level are applied to the level of individuals. Thus, even though there may seem to be an association between lower incidence rates of AD and the number of bilinguals living in a country, this association cannot be applied to a particular individual living in that country. In summary, given the limitations of cross-sectional and ecologic studies that have been conducted on this topic, the findings from prospective studies can provide more reliable conclusions regarding the association between multilingualism and AD/dementia.

2.5.3 Dose-response Effect of Multilingualism

2.5.3.1 Speaking Two Versus More Than Two Languages

Some studies have found a dose-response relationship between degrees of multilingualism and the likelihood of AD. A study conducted in Montreal, Canada, investigated the protective effect of multilingualism using monolinguals, native bilinguals (only French and English speakers), and immigrants (whose primary language was not French or English) (Chertkow et al., 2010). Overall, the results did not show a significant protective effect from bilingualism on the age at AD diagnosis (Chertkow et al., 2010). However, there was a five-year delay in the onset of AD diagnosis among immigrants who spoke more than two languages (Chertkow et al., 2010). In contrast to Bialystok et al. (2007), a five-year delay in the age of AD diagnosis was observed among immigrants speaking more than two languages instead of among bilingual immigrants. However, since Bialystok et al. (2007) classified bilinguals as those who spoke *at least* two languages (without having a separate category for speaking more than two languages), the protective effect observed among immigrants speaking more than two languages in Chertkow et al. (2010) might have been concealed in that study. A dose-response effect was also observed in a prospective cohort study of an Israeli Jewish population, which found that the cognitive performance (based on Katzman cognitive screening test and Folstein MMSE scores) among bilinguals versus trilinguals versus those speaking four or more languages differed during the follow-up intervals (Kave et al., 2008). Those speaking more than four languages were found to have a better cognitive state (i.e., having intact cognition versus mildly impaired cognition, or dementia) than bilinguals or trilinguals (Kave et al., 2008), and this effect remained significant even after adjusting for age, birth place, age at immigration and formal education.

Lastly, a retrospective nested case-control study using 232 non-demented participants (44 with cognitive impairment no dementia (CIND) and 188 with intact cognition) was conducted to explore the effect of multilingualism on the risk of CIND (Perquin et al., 2013). In this study, all participants were asked to self-report their age of language acquisition, number of languages spoken (both throughout life and concomitantly), the current practice of each language, and the duration of practice for each language (in years) until the time of study (Perquin et al., 2013). These collected data were put together to create a set of typical and atypical temporal patterns of progression for acquiring multilingualism for analyses. The participants spoke in a range of two to seven languages, and since there were no monolinguals in the sample, the main analysis used bilinguals as the comparison group. Overall, speaking more than two languages (versus two languages) reduced the risk of CIND (OR=0.30, 95% CI=0.10-0.92) and the results did not differ in terms of whether the language was practiced throughout life or concomitantly. A similar trend was observed for those who spoke three languages (versus two languages) and four languages (versus two languages). However, when trilinguals were used as the reference group, those who spoke four languages (versus three languages) or more than four languages (versus three languages) had similar probability of CIND, indicating that speaking four or more languages had the same probability of CIND as the trilinguals. Moreover, when the temporal progression patterns for acquiring multilingualism were examined, participants who progressed from speaking two to speaking three languages experienced a seven-fold protection against CIND (Perquin et al., 2013). Thus, this study found that speaking more than two languages provides more protection against CIND, but this protective effect seems to plateau when higher number of languages (four or more) were spoken (Perquin et al., 2013).

Overall, studies suggest that speaking more than two languages may induce greater protective effects against CIND/dementia/AD than bilingualism.

2.5.3.2 Definitions of Multilingualism

The association between multilingualism and AD/dementia may be influenced by how multilingualism has been defined in a study. Bialystok defined bilinguals as individuals that have spent most of their lives regularly using two or more languages at least since early adulthood (Bialystok et al., 2007), and this same definition was used in other related studies (Craik et al., 2010; Chertkow et al., 2010). A very similar type of definition was used by Alladi et al. (2013), who defined bilingualism as "an ability to meet the communicative demands of the self, and the society in their normal functioning in 2 or more languages in their interaction with the other speakers of any or all of these languages" (Alladi et al., 2013, p. 1939). These definitions of bilingualism had stringent criteria as they not only required proficiency in languages, but also the frequent use of these languages for most of participants' lives. Studies that used stringent criteria for bilingualism found an association between bilingualism and the age of symptom onset or diagnosis of dementia. Thus, using stringent criteria to measure language proficiency can influence the association between bilingualism and AD/dementia.

2.5.4 Effect Modifiers of the Association Between Multilingualism and Dementia/Alzheimer's Disease

2.5.4.1 Influence of Education on the Protective Effects of Multilingualism

Education is another factor that could influence the protective effects of multilingualism. One study showed that an association between bilingualism and AD was significant only when the level of education was low (Gollan et al., 2011). When the level of education was high, education seemed to completely negate the protective effects of bilingualism on AD (Gollan et

al., 2011). However, because the sample size was quite small (n=44), the findings must be interpreted cautiously. In another study, learning English as a second language among non-native English speakers was not significantly associated with overall incidence of dementia (HR=1.26, 95% CI=0.76-2.09) and AD; however, when stratified by education, attaining 16 years of education increased the risk of dementia for non-native English speakers compared to those with less education (HR=3.97; 95% CI=1.62-9.75) (Sanders et al., 2012). Since education is known to be a well-established protective factor against AD, this finding contradicts most previous studies on education and the risk of dementia/AD. The researchers of this study mentioned that unadjusted confounders, such as personality traits, stressful life events, or participation in other cognitively stimulating activities that could reduce the protective effects of education may be partly responsible for the inconsistent findings (Sanders et al., 2012). Thus, investigating the influence of education on the association between multilingualism and AD can be complex. For instance, some studies have found that bilinguals had lower levels of educational attainment (Clare et al., 2015; Bialystok et al., 2014); others found no significant effect of formal education between bilingualism/multilingualism and AD/dementia (Kave et al., 2008; Chertkow et al., 2010; Bialystok et al., 2007). Immigrant multilinguals have been found to be more educated than non-immigrant multilinguals; however, US-born bilinguals and monolinguals did not show any differences in the level of education (Lawton et al., 2015). Thus, the effect of education is not consistent across study populations. Furthermore, because the age at dementia diagnosis was delayed even among illiterate patients in one study, these individuals seem to gain bilingual advantages regardless of education (Alladi et al., 2013). However, because the study population in the Alladi et al. (2013) study was obtained from India, where multiple languages are spoken with a greater frequency of language mixing, the risk of AD associated with illiteracy or even

very low education may be attenuated in multilinguals. Overall, education may play a role in the association between multilingualism and AD/dementia; however, the nature of this relationship remains to be determined.

2.5.4.2 Socioeconomic Status and Immigration Effects on Multilingualism

Other than education, socioeconomic status is another plausible factor that may influence the association between bilingualism and AD. Bialystok et al. (2014) reported that socioeconomic status did not modify the effect of bilingualism on dementia. Another study found no interactions with language except for occupation (Woumans et al., 2015). Often, occupation is used as a proxy measure for socioeconomic status because socioeconomic status is highly correlated with occupational status. Occupation is also a potential promoter of cognitive reserve because of the mental engagement and cognitive stimulation involved with performing the duties of an occupation. Conversely, highly stressful occupations may serve to reduce cognitive reserve. For example, individuals engaging in highly demanding occupations showed an earlier onset of AD symptoms than did those in less demanding occupations, possibly due to high levels of stress and work load (Woumans et al., 2015).

Immigration status is another common confounder in multilingualism-related studies. Since immigrants have a higher likelihood of speaking multiple languages, the study samples usually consist of a greater proportion of immigrants among multilinguals than monolinguals. However, studying the effects of immigration is complex because each immigrant group is different from another in terms of cultural factors, traditions, languages and life experiences. In multilingualism-related studies, immigration status may affect study findings, depending on whether the immigrants learned the second language after migrating to a new country (later age of language acquisition), whether they are living in a second-language dominant environment,

and whether they switch between languages frequently or less frequently. Moreover, general cultural differences of immigrants could play a role in the interpretation of study findings. In one study, a significant number of bilinguals were immigrants; bilinguals were found to be 3.2 years older at the manifestation of dementia symptoms than monolinguals, but they were also admitted to the clinics at a later age perhaps because of different access and usage patterns of healthcare services (Bialystok et al., 2007), potentially influencing the reported results.

Moreover, a selection bias, called the healthy immigrant effect, could also occur if a particular ethnic immigrant population was healthier overall than non-immigrant populations of that same ethnicity (Lawton et al., 2015). In that case, immigrants might have a reduced risk of AD because they have lower levels of comorbidity, although the results would seem to indicate that their multiple language proficiencies led to the protective effect (Lawton et al., 2015). A Canadian study found that multilinguals (50% immigrants) had a five-year delay in the diagnosis of AD compared to native-born bilinguals and monolinguals (Chertkow et al., 2010).

Furthermore, some studies show no significant effect from immigration status on the relationship between multilingualism and AD (Bialystok et al., 2014; Craik et al., 2010). For instance, when studies restricted their study samples to only native participants (i.e., by excluding immigrants) and still obtained results similar to Bialystok et al. (2007), both Alladi et al. (2013) and Woumans et al. (2015) concluded that the protective effects of bilingualism on AD can occur regardless of immigration status. However, restricting samples to only native participants limits the generalizability of study findings to other populations. In summary, both immigration and socioeconomic status may play a role in modifying the association between multilingualism and AD.

2.5.5 Conclusion

Given the complex nature of multilingualism and cognitive resilience, various factors can influence the association between multilingualism and cognitive resilience. Figure 1 highlights factors that may influence the association between multilingualism and AD, dementia, and cognitive resilience.

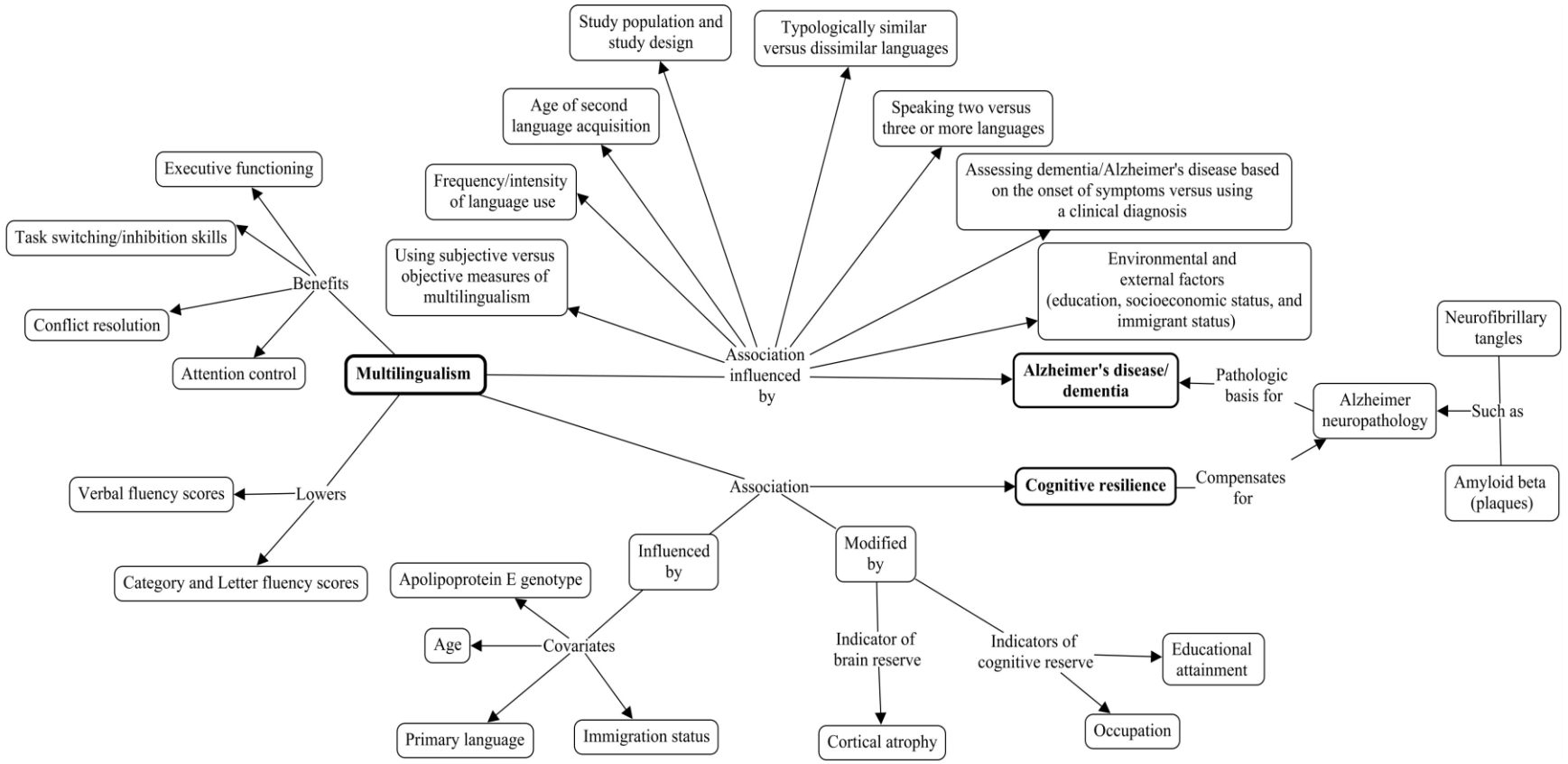


Figure 1: Factors that may influence the association between multilingualism and Alzheimer's disease/dementia and cognitive resilience

3.0 Study Rationale and Research Questions

3.1 Study Rationale

The first two objectives of this study were to investigate whether there was an association of cognitive resilience with (1) multilingualism or (2) type of language. The second two objectives of this study were to explore whether (3) cortical atrophy (an indicator of brain reserve) or (4) education (an indicator of cognitive reserve) modified the association of cognitive resilience with multilingualism or type of language.

Individuals who speak more than one language may have enhanced cognitive flexibility because of the need to constantly switch between languages. In turn, it is possible that higher levels of cognitive flexibility from multilingualism could help build up cognitive resilience. To date, only a few studies have explored whether speaking certain type of languages can produce greater cognitive benefits than others. This research project investigated whether type of language would contribute to cognitive resilience. For example, speaking two languages that are typologically similar can enhance executive functioning as well as attention control more than speaking dissimilar languages, as there is more cognitive demand required to overcome overlapping lexical, syntactic, or phonological similarities among linguistically related languages. Thus, in turn, enhanced executive function can lead to a greater buildup of cognitive resilience.

While it is possible that there is no maximum level of cognitive resilience, it may be that there is a limit to how much cognitive resilience can be increased (i.e., ceiling effect). Thus, this project examined whether an association between multilingualism or type of language and cognitive resilience remained after consideration of an alternate factor (education) contributing to cognitive reserve. In contrast, there are also factors that can reduce brain reserve, such as

cortical atrophy. There may be a point at which the level of brain damage reduces brain reserve such that the potential for multilingualism to compensate via cognitive reserve is exhausted (i.e., floor effect), leading to the onset of dementia symptoms. Thus, a floor effect would indicate that brain reserve acts as a substrate to allow the functioning of cognitive reserve, and that severe depletion of brain reserve can minimize the opportunity for cognitive reserve to function. Therefore, this project also studied whether the presence of cortical atrophy reduced the ability of multilingualism or type of language to enhance cognitive resilience.

This investigation used secondary data from the Nun Study, which is a longitudinal study of 678 Roman Catholic religious sisters from the School Sisters of Notre Dame congregation. The Nun Study had data available on both the number and the type of languages spoken, which were used as exposures in this research project. To date, only a few studies have investigated cognitive resilience with respect to the presence of both dementia and Alzheimer neuropathology. Because the Nun Study had collected data on dementia status before death and had data on the presence of Alzheimer neuropathology through post-mortem examinations, this study was able to operationalize cognitive resilience (the outcome) based on *both* the presence of dementia and Alzheimer neuropathology, unlike the majority of studies. Finally, the Nun Study had data available on factors that influence both cognitive reserve and brain reserve, which helped to determine whether there can be a ceiling or floor effect for cognitive resilience.

Overall, determining whether the number and the type of language spoken influence the likelihood of cognitive resilience, and whether cognitive resilience would be affected by a ceiling or floor effect by the presence of certain factors, could help create more focused preventative strategies to build up cognitive resilience against AD/dementia.

3.2 Research Questions and Hypotheses

1. **Does multilingualism (speaking more than one language) increase the likelihood of cognitive resilience?**

   Hypothesis: Multilingualism increases the likelihood of cognitive resilience.

2. **Does the type of language spoken influence the likelihood of cognitive resilience?**

   Hypothesis: Bilinguals who speak linguistically similar languages will more likely to be cognitively resilient than bilinguals who speak linguistically dissimilar languages.

3. **Does cortical atrophy (an indicator of brain reserve) modify the association of cognitive resilience with multilingualism or type of language spoken?**

   Hypothesis: The presence of cortical atrophy reduces the strength of the association between multilingualism or type of language and cognitive resilience. Since brain reserve may act as a substrate of cognitive reserve, severe depletion of brain reserve (i.e., floor effect) can minimize the opportunity for cognitive reserve to function.

4. **Does education (an indicator of cognitive reserve) modify the association of cognitive resilience with multilingualism or type of language spoken?**

   Hypothesis: The presence of a ceiling effect would indicate that factors that influence cognitive reserve, such as education, can reduce the strength of the association between multilingualism or type of language and cognitive resilience by outcompeting the ability of multilingualism or type of language spoken to contribute to cognitive resilience.

4.0 Methods

4.1 Literature Search

To identify the existing literature on the relationship between multilingualism and cognitive resilience, a comprehensive search was performed using the PubMed Medline database (1950 to present) in September 2017. This search strategy included terms related to multilingualism (as the exposure), and cognitive resilience or AD or dementia (as the outcomes), and was restricted to older populations. Please refer to Appendix A for a detailed description. The search results were restricted to human participants and to articles written in English. The PubMed Medline database search produced 1179 results prior to applying any exclusions. According to the exclusion criteria, the articles were removed if: i) multilingualism was not the exposure; ii) cognitive reserve or cognitive resilience or AD or dementia or cognitive decline was not the outcome; iii) they were validation studies of cognitive assessments or tools; or iv) they focused on language decline or communication barriers following diagnosis of AD. After applying the exclusion criteria, a total of 35 articles were selected for appraisal.

A second search was performed using the PsycINFO database (1840 to present) in September 2017. This search strategy included terms related to multilingualism (as the exposure) and AD or dementia or cognitive resilience (as the outcomes). Please refer to Appendix A for a detailed description. The search results were restricted to human participants. After applying the same exclusion criteria as for the PubMed search, a total of 19 empirical articles was left.

Articles from both the PubMed Medline database and the PsycINFO database were combined (after applying the exclusion criteria), resulting in a total of 54 articles. When the duplicates were removed, 37 empirical articles were eligible for appraisal, plus one additional article (Ljungberg et al., 2016) cited in a review paper was also used for appraisal. Lastly, a total

of 15 relevant reviews that discussed the topic of multilingualism related to cognitive reserve or AD/dementia were kept as supplementary information.

4.2 Data Source: The Nun Study

4.2.1 Study Population

The Nun Study is a longitudinal study centered on the investigation of aging and age-related conditions, such as AD. The original study had its beginning in the School Sisters of Notre Dame congregation in Minnesota as a pilot study in 1986. The Nun Study began in 1991 and included other regions of the United States, with all Sisters born before 1917 eligible to participate. Of the 1031 eligible Sisters, 678 (66%) agreed to participate in this study. Each participant consented to annual cognitive and physical assessments, gave researchers access to their medical and archival records, and agreed to brain donation following death (Snowdon et al., 1996). The participants were 75 years of age or older at baseline, and they did not significantly differ by age, race, country of birth or annual mortality rate in comparison to non-participants (Snowdon et al., 1996).

Homogeneity is a unique characteristic of the Nun Study population, because all participants had similar lifestyle factors, such as diet, socioeconomic status and social activities, after joining the convent. They also had similar marital status, reproductive histories, and tobacco and alcohol use. All participants had equal access to health care services. Moreover, the majority of these participants served as teachers, while a smaller number worked as house sisters (i.e., the sisters who were responsible for household work at the convents). From an epidemiologic perspective, the homogeneity of the Nun Study population helps to minimize the effects of confounders. In addition, the Nun Study allows researchers to compare the heterogeneous early-life lifestyle characteristics of religious sisters (before entering the convent)

with the homogeneous late-life lifestyle of religious sisters (after entering the convent), in order to examine how early-life factors can influence late-life cognition.

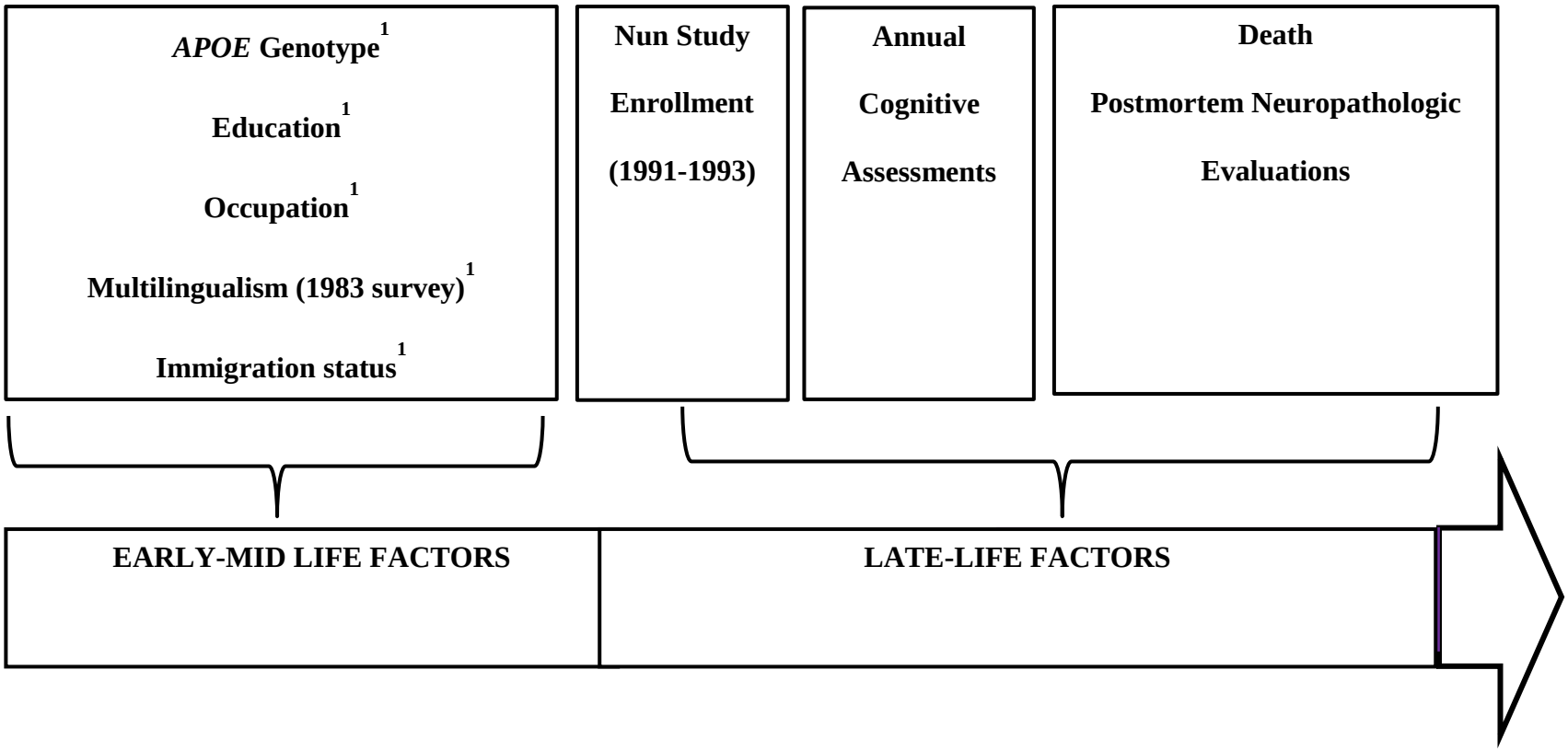
4.2.2 Data Collection

The participants underwent annual physical and cognitive assessments. Cognitive function was assessed through the CERAD neuropsychological battery (Morris et al., 1989) and standard activities of daily living (ADL) measures (Kuriansky & Gurland, 1976). The CERAD battery included seven types of neuropsychological tests: Mini Mental State Exam (MMSE), Delayed Word Recall, Boston Naming, Word Recognition, Verbal Fluency, Word List Memory, and Constructional Praxis (Morris et al., 1989). The standard ADL criteria, which included basic activities, such as feeding, dressing, and standing, and instrumental activities, such as reading, handling money, and taking medications, were measured from performance-based assessments (Kuriansky & Gurland, 1976), instead of using self-reported data that are subject to biases (Riley, Snowdon, & Markesbery, 2002; Tyas et al., 2007).

The neuropathological assessments were performed by a single neuropathologist, who was blinded to the cognitive status of the participants (Riley et al., 2002). In order to quantify the degree of Alzheimer neuropathology (i.e., senile plaques and neurofibrillary tangles) through microscopic examinations, the brain areas were cut into sections of eight microns thick. *APOE* genotyping was conducted either by using buccal cells from living participants, or by using brain tissue from diseased participants (Mortimer, Snowdon, & Markesbery, 2009; Saunders et al., 1996).

The Nun Study researchers also had access to convent archival records, which included birth certificates, hand-written autobiographies, high school transcripts and results from a survey administered in 1983 by the School Sisters of Notre Dame (Patzwald & Wildt, 2004). The birth

certificates provided data on the age of participants. Measures such as written language skills (idea density and grammatical complexity) and emotional expressivity were assessed from the hand-written autobiographies. The high school transcripts provided data on participants' academic performance. The results from the 1983 survey provided data on the participants' language proficiency (i.e., the number and types of languages spoken) and information on educational attainment and family background (Patzwald & Wildt, 2004) *(see section 4.3.2 for further details on measures).*



[1] *APOE* genotype, education, and multilingualism are all exposures present prior to the start of the Nun Study, although data on these exposures were collected (*APOE*) or extracted from archival records (e.g., education, occupation) or the 1983 survey (e.g., multilingualism, immigration status, primary language) during the course of the study.

Figure 2: Nun Study data collection timeline

4.3 Proposed Project

4.3.1 Study Sample

The study sample excluded participants with missing data on the number and type of languages spoken and covariates (age at death, *APOE*-ε4 status, educational attainment, occupation, primary language and immigration status) (see Figure 3). Since the presence of Alzheimer neuropathology and dementia status of participants before death were required to define cognitive resilience (see section 4.3.2.2), the analytic samples included deceased participants only and those who were classified as having "definite" or "probable" AD based on CERAD criteria (i.e., CERAD sample), or who had an "intermediate" or "high" likelihood of AD based on NIA-RI criteria (i.e., NIA-RI sample) criteria (see Figure 3a). According to the exclusion criteria, participants who were classified as having "no" or "possible" AD were excluded from the CERAD sample, whereas those who had "no" or "low" likelihood of AD were excluded from the NIA-RI sample, as they did not or were less likely to have Alzheimer neuropathology. In terms of dementia status, there were no participants with missing data on dementia status at the last cognitive assessment.

This research study used eight different analytic samples (see Figures 3a and 3b). The main CERAD sample (i.e., CERAD sample A) and the main NIA-RI sample (i.e., NIA-RI sample A) excluded participants with missing data on the exposure, outcome and the following covariates: age at death, *APOE*-ε4 status, education, immigration status, and primary language. Since the Nun Study participants were highly educated and the majority served as teachers, there were very few participants who had only completed high school or less and who were not teachers, making control of these factors by multivariable modelling problematic. Therefore, to

ensure stringent control for confounding by education and occupation, both of the samples were restricted to university-educated teachers (labelled as CERAD sample B and NIA-RI sample B). Next, both CERAD and NIA-RI samples A were restricted to exclude those with missing data on atrophy to create two samples (i.e., CERAD or NIA-RI samples C) for analyses of cortical atrophy. The CERAD and NIA-RI samples D reflect CERAD and NIA-RI samples C further restricted to university-educated teachers.

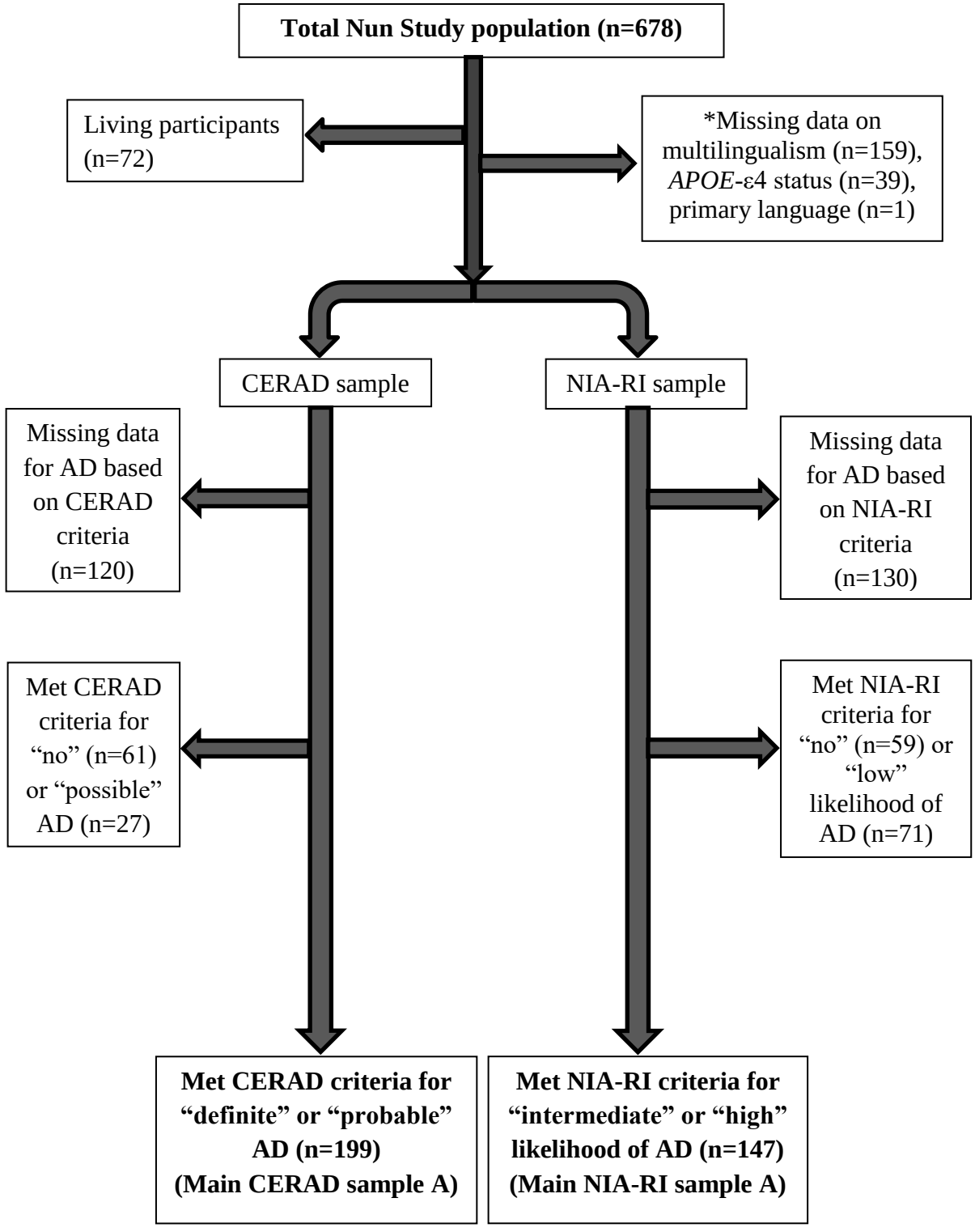


Figure 3a: Flowchart of main analytic samples (CERAD and NIA-RI samples A)

* No missing data for education, occupation, immigration status, and dementia status at the last cognitive assessment.

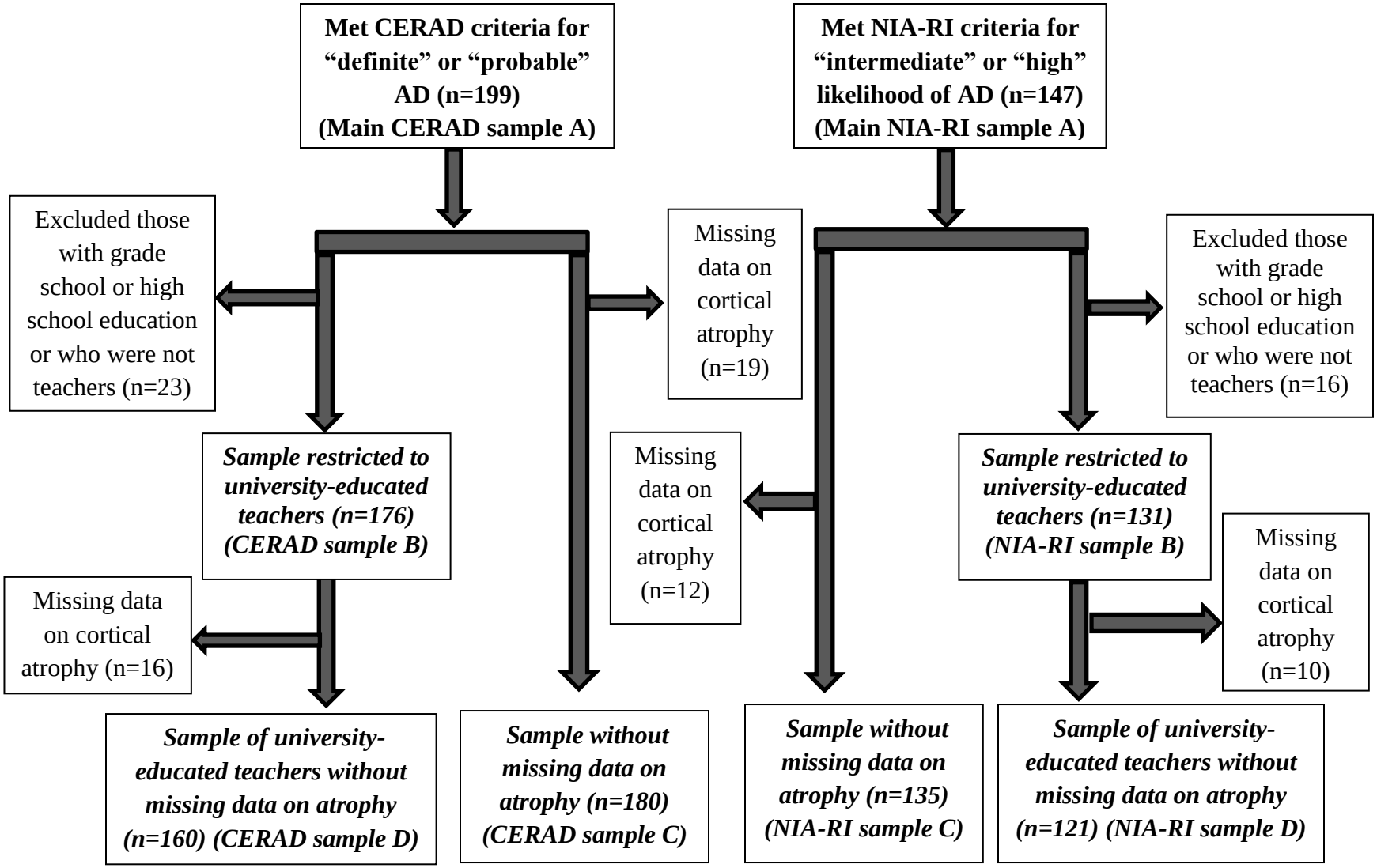


Figure 3b: Flowchart of analytic samples CERAD and NIA-RI B, C, and D

4.3.2 Measures

4.3.2.1 Exposure

Multilingualism data were extracted from the School Sisters of Notre Dame survey conducted in 1983 (prior to the Nun Study), which was designed to help match religious sisters to foreign missionary work. On the questionnaire, the sisters were asked to "specify their language proficiency by indicating which languages were their first, second, and other languages" (Patzwald & Wildt, 2004, p. 95). Therefore, in this study multilingualism was assessed based on the number of languages *spoken* only and other aspects of multilingualism, such as reading ability, language comprehension, frequency and intensity of language use, and age at language acquisition, were not considered in the definition. Overall, participants reported speaking from one to five languages. However, since relatively few participants spoke four or five languages, these two categories were combined. Multilingualism in this study was categorized in three ways: speaking two languages versus one language, or three languages versus one language, or four or more languages versus one language (i.e., a four-level multilingualism variable with one language as the reference group); speaking two or more languages versus one language; and speaking four or more languages versus one to three languages. The types of languages spoken by the Nun Study participants in this study were English, German, French, Spanish, Latin, Polish, and Italian. All participants spoke English. The number of participants who spoke Italian was very small. Since Spanish and Italian are two typologically similar languages, they were combined. A separate variable was derived combining French, Spanish, and Italian (i.e., romance languages).

4.3.2.2 Outcome

The outcome of this research project was cognitive resilience, which is conceptually defined as the ability to *prevent* or *delay* the onset of dementia despite the presence of Alzheimer neuropathology (Stern, 2002). However, this current study focused only on the *prevention* of dementia (i.e., the absence of clinical symptoms of dementia) at the last cognitive assessment before death, despite the presence of Alzheimer neuropathology in operationalizing this concept. Participants were classified as having cognitive resilience if they did not have dementia at the last assessment before death (i.e., only participants who were classified as having intact cognition as well as cognitive impairments milder than dementia according to the DSM-IV criteria were included), and were classified as having 'definite' or 'probable' AD based on CERAD neuropathologic criteria (Mirra et al., 1991), or 'intermediate' or 'high' likelihood of AD based on the NIA-RI neuropathologic criteria (Hyman et al., 2012).

4.3.2.3 Covariates

In the Nun Study, participants were restricted to those who were 75 or older at baseline. In this research project, **age** was further controlled by using the participants' age at death as a covariate. ***APOE*-ε4 status** was defined as a dichotomous (yes/no) variable. The two categories of this variable included the presence of at least one *APOE*-ε4 allele or no *APOE*-ε4 alleles.

Data on **educational attainment** were obtained from the 1983 questionnaire conducted by the School Sisters of Notre Dame religious congregation (Patzwald & Wildt, 2004). Educational attainment was categorized as grade school, high school, undergraduate degree (Bachelor's degree), and graduate degree (Master's degree or PhD). Grade school and high school were combined (i.e., completed high school or less) for analyses because of small sample sizes. When using samples A and C (see Figure 3a and 3b), education was defined as a three-

level variable: high school or less, undergraduate degree, and graduate degree. In CERAD and NIA-RI samples B (see Figure 2b), restricted to university-educated teachers, the education variable only included participants who had completed undergraduate or graduate degrees.

Information on **occupation** was obtained from mission cards, available in all provinces, which listed the entire employment history of each Nun Study participant after entering the convent (Patzwald & Wildt, 2004). Occupation was coded as a dichotomous variable, where one category included all teachers, while the other category included the rest of the participants (e.g., house sisters who were responsible for domestic duties). Since the majority of the Nun Study participants were teachers, the sample size of those with other occupations was very small and thus, to fully address confounding from occupation, the analyses were repeated using the B samples (see Figure 2b), which were restricted to university-educated teachers.

Immigration status was defined as whether the participant was born in the United States (yes/no), and **speaking English as the primary language** was also used as a dichotomous variable (yes/no) in this research project.

Cortical atrophy was assessed during the post mortem gross neuropathologic evaluations conducted by a board-certified neuropathologist. Prior to sectioning of the brain, the neuropathologist examined the whole brain and rated the presence and degree of atrophy observed in the neocortex (Riley et al., 2002). In this research project, cortical atrophy was defined as a dichotomous variable (presence versus absence of any atrophy).

4.3.3 Data analysis

4.3.3.1 Descriptive analyses

Univariate and bivariate analyses were performed on all variables. Pearson chi-square tests, including Fisher's exact test for small cell sizes where appropriate, were used to examine

relationships between categorical variables. T-tests were undertaken to determine if the mean of a continuous variable was different across the two subgroups of a dichotomous categorical variable; if the variances were unequal, the p-value from the Satterthwaite method was used, instead of assuming pooled variances.

4.3.3.2 Multivariable analyses

Logistic regression analyses were used to address the research questions. Because of small sample sizes and separability issues with data points using standard logistic regression, all first-order interactions between the exposure variables and each of the covariates were assessed using Firth regression, and any statistically significant interactions were reported (see section 5.0). Firth regression uses a penalized likelihood approach to predict the likelihood of an event when the sample size is small or when the data are inseparable (Rainey, 2016). In this research study, the stratified analyses were also performed using Firth regression.

All analyses were completed using SAS 9.4 statistical software (SAS Institute Inc., Cary, North Carolina). An assessment of model fit was performed for each model using the Hosmer-Lemeshow goodness of fit test. Residual diagnostics were used to identify influential outliers using DFBETA, C and CBAR plots, where participants with values greater than ±1.96 were excluded from the models and the models re-run. Collinearity between the independent variables was examined using the PROC REG command in SAS (SAS Institute Inc., 2009). Multicollinearity between the independent variables was identified if two or more variance proportions were higher than 0.90 (with a condition index >30), or if the variance inflation factor was higher than ten (Kleinbaum, Kupper, & Muller, 1988).

4.3.4 Ethics

The Nun Study received its original ethics clearance from the University of Kentucky. To protect the identity of the Nun Study participants, they are identified by a randomly assigned number. Neuropathologic assessments of deceased participants are assigned an additional code for further protection. The data of the Nun Study are safely stored in a protected database with restricted access, using locked cabinets and password-protected computers, and are only accessible to research members who have signed a confidentiality agreement. The present research project falls under the umbrella of a larger project, which has received ethics approval by the Office of Research Ethics at the University of Waterloo (ORE 20174).

5.0 Results

5.1 Research question 1: Does multilingualism (speaking more than one language) increase the likelihood of cognitive resilience?

5.1.1 Descriptive results for research question 1

Table 1 summarizes the results from descriptive analyses on cognitive resilience using both CERAD (n=199) and NIA-RI (n=147) main samples (i.e., CERAD sample A and NIA-RI sample A) (See Figure 3a).

5.1.1.1 Association between multilingualism and cognitive resilience

In both analytic samples, the majority of participants were bilinguals, with the second highest group monolinguals, followed by those who spoke three languages. Table 1 shows that speaking four or more languages was significantly more common in cognitively resilient participants in the NIA-RI sample A (11.6% versus 2.9%, p=0.048), while in the CERAD sample A, a similar finding was observed, but was not statistically significant (6.0% versus 2.6%, p=0.29).

5.1.1.2 Association between the covariates and cognitive resilience

Within the CERAD sample A, *APOE*-ε4 status was significantly associated with cognitive resilience: the possession of at least one *APOE*-ε4 allele was more common in those who were not cognitively resilient (39.1% versus 20.2%, p=0.01). A similar finding was observed in the NIA-RI sample A (43.3% versus 27.9%, p=0.12), but was not statistically significant. The mean age at death of participants was similar in the CERAD (mean=91.9 years; SD=5.0) and NIA-RI (mean=91.6 years; SD=4.7) samples A. The association between education and cognitive resilience was not statistically significant; however, lower levels of education (i.e., high school or less) were more common in those who were not cognitively resilient, as shown in the results from CERAD (14.8% versus 7.1%, p=0.26) and NIA-RI (12.5% versus 7.0%, p=0.14)

samples A. With respect to occupation, greater than 90% of the participants were teachers in both samples, and no significant association was observed between occupation and cognitive resilience. However, between occupation and education, a statistically significant association was observed in both CERAD ($p<0.0001$) and NIA-RI ($p<0.0001$) samples A: all participants who had attained an undergraduate or graduate degree were teachers (see Tables C1 and C2 in Appendix C). Since both of these covariates were highly associated with each other, only education was used as a covariate in the multivariable analyses. Furthermore, Table 1 shows that in both analytic samples, greater than 85% of the participants were born in the United States and spoke English as their primary language; however, neither the immigration status nor primary language were significantly associated with cognitive resilience. A statistically significant association was observed between primary language and immigration status, where the majority of participants who were born in the United States also spoke English as their primary language, as shown in the CERAD ($p<0.0001$) and NIA-RI ($p=0.0001$) samples (see Tables C3 and C4 in Appendix C).

5.1.1.3 Association between multilingualism and covariates

The results from the CERAD sample A showed that the number of languages spoken (i.e., one, two, three, or four or more languages) was significantly associated with education ($p=0.049$), English as primary language ($p=0.005$), and immigration status ($p=0.03$) (data not shown). On the other hand, in the NIA-RI sample A, the number of languages spoken was significantly associated with English as primary language ($p=0.01$) and immigration status ($p=0.046$) only.

Analyses were repeated in samples restricted to university-educated teachers as an alternative strategy to control potential confounding by education and occupation. The

descriptive results were essentially the same in these CERAD or NIA-RI restricted samples (i.e., CERAD and NIA-RI samples B) (see Figure 3b) (see Appendix C, Table C5).

Table 1: Sample characteristics by cognitive resilience status, CERAD and NIA-RI samples A[1]

Variables	Cognitive resilience (CERAD criteria) (n=199)			Cognitive resilience (NIA-RI criteria) (n=147)		
	Yes	No	Total	Yes	No	Total
Exposures						
Number of languages spoken (%)						
1	32.1	24.4	27.6	34.9	31.7	32.7
2	48.8	55.7	52.8	41.9	50.0	47.6
3	13.1	17.4	15.6	11.6	15.4	14.3
4	3.6	1.7	2.5	7.0	1.9	3.4
5	2.4	0.9	1.5	4.7	1.0	2.0
Speaking two or more languages (%)	67.9	75.7	72.4	65.1	68.3	67.4
Speaking four or more languages (%)	6.0	2.6	4.0	11.6	2.9*	5.4
Covariates						
Age at death, years (SD)	91.40 (4.82)	92.22 (5.11)	91.87 (4.99)	91.18 (4.19)	91.75 (4.91)	91.59 (4.71)
Education (%)						
High school or less	7.1	14.8	11.6	7.0	12.5	10.9
Undergraduate degree	44.1	40.9	42.2	44.2	44.2	44.2
Graduate degree	48.8	44.4	46.2	48.8	43.3	44.9
Presence of *APOE*-ε4 allele (%)	20.2	39.1*	31.2	27.9	43.3	38.8
Occupation (%)						
Teacher	95.2	92.2	93.5	95.4	92.3	93.2
Primary language (%)						
English	88.1	87.0	87.4	88.4	86.5	87.1
Immigration status (%)						
Born in the United States	94.1	93.0	93.5	95.4	93.3	93.9

*significantly associated with cognitive resilience (p<0.05). [1]CERAD or NIA-RI main samples. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; SD = Standard deviation

5.1.2 Multivariable results for research question 1

Tables 2, 3, and 4 present the results from a series of logistic regression analyses performed to investigate the association between multilingualism and cognitive resilience, using the CERAD (Tables 2a, 3a, and 4a) and NIA-RI (Tables 2b, 3b, and 4b) samples A. Tables C6, C7, and C8 in Appendix C present parallel analyses performed using the CERAD (Tables C6a, C7a, and C8a) and NIA-RI (Tables C6b, C7b, and C8b) samples B. Tables 2, 3, and 4 reflect the three different definitions of multilingualism employed in the analyses (speaking two, three, or four or more languages versus one (i.e., four-level multilingualism variable with monolinguals as the reference group), speaking two or more languages versus one language, and speaking four or more languages versus fewer languages), respectively. A series of models (models b through j) in Tables 2 through 4 were sequentially adjusted for the following covariates: *APOE*-ε4 status, age at death, primary language, and education. In the NIA-RI sample A, none of these covariates were significantly associated with cognitive resilience; however, in the CERAD sample A, *APOE*-ε4 status was significantly associated with cognitive resilience. When immigration status was included in the logistic regression models, it was not a significant predictor and did not substantially affect the point estimate of the association between multilingualism and cognitive resilience, but did affect the precision of this estimate, widening the confidence intervals. Moreover, whether including both primary language and immigration status in the same model or only one of these covariates in the models did not make a significant difference in the results. Since primary language and immigration status were significantly associated with each other (as shown by the chi-square tests in section 5.1.1.2), only primary language was included in the final logistic regression models.

Tables 2a and 2b present the results of models defining multilingualism as a four-level multilingualism variable (with monolinguals as the reference group) in the CERAD and NIA-RI samples A, respectively. Although not statistically significant, the crude model (model a) and the models adjusted for covariates (models b through j) suggested a possible beneficial influence of speaking four or more languages versus one language on cognitive resilience in both CERAD and NIA-RI samples A, as the odds ratios were greater than one in the fully adjusted models (e.g., CERAD model j: OR=1.91, 95% CI=0.39-11.05; and NIA-RI model j: OR=4.06, 95% CI=0.78-24.67). On the other hand, no evidence of a benefit of speaking two or three languages on cognitive resilience was observed.

Tables 3a and 3b present the results based on defining multilingualism as speaking two or more languages versus one. In the fully adjusted model (j), in both Tables 3a and 3b, no evidence of a benefit of speaking two or more languages on cognitive resilience was observed as the odds ratios were less than one in CERAD (OR=0.66, 95% CI=0.33-1.30) and NIA-RI (OR=0.86, 95% CI=0.38-1.96) samples A, and were not statistically significant in either the crude models or after adjustment for covariates.

Table 2a: The association between a four-level multilingualism variable (speaking two, three, or four or more languages versus one) and cognitive resilience, CERAD sample A[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=199) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals)	0.66 (0.34-1.28)	-	0.64 (0.32-1.25)	-	0.66 (0.34-1.29)	-	0.66 (0.34-1.29)	-	0.69 (0.35-1.35)	0.65 (0.32-1.31)
Speaking two languages										
Speaking three languages	0.57 (0.23-1.40)	-	0.54 (0.21-1.34)	-	0.57 (0.22-1.40)	-	0.56 (0.22-1.41)	-	0.58 (0.22-1.45)	0.52 (0.19-1.38)
Speaking four or more languages	1.73 (0.39-9.09)	-	1.87 (0.40-10.23)	-	1.89 (0.42-10.05)	-	1.72 (0.38-9.06)	-	1.61 (0.35-8.59)	1.91 (0.39-11.05)
Presence of *APOE*-ε4 allele	-	**0.40 (0.20-0.75)**	**0.38 (0.19-0.72)**	-	-	-	-	-	-	**0.35 (0.17-0.67)**
Age at death (years)	-	-	-	0.97 (0.91-1.02)	0.96 (0.91-1.02)	-	-	-	-	0.96 (0.90-1.02)
Primary language (English versus other)	-	-	-	-	-	1.11 (0.48-2.68)	0.94 (0.39-2.36)	-	-	0.77 (0.29-2.07)
Education (versus high school or less)	-	-	-	-	-	-	-	2.23 (0.84-6.69)	2.02 (0.75-6.11)	2.34 (0.81-7.52)
Undergraduate degree										

	Cognitive resilience based on CERAD neuropathologic criteria (n=199) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Graduate degree	-	-	-	-	-	-	-	2.28 (0.86-6.79)	2.14 (0.80-6.43)	2.33 (0.79-7.69)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD main sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CERAD=Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table 2b: The association between a four-level multilingualism variable (speaking two, three, or four languages versus one) and cognitive resilience, NIA-RI sample A[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=147) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals) Speaking two languages	0.76 (0.34-1.73)	-	0.73 (0.32-1.68)	-	0.79 (0.35-1.80)	-	0.77 (0.33-1.79)	-	0.77 (0.34-1.76)	0.79 (0.33-1.88)
Speaking three languages	0.69 (0.20-2.14)	-	0.67 (0.19-2.10)	-	0.67 (0.19-2.09)	-	0.70 (0.19-2.23)	-	0.69 (0.19-2.22)	0.65 (0.17-2.22)
Speaking four or more languages	3.67 (0.80-19.83)	-	3.70 (0.79-20.40)	-	4.15 (0.88-23.06)	-	3.69 (0.80-20.09)	-	3.43 (0.73-18.96)	4.06 (0.78-24.67)
Presence of *APOE*-ε4 allele	-	0.51 (0.23-1.08)	0.49 (0.22-1.06)	-	-	-	-	-	-	0.46 (0.20-1.00)
Age at death (in years)	-	-	-	0.97 (0.90-1.05)	0.96 (0.89-1.04)	-	-	-	-	0.96 (0.88-1.04)
Primary language (English versus other)	-	-	-	-	-	1.18 (0.42-3.87)	1.06 (0.35-3.65)	-	-	1.05 (0.32-3.86)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	1.79 (0.51-8.45)	1.61 (0.45-7.65)	1.58 (0.41-7.83)

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=147) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Graduate degree	-	-	-	-	-	-	-	2.02 (0.58-9.50)	1.74 (0.49-8.28)	1.65 (0.41-8.53)

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI main sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CI=Confidence Interval; NIA-RI=National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio.

Table 3a: The association between speaking two or more languages (versus one language) and cognitive resilience, CERAD sample A[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=199) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals)	0.68 (0.36-1.27)	-	0.65 (0.34-1.24)	-	0.68 (0.36-1.28)	-	0.68 (0.36-1.29)	-	0.70 (0.37-1.32)	0.66 (0.33-1.30)
Speaking two or more languages	-	**0.40 (0.20-0.75)**	**0.39 (0.20-0.74)**	-	-	-	-	-	-	**0.36 (0.18-0.69)**
Presence of *APOE*-ε4 allele	-	-	-	0.97 (0.91-1.02)	0.97 (0.91-1.02)	-	-	-	-	0.97 (0.91-1.03)
Age at death (in years)	-	-	-	-	-	1.11 (0.48-2.68)	0.98 (0.41-2.42)	-	-	0.80 (0.31-2.11)
Primary language (English versus other)	-	-	-	-	-	-	-	2.23 (0.84-6.69)	2.10 (0.78-6.33)	2.41 (0.84-7.70)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	2.28 (0.86-6.79)	2.24 (0.84-6.69)	2.46 (0.85-7.97)
Graduate degree										

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD main sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CERAD=Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table 3b: The association between speaking two or more languages (versus one language) and cognitive resilience, NIA-RI sample A[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=147) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals)	0.87 (0.41-1.87)	-	0.84 (0.40-1.82)	-	0.88 (0.42-1.91)	-	0.89 (0.41-1.96)	-	0.87 (0.41-1.88)	0.86 (0.38-1.96)
Speaking two or more languages	-	0.51 (0.23-1.08)	0.50 (0.23-1.07)	-	-	-	-	-	-	0.47 (0.21-1.01)
Presence of *APOE*-ε4 allele	-	-	-	0.97 (0.90-1.05)	0.98 (0.90-1.05)	-	-	-	-	0.98 (0.90-1.06)
Age at death (in years)	-	-	-	-	-	1.18 (0.42-3.87)	1.13 (0.38-3.82)	-	-	1.06 (0.34-3.79)
Primary language (English versus other)	-	-	-	-	-	-	-	1.79 (0.51-8.45)	1.75 (0.49-8.28)	1.74 (0.46-8.57)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	2.02 (0.58-9.50)	2.02 (0.58-9.50)	2.03 (0.52-10.27)
Graduate degree										

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI main sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CI=Confidence Interval; NIA-RI=National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

Lastly, the results presented in Tables 4a and 4b were based on collapsing the multilingualism variable into two categories: speaking four or more languages versus fewer languages. In the CERAD sample A, the association between multilingualism and cognitive resilience was not statistically significant even after adjusting for the covariates. However, an odds ratio of greater than one in these models could suggest a possible beneficial influence on cognitive resilience from speaking four or more languages versus fewer languages (see Table 4a). In the NIA-RI sample A, this association reached statistical significance in the crude model (OR=4.43, 95% CI=1.04 -22.44), and remained significant after adjusting for *APOE*-ε4 status, age at death, primary language, and education (OR=5.00, 95% CI=1.08-27.56).

When further analyses were performed using CERAD or NIA-RI samples B, restricted to university-educated teachers, the findings were similar to the results from the CERAD and NIA-RI samples A, and are presented in Appendix C (see Tables C6, C7, and C8). In summary, a significant association was observed between multilingualism and cognitive resilience only when multilingualism was defined as speaking four or more languages versus fewer languages in the NIA-RI samples A and B. In all of these models, no influential outliers were identified through residual diagnostics and no multicollinearity was present between any of the exposure variables and covariates in the models.

Table 4a: The association between speaking four or more languages (versus fewer languages) and cognitive resilience, CERAD sample A[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=199) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus one to three languages) Speaking four or more languages	2.36 (0.56-11.79)	-	2.63 (0.61-13.63)	-	2.58 (0.61-13.02)	-	2.36 (0.56-11.79)	-	2.18 (0.51-10.94)	2.76 (0.61-14.86)
Presence of *APOE*-ε4 allele	-	**0.40 (0.20-0.75)**	**0.39 (0.20-0.73)**	-	-	-	-	-	-	**0.35 (0.18-0.68)**
Age at death (in years)	-	-	-	0.97 (0.91-1.02)	0.96 (0.91-1.02)	-	-	-	-	0.96 (0.90-1.02)
Primary language (English versus other)	-	-	-	-	-	1.11 (0.48-2.68)	1.11 (0.48-2.69)	-	-	0.93 (0.36-2.41)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	2.23 (0.84-6.69)	2.19 (0.82-6.58)	2.41 (0.84-7.69)
Graduate degree	-	-	-	-	-	-	-	2.28 (0.86-6.79)	2.17 (0.81-6.48)	2.19 (0.75-7.11)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD main sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-*ε*4; CERAD=Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table 4b: The association between speaking four or more languages (versus fewer languages) and cognitive resilience, NIA-RI sample A[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=147) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus one to three languages) Speaking four or more languages	**4.43 (1.04 - 22.44)**	-	**4.57 (1.05- 23.61)**	-	**4.94 (1.13- 25.64)**	-	**4.43 (1.04- 22.46)**	-	4.16 (0.96- 21.41)	**5.00 (1.08- 27.56)**
Presence of *APOE*-ε4 allele	-	0.51 (0.23- 1.08)	0.50 (0.22- 1.07)	-	-	-	-	-	-	0.46 (0.20- 1.01)
Age at death (in years)	-	-	-	0.97 (0.90- 1.05)	0.96 (0.89- 1.04)	-	-	-	-	0.96 (0.88- 1.04)
Primary language (English versus other)	-	-	-	-	-	1.18 (0.42- 3.87)	1.18 (0.41- 3.94)	-	-	1.18 (0.38- 4.17)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	1.79 (0.51- 8.45)	1.70 (0.48- 8.04)	1.60 (0.42- 7.91)
Graduate degree	-	-	-	-	-	-	-	2.02 (0.58- 9.50)	1.75 (0.49- 8.29)	1.56 (0.39- 8.00)

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI main sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CI=Confidence Interval; NIA-RI=National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

5.2 Research question 2: Does the type of language spoken influence the likelihood of cognitive resilience?

5.2.1 Descriptive results for research question 2

Tables 5a and 5b summarize the results from descriptive analyses on cognitive resilience using CERAD and NIA-RI samples A, respectively. In all samples, all participants spoke English. The second most common language spoken was German, followed by French.

5.2.1.1 Association between type of language spoken and cognitive resilience

Within the CERAD sample A, Table 5a shows that speaking German was significantly less common in participants who were cognitively resilient than in those who were not (33.3% versus 66.7%, p=0.04). While a similar finding was observed in the NIA-RI sample A, it was not statistically significant (23.2% versus 76.8%, p=0.28). Moreover, speaking Spanish, speaking Spanish or Italian languages, romance languages (i.e., defined as speaking Spanish or French or Italian), or being proficient in Latin were less common in those who were cognitively resilient in CERAD or NIA-RI samples A. Conversely, within the CERAD sample A, speaking French or Polish was *more* common in those who were cognitively resilient, but the same trends were not observed in the results from the NIA-RI sample A. Except for speaking German, no associations between type of language spoken and cognitive resilience were statistically significant. Tables D1a and D1b in Appendix D show the descriptive results parallel to Tables 5a and 5b, but based on CERAD and NIA-RI samples B. The results from both the restricted (Tables D1a and D1b) and main (Table 5a and 5b) samples followed similar trends, with speaking German significantly associated with cognitive resilience.

Table 5a: The distribution of type of language by cognitive resilience status, CERAD sample A[1]

Variables[2]	Cognitive resilience (CERAD criteria) (n=199)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	33.3 (29)	66.7* (58)	43.7 (87)
Speaking French	54.1 (20)	46.0 (17)	18.6 (37)
Speaking Spanish	40.9 (9)	59.1 (13)	11.1 (22)
Speaking Spanish or Italian	44.4 (12)	55.6 (15)	13.6 (27)
Speaking romance languages[3]	48.2 (26)	51.9 (28)	27.1 (54)
Speaking Latin	35.7 (5)	64.3 (9)	7.0 (14)
Speaking Polish	57.1 (12)	42.9 (9)	10.6 (21)

*Significantly associated with cognitive resilience (p<0.05). [1]CERAD main sample. [2]All participants spoke English. [3]Spoke French, Spanish, or Italian. **Abbreviations:** CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria.

Table 5b: The distribution of type of language by cognitive resilience status, NIA-RI sample A[1]

Variables[2]	Cognitive resilience (NIA-RI criteria) (n=147)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	23.2 (13)	76.8 (43)	38.1 (56)
Speaking French	40.7 (11)	59.3 (16)	18.4 (27)
Speaking Spanish	35.3 (6)	64.7 (11)	11.6 (17)
Speaking Spanish or Italian	35.0 (7)	65.0 (13)	13.6 (20)
Speaking romance languages[3]	35.9 (14)	64.1 (25)	26.5 (39)
Speaking Latin	35.7 (5)	64.3 (9)	9.5 (14)
Speaking Polish	50.0 (8)	50.0 (8)	10.9 (16)

*Significantly associated with cognitive resilience (p<0.05). [1]NIA-RI main sample. [2]All participants spoke English. [3]Spoke French, Spanish, or Italian. **Abbreviations:** NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria.

5.2.1.3 Association between speaking German and covariates

Since the chi-square results indicated a statistically significant association between speaking German and cognitive resilience, the relationship between speaking German and each of the covariates in both CERAD and NIA-RI samples A was further examined (see Tables 6 and 7). In analyses stratified by German speakers, none of the covariates were significantly associated with cognitive resilience in the CERAD sample A (Table 6). However, *APOE*-ε4 frequency was significantly lower in individuals without cognitive resilience among those who did not speak German (21.8% versus 45.6%, p=0.01). Within the NIA-RI sample A, no significant associations were observed between the covariates and cognitive resilience either among those who spoke German or those who did not speak German (Table 7).

Table 6: Sample characteristics by cognitive resilience and German-speaking status, CERAD sample A[1]

Variables	Speaking German			
	Yes (n=87)		No (n=112)	
	Cognitive resilience		Cognitive resilience	
	Yes (n=29)	No (n=58)	Yes (n=55)	No (n=57)
Age at death, years (SD)	92.66 (4.97)	92.98 (5.13)	90.73 (4.64)	91.44 (5.01)
Age at death, years (categorical) (%)				
≥75 to <80	0.0	0.0	0.0	0.0
≥80 to <85	3.5	3.5	9.1	8.8
≥85 to <90	34.5	27.6	27.3	29.8
≥90 to <95	34.5	36.2	47.3	42.1
≥95	27.6	32.8	16.4	19.3
Education (%)				
High school or less	13.8	19.0	3.6	10.5
Undergraduate degree	41.4	36.2	45.5	45.6
Graduate degree	44.8	44.8	50.9	43.9
Presence of *APOE*-ε4 allele (%)	17.2	32.8	21.8	45.6*
Occupation (%)				
Teacher	90.0	90.0	98.2	94.7
Primary language (%)				
English	79.3	84.5	92.7	89.5
Immigration status (%)				
Born in United States	82.8	90.0	100.0	96.5

*Significantly associated with speaking German ($p<0.05$). [1]CERAD main sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; SD = Standard deviation

Table 7: Sample characteristics by cognitive resilience and German-speaking status, NIA-RI sample A[1]

Variables	Speaking German			
	Yes (n=56)		No (n=91)	
	Cognitive resilience		Cognitive resilience	
	Yes (n=13)	No (n=43)	Yes (n=30)	No (n=61)
Age at death, years (SD)	93.44 (4.83)	92.69 (4.33)	90.21 (3.54)	91.09 (5.21)
Age at death, years (categorical) (%)				
≥75 to <80	0.0	0.0	0.0	3.3
≥80 to <85	7.7	0.0	6.7	8.2
≥85 to <90	15.4	30.2	33.3	27.9
≥90 to <95	38.5	41.9	50.0	42.6
≥95	38.5	27.9	10.0	18.0
Education (%)				
High school or less	7.7	16.3	6.7	9.8
Undergraduate degree	46.2	34.9	43.3	50.8
Graduate degree	46.2	48.8	50.0	39.3
Presence of *APOE*-ε4 allele (%)	23.1	44.2	30.0	42.6
Occupation (%)				
Teacher	92.3	88.4	96.7	95.1
Primary language (%)				
English	84.6	83.7	90.0	88.5
Immigration status (%)				
Born in United States	84.6	90.7	100.0	95.1

*Significantly associated with speaking German (p<0.05). [1]NIA-RI main sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; SD = Standard deviation

5.2.2 Multivariable results for research question 2

Tables 8a and 8b present the results from logistic regression analyses performed to examine whether the type of language influences the likelihood of cognitive resilience using CERAD and NIA-RI samples A. These tables show a series of models where the type of language (the exposure variable) was adjusted for the following covariates: *APOE*-ε4 status, age at death, education (undergraduate degree versus high school or less, and graduate degree versus high school or less), primary language, and immigration status. Tables D2 and D3 in Appendix D present the results of parallel analyses for CERAD and NIA-RI samples B, restricted to university-educated teachers.

In the CERAD sample A (Table 8a), those who spoke German had a significantly lower likelihood of cognitive resilience, and this association remained so after adjusting for *APOE*-ε4 status, age at death, education, primary language, and immigration status individually, and also for all covariates combined (OR=0.50, 95% CI=0.27-0.94). Moreover, no significant interactions were observed between speaking German and any of the covariates (*APOE*-ε4 status, age at death, education, primary language, and immigration status) in CERAD samples A and B. With respect to other types of languages, no evidence of a benefit of being proficient in French, Spanish, Spanish or Italian languages, romance languages, Polish, or Latin was observed. In the CERAD sample B (restricted sample) the results showed trends similar to the results from CERAD sample A (main sample) (see Table D2, Appendix D).

In the NIA-RI sample A (Table 8b), although none of the results were statistically significant, the direction of effect was consistent with the suggestion that speaking German might be associated with a lower likelihood of cognitive resilience. Moreover, no significant interactions were observed between speaking German and any of the covariates (*APOE*-ε4 status,

age at death, education, primary language, and immigration status) in NIA-RI samples A and B. In Table 8b, model 4, speaking Polish *significantly* increased the odds of cognitive resilience, only when adjusted for primary language; it was not significant in the fully adjusted model. Compared to the results in Table 8b, the same trends were observed in Table D3 (Appendix D) using the NIA-RI sample B, except that speaking Polish was not a significant contributor to cognitive resilience in any of the models.

Furthermore, a sensitivity analysis was performed to stratify the models of type of language and cognitive resilience by the number of languages spoken. When the CERAD sample A was restricted to those who were bilinguals only (n=105), consistent with previous results, speaking German still significantly reduced the likelihood of cognitive resilience in the fully adjusted model (OR=0.41, 95% CI=0.17-0.99). In terms of the other types of languages, none of the results were statistically significant when restricted to bilinguals as in the samples unrestricted by number of languages. When the NIA-RI sample A was restricted to those who were bilinguals only (n=70), all the results were not statistically significant and followed a pattern consistent with previous results. Because of the very small sample sizes obtained when the samples were restricted to those speaking three languages, or four or more languages, logistic regression models could not be constructed within these strata.

In the CERAD samples A and B, speaking German significantly reduced the likelihood of cognitive resilience. In the NIA-RI sample A, speaking Polish significantly contributed to cognitive resilience only when adjusted for primary language, and became nonsignificant in the fully adjusted models.

Table 8a: The association between type of language and cognitive resilience, CERAD sample A*

Variables**	Cognitive resilience (n=199) (OR, 95% CI)							
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**
Speaking German	**0.52 (0.29-0.92)**	**0.47 (0.26-0.85)**	**0.54 (0.30-0.97)**	**0.55 (0.30-0.98)**	**0.52 (0.29-0.92)**	**0.51 (0.28-0.92)**	**0.50 (0.27-0.94)**	**0.50 (0.27-0.94)**
Speaking French	1.80 (0.88-3.73)	2.02 (0.96-4.31)	1.75 (0.85-3.65)	1.76 (0.84-3.76)	1.80 (0.87-3.73)	1.79 (0.87-3.72)	1.99 (0.91-4.41)	1.99 (0.91-4.41)
Speaking Spanish	0.94 (0.37-2.30)	0.95 (0.37-2.35)	0.90 (0.35-2.21)	0.96 (0.37-2.36)	0.95 (0.37-2.32)	0.95 (0.37-2.34)	0.91 (0.35-2.30)	0.91 (0.35-2.30)
Speaking Spanish or Italian	1.11 (0.48-2.51)	1.10 (0.47-2.53)	1.10 (0.48-2.49)	1.11 (0.48-2.52)	1.12 (0.49-2.54)	1.12 (0.49-2.54)	1.07 (0.46-2.50)	1.07 (0.45-2.50)
Speaking romance languages***	1.39 (0.74-2.62)	1.49 (0.78-2.86)	1.35 (0.71-2.54)	1.38 (0.72-2.64)	1.40 (0.74-2.63)	1.40 (0.74-2.62)	1.44 (0.74-2.83)	1.44 (0.74-2.83)
Proficiency in Latin	0.75 (0.22-2.25)	0.77 (0.23-2.38)	0.76 (0.23-2.29)	0.71 (0.21-2.17)	0.75 (0.22-2.27)	0.75 (0.22-2.25)	0.74 (0.21-2.37)	0.73 (0.21-2.36)
Speaking Polish	1.96 (0.79-5.04)	1.87 (0.74-4.89)	1.86 (0.74-4.80)	1.80 (0.72-4.64)	2.09 (0.82-5.52)	1.98 (0.80-5.09)	1.58 (0.61-4.21)	1.62 (0.60-4.49)

Significant values are **bolded** in the table. *CERAD main sample. **All participants spoke English. ***Spoke French or Spanish or Italian. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (undergraduate degree versus high school or less, and graduate degree versus high school or less). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education and immigration status only. [7]Adjusted for *APOE*-ε4 status, age at death, education, immigration status and primary language. **Abbreviations**: *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table 8b: The association between type of language and cognitive resilience, NIA-RI sample A*

Variables**	Cognitive resilience (n=147) (OR, 95% CI)							
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**
Speaking German	0.62 (0.28-1.29)	0.61 (0.28-1.30)	0.64 (0.29-1.36)	0.62 (0.28-1.32)	0.62 (0.28-1.30)	0.63 (0.28-1.33)	0.64 (0.28-1.41)	0.64 (0.28-1.41)
Speaking French	1.89 (0.78-4.48)	2.02 (0.82-4.89)	1.84 (0.75-4.39)	1.81 (0.72-4.42)	1.88 (0.77-4.46)	1.86 (0.76-4.43)	1.85 (0.73-4.67)	1.85 (0.73-4.67)
Speaking Spanish	1.37 (0.45-3.88)	1.41 (0.45-4.05)	1.34 (0.43-3.82)	1.42 (0.46-4.10)	1.39 (0.45-3.93)	1.46 (0.47-4.23)	1.46 (0.46-4.34)	1.45 (0.46-4.33)
Speaking Spanish or Italian	1.36 (0.48-3.61)	1.38 (0.48-3.72)	1.35 (0.47-3.59)	1.39 (0.48-3.73)	1.38 (0.48-3.69)	1.43 (0.50-3.85)	1.42 (0.49-3.92)	1.43 (0.49-3.93)
Speaking romance languages***	1.53 (0.69-3.31)	1.61 (0.72-3.56)	1.49 (0.67-3.24)	1.51 (0.67-3.33)	1.54 (0.69-3.34)	1.54 (0.69-3.35)	1.55 (0.68-3.49)	1.56 (0.68-3.51)
Proficiency in Latin	1.39 (0.41-4.30)	1.37 (0.39-4.29)	1.43 (0.41-4.44)	1.33 (0.38-4.19)	1.41 (0.41-4.40)	1.40 (0.41-4.32)	1.33 (0.37-4.37)	1.35 (0.37-4.47)
Speaking Polish	2.74 (0.94-8.01)	2.36 (0.79-7.02)	2.66 (0.91-7.83)	2.68 (0.92-7.83)	**3.16 (1.03-9.96)**	2.86 (0.97-8.48)	2.27 (0.74-6.96)	2.50 (0.78-8.17)

Significant values are **bolded** in the table. *NIA-RI main sample. **All participants spoke English. ***Spoke French or Spanish or Italian. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (undergraduate degree versus high school or less, and graduate degree versus high school or less). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education and immigration status only. [7]Adjusted for *APOE*-ε4 status, age at death, education, immigration status and primary language. **Abbreviations**: CI = Confidence intervals; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

5.3 Research question 3: Does cortical atrophy (an indicator of brain reserve) modify the association between multilingualism or type of language spoken and cognitive resilience?

The descriptive results using the CERAD atrophy sample, n=180, (i.e., CERAD sample C - see Figure 3b) and NIA-RI atrophy sample, n=135, (i.e., NIA-RI sample C - see Figure 3b), after excluding participants with missing data on atrophy, are presented in Table E1 in Appendix E. The descriptive results using the CERAD restricted (i.e., restricted to university-educated teachers) atrophy sample, n=160, (i.e., CERAD sample D - see Figure 3b) and NIA-RI restricted atrophy sample, n=121, (i.e., NIA-RI sample D – see Figure 3b) are shown in Table E2 in Appendix E.

5.3.1 Multilingualism

5.3.1.1 Descriptive results for research question 3

In both CERAD and NIA-RI samples C (Table E1, Appendix E), the majority of participants were bilingual, and monolinguals were the next most common. Although not statistically significant, speaking four or more languages was more common in cognitively resilient participants, as shown in the CERAD (4.0% versus 2.9%, p=0.77) and NIA-RI (7.7% versus 3.1%, p=0.80) samples C. The descriptive results by cognitive resilience status using CERAD or NIA-RI samples D were essentially the same as the results from CERAD or NIA-RI samples C. While *APOE*-ε4 status was significantly associated with cognitive resilience only in the CERAD sample C, the presence of atrophy was significantly associated with cognitive resilience in both CERAD and NIA-RI samples C.

5.3.1.2 Multivariable results for research question 3

Tables 9, 10, and 11 present the results from a series of logistic regression analyses performed to investigate whether the association between multilingualism and cognitive

resilience is modified by the presence of cortical atrophy (i.e., a floor effect), using both CERAD and NIA-RI atrophy samples C. The results presented in Tables 9, 10, and 11 were based on the three different definitions of multilingualism (four-level multilingualism variable with monolinguals as the reference group, speaking two or more languages versus one, and speaking four or more languages versus fewer languages). The models b through m in Tables 9 through 11 were sequentially adjusted for the following covariates: *APOE*-ε4 status, age at death, primary language, education, and atrophy. In terms of the covariates, both *APOE*-ε4 status (OR=0.42, 95% CI=0.21-0.82 for fully adjusted model) and atrophy (OR=0.21, 95% CI=0.09-0.43 for fully adjusted model) were consistently and significantly associated with cognitive resilience in the models of CERAD sample C (Table 9a), while in the NIA-RI sample C, only atrophy (OR=0.25, 95% CI=0.10-0.60) was a significant covariate in all models (Table 9b).

Tables 9a and 9b present the results of models defining multilingualism as a four-level variable (with monolinguals as the reference group). In the CERAD sample C, the nonsignificant association between cognitive resilience and speaking four or more languages compared to speaking one language, did not differ in the fully adjusted models *without* atrophy (i.e., model j) (OR=1.15, 95% CI=0.18-7.65) and *with* atrophy (i.e., model m) (OR=1.13, 95% CI=0.17-7.57). Likewise, in the NIA-RI sample C, the results did not differ by atrophy status and were not statistically significant. However, they suggested a possible benefit from speaking four or more languages versus one language, as shown in the fully adjusted models *without* atrophy (i.e., model j) (OR=2.41, 95% CI=0.37-16.19) and *with* atrophy (i.e., model m) (OR=2.60, 95% CI=0.39-17.72). When the analyses were performed in the CERAD and NIA-RI sample D, similar findings were observed (data not shown).

Table 9a: The association between a four-level multilingualism variable (speaking two, three, or four or more languages versus one) and cognitive resilience, CERAD sample C[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=180) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Multilingualism (versus monolinguals)	0.68 (0.34-1.37)	-	0.64 (0.32-1.31)	-	0.69 (0.34-1.39)	-	0.66 (0.33-1.35)	-	0.71 (0.35-1.43)	0.65 (0.31-1.36)	-	0.72 (0.34-1.50)	0.72 (0.33-1.55)
Speaking two languages													
Speaking three languages	0.55 (0.21-1.40)	-	0.50 (0.19-1.31)	-	0.56 (0.21-1.43)	-	0.52 (0.19-1.38)	-	0.55 (0.20-1.43)	0.47 (0.16-1.31)	-	0.70 (0.26-1.88)	0.67 (0.22-1.96)
Speaking four or more languages	1.04 (0.18-6.12)	-	1.21 (0.20-7.42)	-	1.12 (0.19-6.66)	-	1.01 (0.17-5.98)	-	0.95 (0.16-5.63)	1.15 (0.18-7.65)	-	0.97 (0.15-6.20)	1.13 (0.17-7.57)
Presence of *APOE*-ε4 allele	-	**0.42 (0.21-0.82)**	**0.40 (0.20-0.78)**	-	-	-	-	-	-	**0.37 (0.18-0.73)**	-	-	**0.45 (0.21-0.91)**
Age at death (in years)	-	-	-	0.95 (0.90-1.01)	0.95 (0.89-1.01)	-	-	-	-	0.95 (0.89-1.02)	-	-	0.96 (0.90-1.03)
Primary language (English versus other)	-	-	-	-	-	1.00 (0.42-2.45)	0.84 (0.34-2.13)	-	-	0.68 (0.25-1.84)	-	-	1.01 (0.34-3.07)

	Cognitive resilience based on CERAD neuropathologic criteria (n=180) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	2.22 (0.78-7.35)	2.00 (0.69-6.72)	2.28 (0.73-8.13)	-	-	1.80 (0.56-6.57)
Graduate degree	-	-	-	-	-	-	-	2.46 (0.86-8.13)	2.39 (0.83-7.97)	2.46 (0.76-9.07)	-	-	1.81 (0.54-6.84)
Atrophy (present versus absent)	-	-	-	-	-	-	-	-	-		**0.21 (0.09-0.43)**	**0.21 (0.10-0.44)**	**0.26 (0.11-0.57)**

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD atrophy sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table 9b: The association between a four-level multilingualism variable (speaking two, three, or four or more languages versus one) and cognitive resilience, NIA-RI sample C[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=135) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Multilingualism (versus monolinguals) Speaking two languages	0.76 (0.33-1.78)	-	0.74 (0.32-1.74)	-	0.80 (0.34-1.89)	-	0.80 (0.34-1.92)	-	0.79 (0.34-1.88)	0.84 (0.35-2.08)	-	0.78 (0.33-1.91)	0.96 (0.38-2.48)
Speaking three languages	0.71 (0.20-2.27)	-	0.69 (0.19-2.21)	-	0.67 (0.19-2.16)	-	0.77 (0.21-2.54)	-	0.73 (0.19-2.46)	0.70 (0.18-2.46)	-	0.97 (0.26-3.27)	1.11 (0.27-4.20)
Speaking four or more languages	2.14 (0.36-12.91)	-	2.28 (0.37-13.96)	-	2.43 (0.40-15.04)	-	2.26 (0.37-13.86)	-	1.88 (0.31-11.51)	2.41 (0.37-16.19)	-	2.04 (0.31-13.22)	2.60 (0.39-17.72)
Presence of *APOE*-ε4 allele	-	0.62 (0.28-1.35)	0.59 (0.26-1.30)	-	-	-	-	-	-	0.55 (0.23-1.22)	-	-	0.66 (0.27-1.54)
Age at death (in years)	-	-	-	0.94 (0.87-1.02)	0.94 (0.86-1.02)	-	-	-	-	0.95 (0.86-1.04)	-	-	0.94 (0.85-1.03)
Primary language (English versus other)	-	-	-	-	-	1.49 (0.50-5.55)	1.40 (0.43-5.42)	-	-	1.21 (0.35-4.96)	-	-	2.21 (0.56-10.50)

Cognitive resilience based on NIA-RI neuropathologic criteria (n=135) (OR, 95% CI)

	Model a	Model b	Model c	Model d	Model e	Model f	Model g	Model h	Model i	Model j	Model k	Model l	Model m
Education (versus high school or less)	-	-	-	-	-	-	-	5.49 (0.98-103.20)	5.04 (0.89-95.30)	4.64 (0.79-88.90)	-	-	2.98 (0.49-57.65)
Undergraduate degree	-	-	-	-	-	-	-	6.50 (1.16-122.45)	6.04 (1.07-114.25)	5.04 (0.82-98.26)	-	-	3.00 (0.47-59.27)
Graduate degree	-	-	-	-	-	-	-	-	-	-	**0.25 (0.10-0.60)**	**0.25 (0.10-0.61)**	**0.26 (0.09-0.68)**
Atrophy (present versus absent)	-	-	-	-	-	-	-	-	-	-	**0.25 (0.10-0.60)**	**0.25 (0.10-0.61)**	**0.26 (0.09-0.68)**

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI atrophy sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CI=Confidence Interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

Tables 10a and 10b present the results for multilingualism as a two-level variable (i.e., speaking two or more languages versus one language). Based on the results from CERAD and NIA-RI samples C, no evidence of a benefit of speaking two or more languages on cognitive resilience was observed in the fully adjusted models *without* atrophy (i.e., model j) (CERAD: OR=0.63, 95% CI=0.30-1.28; NIA-RI: OR=0.87, 95% CI=0.38-2.05) or *with* atrophy (i.e., model m) (CERAD: OR=0.72, 95% CI=0.34-1.53; NIA-RI: OR=1.06, 95% CI=0.44-2.63), as the results were not statistically significant. When the analyses were performed in the CERAD and NIA-RI atrophy samples D, similar findings were observed (data not shown).

Table 10a: The association between speaking two or more languages (versus one language) and cognitive resilience, CERAD sample C[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=180) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Multilingualism (versus monolinguals) Speaking two or more languages	0.66 (0.34-1.29)	-	0.63 (0.32-1.24)	-	0.67 (0.35-1.31)	-	0.65 (0.33-1.28)	-	0.68 (0.35-1.34)	0.63 (0.30-1.28)	-	0.72 (0.36-1.47)	0.72 (0.34-1.53)
Presence of *APOE*-ε4 allele	-	**0.42 (0.21-0.82)**	**0.41 (0.20-0.80)**	-	-	-	-	-	-	**0.38 (0.19-0.75)**	-	-	**0.46 (0.22-0.93)**
Age at death (in years)	-	-	-	0.95 (0.90-1.01)	0.95 (0.90-1.01)	-	-	-	-	0.95 (0.89-1.02)	-	-	0.96 (0.90-1.03)
Primary language (English versus other)	-	-	-	-	-	1.00 (0.42-2.45)	0.87 (0.36-2.19)	-	-	0.70 (0.26-1.89)	-	-	1.03 (0.35-3.06)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	2.22 (0.78-7.35)	2.06 (0.71-6.88)	2.32 (0.75-8.24)	-	-	1.83 (0.57-6.65)
Graduate degree	-	-	-	-	-	-	-	2.46 (0.86-8.13)	2.39 (0.83-7.95)	2.44 (0.77-8.83)	-	-	1.84 (0.56-6.86)

	Cognitive resilience based on CERAD neuropathologic criteria (n=180) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Atrophy (present versus absent)	-	-	-	-	-	-	-	-	-	-	**0.21 (0.09-0.43)**	**0.21 (0.10-0.44)**	**0.25 (0.11-0.55)**

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD atrophy sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table 10b: The association between speaking two or more languages (versus one language) and cognitive resilience, NIA-RI sample C[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=135) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Multilingualism (versus monolinguals) Speaking two or more languages	0.81 (0.37-1.80)	-	0.80 (0.36-1.78)	-	0.83 (0.38-1.87)	-	0.87 (0.39-1.97)	-	0.83 (0.38-1.89)	0.87 (0.38-2.05)	-	0.88 (0.39-2.04)	1.06 (0.44-2.63)
Presence of *APOE*-ε4 allele	-	0.62 (0.28-1.35)	0.62 (0.27-1.34)	-	-	-	-	-	-	0.57 (0.25-1.27)	-	-	0.68 (0.29-1.58)
Age at death (in years)	-	-	-	0.94 (0.87-1.02)	0.95 (0.87-1.03)	-	-	-	-	0.95 (0.87-1.04)	-	-	0.95 (0.86-1.04)
Primary language (English versus other)	-	-	-	-	-	1.49 (0.50-5.55)	1.41 (0.45-5.43)	-	-	1.20 (0.35-4.82)	-	-	2.14 (0.55-9.90)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	5.49 (0.98-103.20)	5.31 (0.94-100.04)	4.94 (0.85-94.45)	-	-	3.11 (0.51-60.09)
Graduate degree	-	-	-	-	-	-	-	6.50 (1.16-122.45)	6.45 (1.15-121.58)	5.51 (0.91-106.69)	-	-	3.32 (0.53-65.14)

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=135) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Atrophy (present versus absent)	-	-	-	-	-	-	-	-	-		**0.25 (0.10-0.60)**	**0.25 (0.10-0.60)**	**0.26 (0.10-0.66)**

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI atrophy sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CI=Confidence Interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

Lastly, Tables 11a and 11b present the results from the CERAD and NIA-RI samples C, based on defining multilingualism as speaking four or more languages versus fewer languages. In both samples, an odds ratio of greater than one suggested a possible beneficial influence from speaking four or more languages on cognitive resilience, compared to speaking one to three languages as shown in the fully adjusted models *without* atrophy (i.e., model j) (CERAD: OR=1.70, 95% CI=0.28-10.46; NIA-RI: OR=2.81, 95% CI=0.47-17.13) and *with* atrophy (i.e., model m) (CERAD: OR=1.46, 95% CI=0.24-9.08; NIA-RI: OR=2.61, 95% CI=0.44-15.99). However, these associations were not statistically significant. When the analyses were performed using the CERAD and NIA-RI samples D, similar findings were observed (data not shown).

Overall, using Firth regression in both CERAD and NIA-RI samples C, all interactions between atrophy and multilingualism (testing all three definitions used in the analysis) were not statistically significant. Moreover, in all of these models, no influential outliers were identified through residual diagnostics and no multicollinearity was present between any of the exposure variables. In summary, comparing the models with and without adjusting for atrophy, the association between multilingualism and cognitive resilience did not substantially change in both CERAD and NIA-RI samples C and D.

Table 11a: The association between speaking four or more languages (versus fewer languages) and cognitive resilience, CERAD sample C[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=180) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model 1**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Multilingualism (versus one to three languages) Speaking four or more languages	1.42 (0.26-7.84)	-	1.70 (0.30-9.88)	-	1.51 (0.27-8.48)	-	1.42 (0.26-7.85)	-	1.28 (0.23-7.11)	1.70 (0.28-10.46)	-	1.23 (0.20-7.39)	1.46 (0.24-9.08)
Presence of *APOE*-ε4 allele	-	**0.42 (0.21-0.82)**	**0.42 (0.21-0.81)**	-	-	-	-	-	-	**0.38 (0.19-0.75)**	-	-	**0.46 (0.22-0.93)**
Age at death (in years)	-	-	-	0.95 (0.90-1.01)	0.95 (0.90-1.01)	-	-	-	-	0.95 (0.89-1.01)	-	-	0.96 (0.89-1.02)
Primary language (English versus other)	-	-	-	-	-	1.00 (0.42-2.45)	1.00 (0.42-2.46)	-	-	0.82 (0.32-2.17)	-	-	1.15 (0.41-3.35)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	2.22 (0.78-7.35)	2.20 (0.77-7.31)	2.38 (0.77-8.41)	-	-	1.85 (0.58-6.75)
Graduate degree	-	-	-	-	-	-	-	2.46 (0.86-8.13)	2.42 (0.85-8.06)	2.30 (0.72-8.31)	-	-	1.75 (0.53-6.56)

	Cognitive resilience based on CERAD neuropathologic criteria (n=180) (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model 1**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Atrophy (present versus absent)	-	-	-	-	-	-	-	-	-	-	**0.21 (0.09-0.43)**	**0.21 (0.09-0.43)**	**0.24 (0.11-0.53)**

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD atrophy sample. *APOE*-ε4=Apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria, CI=Confidence Interval; OR=Odds Ratio

Table 11b: The association between speaking four or more languages (versus fewer languages) and cognitive resilience, NIA-RI sample C[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria, (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Multilingualism (versus one to three languages) Speaking four or more languages	2.58 (0.46-14.53)	-	2.78 (0.49-15.96)	-	2.88 (0.50-16.59)	-	2.63 (0.47-14.90)	-	2.23 (0.39-12.62)	2.81 (0.47-17.13)	-	2.31 (0.38-13.88)	2.61 (0.44-15.99)
Presence of *APOE*-ε4 allele	-	0.62 (0.28-1.35)	0.60 (0.26-1.32)	-	-	-	-	-	-	0.55 (0.24-1.23)	-	-	0.65 (0.27-1.53)
Age at death (in years)	-	-	-	0.94 (0.87-1.02)	0.94 (0.86-1.02)	-	-	-	-	0.95 (0.86-1.03)	-	-	0.94 (0.85-1.03)
Primary language (English versus other)	-	-	-	-	-	1.49 (0.50-5.55)	1.52 (0.50-5.71)	-	-	1.32 (0.40-5.23)	-	-	2.19 (0.59-9.85)
Education (versus high school or less) Undergraduate degree	-	-	-	-	-	-	-	5.49 (0.98-103.20)	5.34 (0.95-100.41)	4.75 (0.81-90.80)	-	-	2.97 (0.49-57.46)
Graduate degree	-	-	-	-	-	-	-	6.50 (1.16-122.45)	6.12 (1.08-115.48)	4.89 (0.80-94.92)	-	-	3.04 (0.48-59.79)

	Cognitive resilience based on NIA-RI neuropathologic criteria, (OR, 95% CI)												
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**	**Model k**	**Model l**	**Model m**
Atrophy (present versus absent)	-	-	-	-	-	-	-	-	-	-	**0.25 (0.10-0.60)**	**0.26 (0.11-0.61)**	**0.26 (0.10-0.67)**

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI atrophy sample. *APOE*-ε4=Apolipoprotein E-*ε*4; CI=Confidence Interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

5.3.1.3 Analyses stratified by the presence of atrophy for research question 3

Tables E3 through E8 (in Appendix E) present the results from stratified analyses using the CERAD samples C and D, while Tables E9 and E10 (in Appendix E) show the results from stratified analyses when using NIA-RI samples C and D. Based on the results, when the fully adjusted model (without atrophy) was stratified further by the presence of atrophy, the association between multilingualism and cognitive resilience remained not significant in both strata, but affected the precision of the estimates, by widening the confidence intervals. The stratified results from both samples C and D showed similar trends. Because of the lack of precision of the estimates, the results were less interpretable.

5.3.2 Type of Language

5.3.2.1 Descriptive results for research question 3

Tables 12a and 12b present the descriptive results on cognitive resilience using the CERAD and NIA-RI samples C. Based on the results, speaking German was still less common in participants who were cognitively resilient after excluding those with missing atrophy data, and this association was statistically significant in the CERAD sample C (32.1% versus 67.9%, p=0.028). In the NIA-RI sample C, a similar result was observed, but was not statistically significant (22.2% versus 77.8%, p=0.23). With respect to the other type of languages analyzed, none of the associations were statistically significant in CERAD or NIA-RI samples C. With respect to the CERAD or NIA-RI samples D (restricted), the trends observed were comparable to those of the samples C (see Tables E11a and E11b in Appendix E).

Table 12a: The distribution of type of language by cognitive resilience status, CERAD sample C[1]

Variables[2]	Cognitive resilience (CERAD criteria) (n=180)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	32.1 (26)	67.9* (55)	45.0 (81)
Speaking French	53.1 (17)	46.9 (15)	17.8 (32)
Speaking Spanish	31.6 (6)	68.4 (13)	10.6 (19)
Speaking Spanish and Italian	39.1 (9)	60.9 (14)	12.8 (23)
Speaking romance languages[3]	45.8 (22)	54.2 (26)	26.7 (48)
Speaking Latin	27.3 (3)	72.7 (8)	6.1 (11)
Speaking Polish	57.9 (11)	42.1 (8)	10.6 (19)

*Significantly associated with cognitive resilience ($p<0.05$). [1]CERAD atrophy sample. [2]All participants spoke English. [3]Spoke French, Spanish, or Italian. **Abbreviations:** CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria.

Table 12b: The distribution of type of language by cognitive resilience status, NIA-RI sample C[1]

Variables[2]	Cognitive resilience (NIA-RI criteria) (n=135)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	22.2 (12)	77.8 (42)	40.0 (54)
Speaking French	39.1 (9)	60.9 (14)	17.0 (23)
Speaking Spanish	26.7 (4)	73.3 (11)	11.1 (15)
Speaking Spanish or Italian	29.4 (5)	70.6 (12)	12.6 (17)
Speaking romance languages[3]	34.3 (12)	65.7 (23)	25.9 (35)
Speaking Latin	27.3 (3)	72.7 (8)	8.1 (11)
Speaking Polish	50.0 (7)	50.0 (7)	10.4 (14)

*Significantly associated with cognitive resilience ($p<0.05$). [1]NIA-RI atrophy sample. [2]All participants spoke English. [3]Spoke French, Spanish, or Italian. **Abbreviations:** NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria.

5.3.2.2 Multivariable results for research question 3

Tables 13a and 13b present the results from the CERAD and NIA-RI samples C. Tables E12 and E13 in Appendix E show results from the CERAD and NIA-RI samples D. The covariate presence of atrophy was significantly associated with cognitive resilience in both CERAD and NIA-RI samples C and D (data not shown).

In the CERAD sample C, speaking German significantly lowered the odds of cognitive resilience, even after adjusting for *APOE*-ε4 status, age at death, education, primary language, and immigration status (OR=0.47, 95% CI=0.24-0.91) (Table 13a). When adjusted for presence of atrophy, the association between speaking German and cognitive resilience was no longer statistically significant, and this remained so when adjusted for all covariates (OR=0.55, 95% CI=0.27-1.09). However, the direction of effect of the association remained the same before and after adjusting for atrophy. Languages other than German were not significantly associated with cognitive resilience in any models, regardless of the inclusion or exclusion of atrophy as a covariate. In the CERAD sample D (restricted), similar findings were observed when adjusted for atrophy, where the association between speaking German and cognitive resilience became nonsignificant (model 7), or was attenuated to become very close to being nonsignificant in the fully adjusted model with atrophy (model 8). (see Table E12, Appendix E).

On the other hand, in the NIA-RI atrophy sample C, none of the languages spoken were statistically significantly associated with cognitive resilience even before adjusting for atrophy. Although not significant, the results still suggested that speaking German reduced the likelihood of cognitive resilience. After adjusting for the presence of atrophy (models 7 and 8) the results remained not statistically significant. The results from the NIA-RI sample D (restricted) were comparable to the results from the NIA-RI sample C (see Table E13, Appendix E).

In summary, adjusting for atrophy only caused substantial changes to the association between speaking German and cognitive resilience in the CERAD samples C and D.

Table 13a: The association between the type of language and cognitive resilience, CERAD sample C*

Variables**	Cognitive resilience (n=180) (OR, 95% CI)								
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**	**Model 8-adjusted[8]**
Speaking German	**0.48 (0.26-0.88)**	**0.44 (0.23-0.82)**	**0.52 (0.28-0.96)**	**0.51 (0.27-0.93)**	**0.48 (0.26-0.88)**	**0.47 (0.25-0.87)**	**0.47 (0.24-0.91)**	0.57 (0.30-1.08)	0.55 (0.27-1.09)
Speaking French	1.76 (0.82-3.83)	1.92 (0.87-4.30)	1.68 (0.77-3.69)	1.69 (0.76-3.77)	1.76 (0.82-3.84)	1.76 (0.82-3.85)	1.87 (0.82-4.35)	1.91 (0.85-4.32)	2.00 (0.86-4.72)
Speaking Spanish	0.62 (0.21-1.64)	0.64 (0.21-1.73)	0.55 (0.18-1.48)	0.63 (0.21-1.69)	0.61 (0.21-1.64)	0.61 (0.20-1.64)	0.56 (0.18-1.58)	0.75 (0.24-2.07)	0.70 (0.22-2.00)
Speaking Spanish or Italian	0.89 (0.35-2.14)	0.87 (0.34-2.14)	0.85 (0.33-2.06)	0.89 (0.35-2.18)	0.89 (0.35-2.15)	0.89 (0.35-2.15)	0.82 (0.32-2.06)	1.06 (0.40-2.67)	1.01 (0.38-2.60)
Speaking Romance Languages***	1.26 (0.65-2.46)	1.33 (0.67-2.64)	1.19 (0.60-2.34)	1.24 (0.62-2.46)	1.26 (0.65-2.46)	1.26 (0.65-2.46)	1.26 (0.62-2.57)	1.35 (0.67-2.74)	1.39 (0.67-2.90)
Proficiency in Latin	0.51 (0.11-1.82)	0.52 (0.11-1.89)	0.49 (0.10-1.77)	0.48 (0.10-1.75)	0.50 (0.11-1.82)	0.51 (0.11-1.82)	0.45 (0.09-1.73)	0.35 (0.07-1.39)	0.35 (0.07-1.46)
Speaking Polish	2.08 (0.80-5.65)	2.03 (0.77-5.61)	1.92 (0.73-5.24)	1.91 (0.73-5.20)	2.18 (0.81-6.13)	2.09 (0.80-5.67)	1.68 (0.58-4.99)	1.60 (0.57-4.60)	1.50 (0.49-4.70)

Statistically significant values are **bolded** ($p<0.05$). *CERAD atrophy sample. **All participants spoke English. ***Spoke French or Spanish or Italian. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (undergraduate degree versus high school or less, and graduate degree versus high school or less). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education, primary language, and immigration status. [7]Adjusted for atrophy (atrophy present versus absent) [8]Adjusted for *APOE*-ε4 status, age at death, education, primary language, immigration status, and atrophy. **Abbreviations**: CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table 13b: The association between the type of language and cognitive resilience, NIA-RI sample C*

Variables**	Cognitive resilience (n=135) (OR, 95% CI)								
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**	**Model 8-adjusted[8]**
Speaking German	0.57 (0.25-1.24)	0.58 (0.25-1.26)	0.63 (0.27-1.39)	0.60 (0.26-1.32)	0.58 (0.26-1.26)	0.58 (0.25-1.27)	0.66 (0.28-1.51)	0.67 (0.29-1.52)	0.79 (0.32-1.91)
Speaking French	1.76 (0.67-4.44)	1.82 (0.69-4.66)	1.58 (0.59-4.07)	1.59 (0.59-4.15)	1.73 (0.66-4.37)	1.72 (0.65-4.39)	1.55 (0.56-4.18)	2.16 (0.79-5.75)	1.97 (0.70-5.50)
Speaking Spanish	0.88 (0.23-2.78)	0.92 (0.24-2.93)	0.79 (0.20-2.53)	0.99 (0.25-3.26)	0.91 (0.24-2.88)	0.93 (0.24-3.00)	0.94 (0.24-3.20)	1.14 (0.29-3.76)	1.14 (0.28-3.99)
Speaking Spanish or Italian	1.03 (0.31-3.01)	1.04 (0.31-3.08)	0.97 (0.29-2.87)	1.13 (0.33-3.43)	1.08 (0.32-3.19)	1.08 (0.32-3.22)	1.11 (0.32-3.44)	1.22 (0.35-3.74)	1.32 (0.37-4.19)
Speaking Romance Languages ***	1.41 (0.61-3.19)	1.46 (0.62-3.33)	1.29 (0.54-2.97)	1.42 (0.60-3.31)	1.44 (0.62-3.28)	1.43 (0.61-3.24)	1.42 (0.58-3.37)	1.69 (0.70-4.02)	1.76 (0.70-4.35)
Proficiency in Latin	0.92 (0.19-3.37)	0.91 (0.19-3.36)	0.90 (0.19-3.35)	0.86 (0.18-3.28)	0.97 (0.20-3.63)	0.93 (0.19-3.41)	0.87 (0.17-3.47)	0.69 (0.13-2.73)	0.75 (0.14-3.09)
Speaking Polish	2.78 (0.89-8.73)	2.54 (0.80-8.09)	2.59 (0.82-8.20)	2.44 (0.78-7.71)	3.35 (1.02-11.52)	2.92 (0.92-9.36)	2.36 (0.68-8.45)	2.14 (0.63-7.08)	2.20 (0.59-8.20)

Statistically significant values are **bolded** ($p<0.05$). *NIA-RI atrophy sample. **All participants spoke English. ***Spoke French or Spanish or Italian. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (undergraduate degree versus high school or less, and graduate degree versus high school or less). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education, primary language, and immigration status. [7]Adjusted for atrophy (atrophy present versus absent) [8]Adjusted for *APOE*-ε4 status, age at death, education, primary language, immigration status, and atrophy. **Abbreviations**: CI = Confidence intervals; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

5.3.2.3 Analyses stratified by the presence of atrophy for research question 3

As shown in the previous section, the significant association observed between speaking German and cognitive resilience in the CERAD sample C became nonsignificant after adjusting for presence of atrophy, only in the CERAD samples. Therefore, the *stratified analyses* focused only on the effect of speaking German on cognitive resilience using the CERAD samples C and D.

Speaking German did not have a significant interaction with the presence of atrophy in CERAD sample C (p=0.87) or sample D (p=0.61). Within the CERAD sample C, Table 14 shows that when the fully adjusted model for speaking German and cognitive resilience was stratified by the presence/absence of atrophy, the association between speaking German and cognitive resilience became nonsignificant in both strata. Similar results were observed in the CERAD sample D (i.e., restricted atrophy sample) (Table E14, Appendix E).

Table 14: The association between speaking German and cognitive resilience stratified by the presence of atrophy, CERAD sample C[1]

	Cognitive resilience		
	Unstratified model (n=180) OR (95% CI)	**Atrophy present (n=139) OR (95% CI)**	**Atrophy absent (n=41) OR (95% CI)**
Speaking German (Yes versus no)	**0.49 (0.26-0.94)**	0.54 (0.25-1.16)	0.70 (0.14-4.01)
Presence of *APOE*-ε4 allele	**0.37 (0.18-0.73)**	**0.37 (0.15-0.81)**	0.87 (0.13-7.92)
Age at death (years)	0.96 (0.90-1.03)	0.99 (0.92-1.07)	0.84 (0.67-1.02)
Primary language (English versus other)	0.76 (0.29-2.03)	0.59 (0.16-2.29)	2.06 (0.34-11.90)
Education (versus high school or less)	2.17 (0.69-7.76)	1.99 (0.54-8.86)	1.36 (0.01-
Undergraduate degree			120.20)
Graduate degree	2.30 (0.72-8.42)	2.49 (0.65-11.71)	0.82 (0.01-62.96)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

5.3.2.4 Summary of multivariable results

When the models were adjusted for the presence of atrophy, no substantial changes were observed in the association between multilingualism and cognitive resilience in both CERAD and NIA-RI samples C and D, and the results were not statistically significant. When the fully adjusted models were stratified by the presence of atrophy, the association between multilingualism and cognitive resilience remained not statistically significant, but affected the precision of the estimates by the widening of confidence intervals.

Speaking German significantly reduced the likelihood of cognitive resilience in the CERAD samples C and D. However, when the models were *adjusted* for the presence of atrophy,

the direction of the association still suggested that German speakers had reduced odds of cognitive resilience, but this association was not statistically significant. When the models were *stratified* by the presence of atrophy, the association between speaking German and cognitive resilience remained nonsignificant across atrophy strata.

5.4 Research question 4: Does education (an indicator of cognitive reserve) modify the association between multilingualism and cognitive resilience?

5.4.1 Multilingualism

5.4.1.1 Descriptive results for research question 4

In the CERAD sample A (Table 15) and NIA-RI sample A (Table 16), all participants who spoke four or more languages had at least completed an undergraduate degree, regardless of cognitive resilience status. Moreover, the results from both Tables 15 and 16 showed that speaking four or more languages and attaining an undergraduate degree or higher were more common in those who were cognitively resilient than those who were not.

Table 15: The distribution of multilingualism by cognitive resilience and education, CERAD sample A[1] (n=199)

Variables	High school or less		Undergraduate degree		Graduate degree	
	Cognitive resilience		Cognitive resilience		Cognitive resilience	
	Yes	No	Yes	No	Yes	No
Multilingualism**:** Number of languages spoken (%)						
1	16.7	17.7	35.1	36.2	31.7	15.7
2	66.7	64.7	54.1	53.2	41.5	54.9
3	16.7	17.7	5.4	10.6	19.5	23.5
4	0	0	2.7	0	4.9	3.9
5	0	0	2.7	0	2.4	2.0

Bolded values were significantly associated with cognitive resilience ($p<0.05$). [1]CERAD main sample. **Abbreviations:** CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria.

Table 16: The distribution of multilingualism by cognitive resilience and education, NIA-RI sample A[1] (n=147)

Variables	High school or less		Undergraduate degree		Graduate degree	
	Cognitive resilience		Cognitive resilience		Cognitive resilience	
	Yes	No	Yes	No	Yes	No
Multilingualism**:** Number of languages spoken (%)						
1	33.3	23.1	31.6	45.7	38.1	20.0
2	33.3	61.5	52.6	47.8	33.3	48.9
3	33.3	15.4	5.3	6.5	14.3	24.4
4	0	0	5.3	0	9.5	4.4
5	0	0	5.3	0	4.8	2.2

Bolded values were significantly associated with cognitive resilience ($p<0.05$). [1]NIA-RI main sample. **Abbreviations:** NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria

5.4.1.2 Multivariable results for research question 4

In order to investigate whether education modified the association between multilingualism and cognitive resilience, the multivariable models adjusted by education in research question 1 were analyzed further. The models 1h and 1i in Tables 2 to 4 assessed the association between multilingualism and cognitive resilience with education. In all CERAD and NIA-RI samples A, comparing the crude model (model a) with model i in Tables 2, 3, and 4a showed that adjusting for education did not make any substantial changes to the association between multilingualism (when defined as either a four-level multilingualism variable with monolinguals as the reference group, or as speaking two or more languages versus one language) and cognitive resilience. However, according to the crude model in Table 4b, a statistically significant association was observed between speaking four or more languages versus fewer languages and cognitive resilience (OR: 4.43, 95% CI: 1.04-22.44). When the model was adjusted for education the direction of the association remained the same, but the association was no longer statistically significant (OR: 4.16, 95% CI: 0.96-21.41). In the CERAD and NIA-RI samples B, restricted to university-educated teachers (Tables C6-C8 in Appendix C), no substantial differences were observed between the crude model a and model i with respect to the association between multilingualism and cognitive resilience after adjusting for education.

Further, within both CERAD and NIA-RI samples A and B, no interactions were observed between education and multilingualism, based on all three definitions of multilingualism used in this thesis project. With respect to analyses stratified by education, because there were very few participants with high school education or less who spoke four or more languages, models could only be constructed for multilingualism defined as speaking two or more languages versus monolinguals. With Firth regression, this definition of multilingualism

was not significantly associated with cognitive resilience for those with high school education or less (CERAD: OR=0.75, 95% CI=0.05-10.51; NIA-RI: OR=0.28, 95% CI=0.01-9.84), an undergraduate degree (CERAD: OR=0.90, 95% CI=0.35-2.34; NIA-RI: OR=1.63, 95% CI=0.50-5.30), or a graduate degree (CERAD: OR=0.46, 95% CI=0.16-1.32; NIA-RI: OR=0.50, 95% CI=0.15-1.66), although confidence intervals were very wide. When using standard logistic regression, the odds ratios were similar except the models could not be constructed for the low education (high school education or less) stratum. In summary, speaking two or more languages (versus one language) was not significantly associated with cognitive resilience when stratified by education in CERAD and NIA-RI samples A.

5.4.2 Type of Language

5.4.2.1 Descriptive results for research question 4

Within CERAD or NIA-RI samples A, there were very few participants with low education (i.e., up to high school or less) who spoke French, Latin, or Polish (data not shown). For example, among those with low education, only a very small number of participants spoke French in the CERAD and NIA-RI samples A, and all participants who spoke French were not cognitively resilient. Moreover, within the CERAD or NIA-RI samples A, only one participant with low education spoke Latin and this participant was not cognitively resilient. Also, in the CERAD sample A, none of the participants with low education spoke Polish, but in the NIA-RI sample A there was one participant with low education, who spoke Polish and was cognitively resilient. Among those who have completed an undergraduate degree, all participants who spoke Latin were cognitively resilient in both CERAD or NIA-RI samples A (data not shown).

5.4.2.2 Multivariable results for research question 4

To examine whether education modifies the association between type of language spoken and cognitive resilience, the multivariable models adjusted by education in research question 2, were examined in this section. The results from model 3 in Tables 8a and 8b based on CERAD and NIA-RI samples A, respectively, showed that adjusting for education did not make any substantial changes to the association between any of the type of languages and cognitive resilience. When using samples restricted to university-educated teachers (sample B), adjusting for higher levels of education (undergraduate degree and/or graduate degree) also did not result in substantial changes to the association between type of language and cognitive resilience, as shown in model 3 of Tables D2 and D3 in Appendix D.

Moreover, none of the interactions between type of language and cognitive resilience were statistically significant; however, any interaction between being proficient in Latin and cognitive resilience could not be analyzed because of small sample sizes. In addition, using Firth regression, there were no significant associations observed between any of the languages (i.e., German, French (only within CERAD sample), Spanish, Spanish or Italian languages, or romance languages) and cognitive resilience when stratified by education for participants with high school education or less, undergraduate, or graduate degrees within the CERAD and NIA-RI samples A. For example, speaking German was not significantly associated with cognitive resilience for those with high school education or less (CERAD: OR=0.93, 95% CI=0.11-8.13; NIA-RI: OR=0.67, 95% CI=0.06-7.83), an undergraduate degree (CERAD: OR=0.62, 95% CI=0.24-1.61; NIA-RI: OR=1.03, 95% CI=0.32-3.32), or a graduate degree (CERAD: OR=0.40, 95% CI=0.16-1.01; NIA-RI: OR=0.44, 95% CI=0.13-1.42), although confidence intervals were wide. Because there were very few participants with high school education or less who spoke

French (only within the NIA-RI sample A), Latin, and Polish, models could not be constructed for these participants with low education. However, the results showed that there were no significant associations between speaking French, Polish, or being proficient in Latin and cognitive resilience when stratified by education for participants with undergraduate or graduate degrees in both CERAD and NIA-RI samples A. In comparison to the results from Firth regression, using standard logistic regression produced similar odds ratios except the models could not be constructed for the low education (high school education or less) stratum. Overall, no significant associations were observed between type of language and cognitive resilience when stratified by education.

A brief summary of all the results for research questions 1 through 4 are presented in Table 17 on next page.

Table 17: Summary of results for the associations between exposures of interest and cognitive resilience, CERAD and NIA-RI samples A to D**

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
1	Tables 2-4, and Tables C6a-C8b in Appendix C	*Multilingualism* (versus one language)	Unadjusted				
		Speaking two languages		↓	↓	↓	↓
		Speaking three languages		↓	↓	↓	↓
		Speaking four or more languages		↑	↑	↑	↑
		Speaking two languages	Adjusted[1]				
		Speaking three languages		↓	↓	↓	↓
		Speaking four or more languages		↓	↓	↓	↓
				↑	↑	↑	↑
		Multilingualism (versus one language)	Unadjusted				
		Speaking two or more languages		↓	↓	↓	↓
		Speaking two or more languages	Adjusted[1]	↓	↓	↓	↓

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
		Multilingualism (versus one to three language)	Unadjusted				
		Speaking four or more languages		↑	↑*	↑	↑
		Speaking four or more languages	Adjusted[1]	↑	↑*	↑	↑*
2	Tables 8a, 8b, and Tables D2 and D3 in Appendix D	*Type of language spoken*	Unadjusted				
		German		↓*	↓	↓*	↓
		French		↑	↑	↑	↑
		Spanish		↓	↑	↓	↑
		Spanish or Italian		↑	↑	↑	↑
		Romance languages***		↑	↑	↑	↑
		Latin		↓	↑	↓	↑
		Polish		↑	↑	↑	↑

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
		Type of language spoken	Adjusted[2]				
		German		↓*	↓	↓*	↓
		French		↑	↑	↑	↑
		Spanish		↓	↑	↓	↑
		Spanish or Italian		↑	↑	↑	↑
		Romance languages		↑	↑	↑	↑
		Latin		↓	↑	↓	↑
		Polish		↑	↑	↑	↑
3	Tables 9, 10, and 11.	*Multilingualism* (versus one language)	Unadjusted[3]				
		Speaking two languages		↓	↓	↓	↓
	Note: Results based on CERAD or NIA-RI samples D were not	Speaking three languages		↓	↓	↓	↓
		Speaking four or more languages		↑	↑	↑	↑
		Speaking two languages	Adjusted[4]	↓	↓	↓	↓
		Speaking three languages		↓	↑	↓	↑
		Speaking four or more languages		↑	↑	↑	↑

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
	shown in tables.	*Multilingualism* (versus one language)	Unadjusted[3]				
		Speaking two or more languages		↓	↓	↓	↓
		Speaking two or more languages	Adjusted[4]	↓	↑	↓	↑
		Multilingualism (versus one to three language)	Unadjusted[3]				
		Speaking four or more languages		↑	↑	↑	↑
		Speaking four or more languages	Adjusted[4]	↑	↑	↑	↑
3	Tables E3-E10 in Appendix E	*Multilingualism* (versus one language)	Stratified: no atrophy				
		Speaking two languages		↑	-	↑	-
		Speaking three languages		↑	-	↓	-
		Speaking four or more languages		↑	-	↑	-

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
		Speaking two languages	Stratified: atrophy present	↓	-	↓	-
		Speaking three languages		↓	-	↓	-
		Speaking four or more languages		↓	-	↓	-
		Multilingualism (versus one language)	Stratified: no atrophy				
		Speaking two or more languages		↑	↑	↑	↑
		Speaking two or more languages	Stratified: atrophy present	↓	↓	↓	↓
		Multilingualism (versus one to three language)	Stratified: no atrophy				
		Speaking four or more languages		↑	-	↑	-
		Speaking four or more languages	Stratified: atrophy present	↓	-	↓	-

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
	Tables 13a-13b, and Tables E12 and E13 in Appendix E	*Type of language spoken*	Unadjusted				
		German		↓*	↓	↓*	↓
		German	Adjusted[5]	↓	↓	↓*	↓
3	Table 14 and Table E14 in Appendix E	German	Stratified: no atrophy	↓	-	↓	-
		German	Stratified: atrophy present	↓	-	↓	-
4	Tables 2-4, and Tables C6a-C8b in Appendix C (models a and i)	*Multilingualism* (versus one language)	Crude model[6]				
		Speaking two languages		↓	↓	↓	↓
		Speaking three languages		↓	↓	↓	↓
		Speaking four or more languages		↑	↑	↑	↑
		Speaking two languages	Adjusted[7]	↓	↓	↓	↓
		Speaking three languages		↓	↓	↓	↓
		Speaking four or more languages		↑	↑	↑	↑

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
	Tables 2-4, and Tables C6a-C8b in Appendix C (models a and i)	*Multilingualism* (versus one language)	Crude model[6]				
		Speaking two or more languages		↓	↓	↓	↓
		Speaking two or more languages	Adjusted[7]	↓	↓	↓	↓
		Multilingualism (versus one to three language)	Crude model[6]				
		Speaking four or more languages		↑	↑*	↑	↑
		Speaking four or more languages	Adjusted[7]	↑	↑	↑	↑
4	Tables 8a, 8b, and Tables D2 and D3 in Appendix D (crude model and model 3)	*Type of language spoken*	Crude model[6]				
		German		↓*	↓	↓*	↓
		French		↑	↑	↑	↑
		Spanish		↓	↑	↓	↑
		Spanish or Italian		↑	↑	↑	↑
		Romance languages***		↑	↑	↑	↑
		Latin		↓	↑	↓	↑
		Polish		↑	↑	↑	↑

Research Question #	Associated Results Table	Exposure of interest	Model Type	Results (samples A or C)		Results (samples B or D)	
				CERAD	NIA-RI	CERAD	NIA-RI
		Type of language spoken	Adjusted[7]				
		German		↓*	↓	↓*	↓
		French		↑	↑	↑	↑
		Spanish		↓	↑	↓	↑
		Spanish or Italian		↑	↑	↑	↑
		Romance languages***		↑	↑	↑	↑
		Latin		↓	↑	↓	↑
		Polish		↑	↑	↑	↑

*Statistically significant association ($p<0.05$) ** Samples A (CERAD or NIA-RI main samples); Samples B (CERAD or NIR-RI restricted samples); Samples C (CERAD or NIA-RI atrophy samples); Samples D (CERAD or NIA-RI restricted atrophy samples). ***Romance languages: Spoke French or Spanish or Italian

[1]Adjusted for *APOE*-ε4 status, age at death, education, and primary language
[2]Adjusted for *APOE*-ε4 status, age at death, education, immigration status and primary language
[3]Unadjusted model for the presence of atrophy (i.e., only adjusted for *APOE*-ε4 status, age at death, education, and primary language)
[4]Adjusted for *APOE*-ε4 status, age at death, education, primary language, and presence of atrophy
[5]Adjusted for *APOE*-ε4 status, age at death, education, primary language, immigration status, and presence of atrophy
[6]Crude model – not adjusted for any covariates
[7]Adjusted for education

Abbreviations: *APOE*-ε4=Apolipoprotein E-ε4; CERAD=Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; NIA-RI=National Institute on Aging-Reagan Institute neuropathologic criteria
Note: upward arrows indicate a positive association (i.e., odds ratio >1); downward facing arrows indicate a negative association (i.e., odds ratio <1).

6.0 Discussion

6.1 Study Findings

Multilingualism was significantly associated with cognitive resilience only when participants spoke four or more languages (versus speaking fewer languages). Also, the type of language spoken did not significantly influence the likelihood of cognitive resilience. Moreover, no significant evidence was found for the presence of ceiling or floor effects in the association between multilingualism and cognitive resilience. For instance, adjusting for education or cortical atrophy in multivariable models did not cause any substantial changes to the association between multilingualism or type of language and cognitive resilience. However, when the multivariable models assessing type of language and cognitive resilience were adjusted for the presence of atrophy, the statistically significant association observed between speaking German and cognitive resilience became nonsignificant. In addition, interactions between multilingualism and education, multilingualism and atrophy, type of language and education, and type of language and atrophy were not statistically significant. The following sections will discuss in detail the results for each research question.

6.1.1 Research question 1: Does multilingualism (speaking more than one language) increase the likelihood of cognitive resilience?

Based on the three definitions of multilingualism used in this thesis project, only speaking four or more languages (versus a fewer number of languages) significantly contributed to cognitive resilience. However, this association was only significant when using the NIA-RI sample. This may be because the NIA-RI criteria are based on both NP and

NFT pathology, while the CERAD criteria are based on the NP counts only. It is possible that identifying the likelihood of AD based on NFT counts helped better estimate cognitive resilience than the NP counts.

Findings of this current project were consistent with some previous studies. For example, a longitudinal study found that among immigrants, a dose-response protective effect was observed where those who spoke four or more languages had a 9.5-year delay in the diagnosis of AD (Chertkow et al., 2010). Another population-based, longitudinal study observed that those who spoke four or more languages had better cognitive performance (based on Katzman cognitive screening test and Folstein MMSE scores) than bilinguals or trilinguals (Kave et al., 2008), even after adjusting for age, birth place, age at immigration and formal education. Notably, studies that were longitudinal in nature did not find a statistically significant protective effect of bilingualism against the onset of dementia, AD or cognitive decline (Crane et al., 2009; Clare et al., 2014; Lawton et al., 2015; Ljungberg et al., 2016; Mukadam et al., 2017; Sanders et al., 2012; Zahodne et al., 2014). A population-based and retrospective nested case-control study based on 232 participants who had cognitive impairment without dementia (CIND) or did not have any cognitive impairment (i.e., intact cognition) investigated whether multilingualism was associated with the risk of CIND (Perquin et al., 2013). Because this study did not have any life-long monolinguals, the bilinguals in the sample were used as the comparison group in the analyses, and therefore, a potential benefit from bilingualism alone could not be analyzed in this study. Overall, the

results showed that speaking more than two languages was associated with a lower risk of CIND (Perquin et al., 2013). A similar trend was observed for those who spoke three languages (versus two languages) and four languages (versus two languages). Moreover, in this study, participants were asked to specify their age of language acquisition, number of languages spoken, and the duration of practice for each language learned (in years) until the time of the study (Perquin et al., 2013). Using these collected data, six basic temporal patterns of progression for acquiring multilingualism (defined as speaking three or more languages) were created for analysis. Based on the progression patterns observed, the participants who progressed from speaking two to speaking three languages experienced a seven-fold protection against CIND (Perquin et al., 2013).

However, findings from some previous studies were not consistent with the results of the current project. For example, studies that were cross-sectional in nature and had used clinic-based samples observed a protective effect of bilingualism against dementia (Alladi et al., 2013; Bialystok et al., 2007; Craik et al., 2010; Woumans et al., 2015) unlike the results in this current research project. Comparison of study findings from previous literature indicates that studies that were longitudinal and/or had used population-based samples did not find a protective effect of bilingualism against dementia, whereas only studies that were cross-sectional and had used clinic-based samples found a protective effect of bilingualism against dementia or AD. For instance, one study, which had both cross-sectional and longitudinal components, clearly demonstrated that a bilingual benefit against dementia was

apparent only when using a cross-sectional study design (Yeung et al., 2014). As the current study was a population-based longitudinal study, the results of no significant association between bilingualism and cognitive resilience is consistent with literature on similar studies that reported no significant association between bilingualism and AD.

Other than the study design and the type of sample used, other factors, such as sample size, frequency of multiple language use, and age at second language acquisition may influence the protective effect of bilingualism against AD/dementia. With respect to the previous longitudinal studies, the sample size of bilinguals who did not develop dementia might have been too small, with insufficient power to achieve significant results (see review by Bialystok et al., 2017). In this current research project, however, the largest group of participants was bilinguals, and thus, it was unlikely that these results were influenced by insufficient power from a smaller sample of bilinguals. Although there were a smaller number of participants speaking higher numbers of languages, having statistically significant findings on those who spoke four or more languages on cognitive resilience confirms that the samples did have sufficient power to produce significant results.

One longitudinal study that did not observe a protective effect of bilingualism against dementia had selected bilinguals through self-report, by collecting information on whether the participants spoke English or Spanish, without assessing their frequency of language use or their age at second language acquisition (Lawton et al., 2015). As a result, it is possible that factors such as the frequency of language use and age at second language acquisition

could have influenced the protective effect of bilingualism against dementia. Since the current study also did not have data available on the participants' frequency and intensity of language use, the age at second language acquisition, reading ability and language comprehension, these factors may be partially responsible for not seeing a protective effect of bilingualism on cognitive resilience in the current study. For example, the bilinguals in this study might not have spoken the second language frequently or might not have learned to speak the second language at an early age. Alternatively, because the majority of Nun Study participants were bilinguals, speaking two languages was the norm and therefore, a higher number of languages (e.g., four or more languages) were required to be spoken in order to attain significant benefits on cognitive resilience.

The association between multilingualism and cognitive resilience could also be subjected to various confounders, such as socioeconomic status (Morton & Harper, 2007), immigration status (Fuller-Thomson, 2015), education, occupation, and intelligence. In the Nun Study, all participants had similar incomes and therefore, confounding from socioeconomic status was unlikely to explain the results. The healthy immigrant effect could affect the association between multilingualism and cognitive resilience, as immigrants may be selectively better able to cope with challenging situations compared to those who do not immigrate from a country (Fuller-Thomson, 2015). In this study, however, adjusting for both primary language spoken and immigrant status did not cause substantial changes to the association between multilingualism and cognitive resilience. With respect to education and

occupation, because the Nun Study participants were highly educated and the majority served as teachers, there were very few participants who had only completed high school or less and who were not teachers. As a result, adjusting for education in the multivariable models affected the precision of the estimates, and adjusting for occupation in the models was problematic. Therefore, in order to fully address confounding by education and occupation, additional analyses were performed using a sample restricted to university-educated teachers. When the models were run using the restricted sample, speaking four or more languages still contributed to cognitive resilience, even when higher levels of educational attainment (i.e., those who had attained an undergraduate degree or higher) and occupation (i.e., teachers) were held constant by restriction, in addition to adjusting for residual confounding by education (graduate versus undergraduate degree) by multivariable analyses in models adjusted for the standard covariates. Lastly, intelligence may be another underlying factor that could influence the study findings. Since among the definitions of multilingualism only speaking four or more languages (versus fewer languages) significantly contributed to cognitive resilience, there is a possibility that those who spoke four or more languages were significantly different (e.g., had higher levels of intelligence) compared to those who spoke fewer number of languages. One study investigated whether the protective effect of bilingualism on late-life cognition was actually the result of speaking more than one language or whether it was because bilinguals had a higher baseline cognitive ability (e.g., childhood intelligence) than monolinguals (Bak et al., 2014). According to the results,

bilingualism consistently had a positive association with late-life cognition even when childhood intelligence was held constant (Bak et al., 2014). However, the age at second language acquisition produced differential cognitive benefits depending on childhood intelligence. For example, those with high intelligence had more cognitive benefits when the second language was acquired at an early age, whereas those with low intelligence showed benefits to cognition when the second language was acquired at a later age (Bak et al., 2014). To date, no studies to the author's knowledge have investigated the influence of intelligence on the association between four or more languages and cognitive resilience, and this warrants further investigation.

In summary, speaking four or more languages significantly increased the likelihood of cognitive resilience, even after adjusting for *APOE*-ε4 status, age at death, education, and primary language, and also when the sample was restricted to university-educated teachers.

6.1.2 Research question 2: Does the type of language spoken influence the likelihood of cognitive resilience?

The findings from this current study showed that speaking German significantly reduced the likelihood of cognitive resilience after adjusting for *APOE*-ε4 status, age at death, education, primary language, and immigration status, but only in the CERAD samples. The direction of effect in the results from the NIA-RI sample was consistent with that of the CERAD sample, but the association was not statistically significant, perhaps because of the smaller size of the NIA-RI sample. Although not statistically significant in either CERAD or

NIA-RI samples, the odds ratios for speaking French, Polish, romance languages, and either Spanish or Italian languages were greater than one, suggesting that they may increase the likelihood of cognitive resilience. However, the direction of effect for the association between speaking Spanish or being proficient in Latin and cognitive resilience was inconsistent across the CERAD and NIA-RI samples and was not significant, perhaps because of fewer participants who spoke these languages. Thus, the results for an association between speaking Spanish or being proficient in Latin and cognitive resilience were not conclusive in this study.

Since all participants of this study spoke English, the trends observed in this study may have been influenced by the typological distance between English and the other language(s) spoken by the participants. As English is a Germanic language and is linguistically related to German, there is a higher degree of typological similarity between German and English than between many of the other languages, which may lead to more cross-linguistic interference than speaking linguistically unrelated languages (Serratrice et al., 2009). German and English speakers are more likely to use phrases and word orders that are common to both languages, even in inappropriate contexts, than to use phrases and word orders unique to German or English only (Dopke, 1998; Serratrice, 2009). As a result, it is possible that German-English bilinguals experience more cognitive demand while speaking than those who speak more dissimilar languages, as they need to overcome greater cross-linguistic interference when the two languages share close familiarity. With respect to the

other type of languages spoken in this study, the majority of the participants spoke romance languages (e.g., French, Spanish, Italian) or had a proficiency in Latin. Even though English has some lexical similarity derived from Latin, English is not considered a romance language. Therefore, the participants speaking English and romance languages (i.e., linguistically dissimilar or unrelated languages) could contribute differently to cognitive resilience compared to those speaking linguistically related languages, such as English and German. Similarly, since Polish belongs to the West Slavic language group and is linguistically unrelated to English, Polish-English speakers could also contribute differently to cognitive resilience than German-English speakers.

Previous studies have investigated whether the beneficial effects of bilingualism on cognition were a result of typological similarity between the two languages spoken. Bilingualism can enhance executive control by improving conflict resolution skills as well as inhibitory control of the other languages while speaking a particular language (Costa et al., 2008). To date, the findings have been mixed regarding whether bilingualism, when it involves speaking two typologically similar languages, can result in cognitive benefits. For example, one study found that those speaking similar languages (Spanish and Catalan) outperformed the Spanish monolinguals in conflict resolution skills and had enhanced executive control networks (Costa et al., 2008), demonstrating a cognitive benefit of bilingualism when the two languages spoken were similar. There were also stronger cognitive benefits observed when the Spanish-Catalan bilinguals had greater levels of

switching between the languages than those who did not (Costa et al., 2008). Moreover, another study with bilingual older adults showed that those who spoke typologically similar languages, such as Cantonese and Mandarin, had greater gray matter density in the inferior parietal lobule than those who spoke typologically dissimilar languages, such as Cantonese and English (Abutalebi et al., 2015). According to Abutalebi et al. (2015), when speaking similar languages, the individuals experience more cognitive demand to inhibit cross-linguistic interference from languages that have close familiarities, compared to speaking languages that are dissimilar and require lower levels of inhibitory control, as there is much less cross-linguistic interference to overcome.

In addition, studies have shown that the cognitive benefits of bilingualism are not restricted to instances when the two languages spoken are similar, and that speaking two dissimilar languages could also result in cognitive benefits. For example, studies which assessed the cognitive benefits from speaking unrelated languages, such as Korean-English (Yang and Yang, 2016) and Chinese-English (Tao et al., 2011) found that those who spoke either Korean-English or Chinese-English exhibited similar cognitive benefits and outperformed the monolingual counterparts. Because Korean is orthographically different from English, those who were Korean-English bilinguals had activated additional networks for visuospatial processing and to carefully monitor phonemic and semantic differences while speaking, thereby enhancing cognition (Wu et al., 2016). Other studies have investigated the effects from speaking bidialectical languages on cognition (Scaltritti et al.,

2017; Wu et al., 2016), but have found no difference in cognitive benefits between bilinguals and monolinguals irrespective of the similarity between the type of languages. For instance, studies that investigated whether Italian-Venetian bi-dialectics (versus Italian monolinguals) (Scaltritti et al., 2017) or Mandarin-Min bi-dialectics (versus Mandarin monolinguals) (Wu et al., 2016) have better cognitive outcomes than the monolingual counterparts, did not find any significant benefits in speaking typologically related languages. One reason for these contradictory findings could be that although the bidialectical languages have different pronunciations, the two dialectics have comparable lexical and syntactic features, thereby reducing the level of cross-linguistic interference leading to cognitive benefits.

Based on the findings of this current study, speaking linguistically related languages such as German and English significantly reduced the likelihood of cognitive resilience, which is contradictory to what some of the previous studies had observed on the cognitive benefits of speaking typologically similar languages. Relative to German and English language pairing, those who spoke unrelated languages such as Polish and English, or any or all of the romance languages and English, were shown to increase their odds of cognitive resilience, which was also inconsistent with previous findings. However, certain factors may account for these contradictory findings. For example, this study did not have data on the participants' frequency of language use (i.e., the degree of switching between languages). Since most of the German speakers in this study were immigrants, they would have spoken German at an early age and may have learned to speak English after they migrated to the

United States. Because English is the dominant language used in the United States, these participants might not have had much opportunity to switch between German and English after they had settled down in the United States. Thus, the early age of language acquisition and less frequency of language use could have influenced the results. Lastly, there may be additional differences present between German and other language speakers that could influence the association with cognitive resilience. In this study, the German speakers had reduced cognitive resilience after adjusting for *APOE*-ε4 status, age at death, education, primary language, and immigration status. However, there may be other potential confounders, such as atrophy, influencing late-life cognition of German speakers thereby reducing their likelihood of cognitive resilience (see section 6.1.3). In summary, speaking typologically similar languages, such as English and German, significantly reduced the likelihood of cognitive resilience.

6.1.3 Research question 3: Does cortical atrophy (an indicator of brain reserve) modify the association of cognitive resilience with multilingualism or type of language spoken?

The results for research question 3 showed that adjusting for the presence of atrophy did not substantially change the association between multilingualism and cognitive resilience in both CERAD and NIA-RI samples. It was hypothesized that if there was a floor effect for cognitive resilience, the presence of brain damage (e.g., atrophy) could reduce brain reserve such that the factors that contribute to cognitive reserve (e.g., multilingualism) were unable to compensate for any more brain damage. Therefore, if the hypothesis was supported, a

floor effect would indicate that when atrophy is present, the protective effects of multilingualism on cognitive resilience would be weakened. Contrary to the multivariable results observed for research question 1, no significant association was observed between those speaking four or more languages and cognitive resilience (within the atrophy sample), with or without adjusting for the presence of atrophy. Thus, this would indicate that the smaller atrophy sample might have concealed any significant associations between speaking four or more languages and cognitive resilience, regardless of the presence of atrophy. Moreover, the results showed no significant interaction between multilingualism and the presence of atrophy; when the results were stratified by the presence of atrophy in order to fully explore the possibility of a floor effect, none of the stratified results were statistically significant and the precision of the estimates was low as indicated by the wider confidence intervals. Therefore, the study findings did not provide supportive evidence for the "floor effect" hypothesis on cognitive resilience.

In terms of the type of language spoken, within the CERAD atrophy sample, speaking German did not significantly reduce the likelihood of cognitive resilience after adjusting for the presence of atrophy. As a result, this indicated that German speakers might have had greater levels of atrophy than those who spoke other languages, and having more atrophy might have reduced cognitive resilience among German speakers. Moreover, no significant interaction was observed between type of language and the presence of atrophy. To further explore the possibility of a floor effect, the results were stratified by the presence of atrophy

(present or absent). The presence of a floor effect on cognitive resilience would indicate that the association between speaking German and cognitive resilience weakened only when atrophy was present. Conversely, when atrophy is absent, the German speakers should have a stronger association with cognitive resilience. However, the stratified results did not confirm the floor effect hypothesis, as the association between speaking German and cognitive resilience was not significant in any atrophy strata, and there was no trend suggesting a floor effect on cognitive resilience in the presence of atrophy.

In previous studies, bilingualism has been shown to minimize the adverse effects of brain damage on cognitive function. For example, in comparison to monolinguals diagnosed with probable AD, bilinguals with AD had more severe levels of cerebral atrophy in the medial temporal region (hippocampus), a target brain region for Alzheimer pathology, although both bilinguals and monolinguals diagnosed with AD were matched for their overall cognitive and memory performance as well as education (Schweizer et al., 2012). The level of neuropathology in the brain of an individual diagnosed with AD has been correlated to the degree of atrophy within the brain (Schweizer et al., 2012). Since the bilinguals with AD had higher levels of atrophy than their monolingual counterparts, these bilinguals likely had higher levels of neuropathology than monolinguals as well. Yet, these bilinguals were able to maintain similar levels of cognitive function as monolinguals with AD. As a result, this study supported bilingualism as a contributor to cognitive resilience, which enhances the efficient use of available brain networks to compensate for brain damage. Similarly, another study

investigated whether the protective effects of bilingualism could help maintain cognitive function despite the presence of a stroke (another form of brain damage) (Alladi et al., 2016). Stroke can lead to significant brain damage and reduce the amount of brain reserve present. More bilinguals (40.5%) were able to preserve normal cognition following a post-stroke event, compared to monolinguals (19.6%). In addition, in the same study, cognitive impairment, such as vascular dementia or vascular MCI, was found to be more common in monolinguals than in bilinguals (Alladi et al., 2016). In summary, previous research showed that bilinguals were able to maintain better cognitive outcomes following brain damage than monolinguals.

Based on the results of this current study, within the atrophy sample, multilingualism was not shown to contribute to cognitive resilience regardless of the presence or absence of atrophy. One reason for these findings, which are inconsistent with previous research, might be because of differences in the study design and the study population. For instance, a protective effect from bilingualism was found only in studies that were cross-sectional and had used clinic-based populations, while studies that were longitudinal or had used population-based samples did not find any protective effect from bilingualism (see section 6.1.1). Since the previous studies by Schweizer et al. (2012) and Alladi et al. (2016) were cross-sectional studies that had used clinic-based samples, while this current research project was a longitudinal study that had used a population-based sample, the inconsistent findings might have been a result of methodological differences between the studies. Moreover, the

size of the atrophy sample in this study may not have been adequate to reveal a significant protective effect from bilingualism against atrophy. However, because there was no protective effect from bilingualism observed even when the larger analytic samples were used in this research project (e.g., for research question 1), it is unlikely that there was no protective effect of bilingualism observed due to lack of power from the smaller sample.

In summary, adjusting for atrophy did not cause any substantial changes to the association between multilingualism and cognitive resilience; however, the association between speaking German and cognitive resilience was no longer significant when adjusted for atrophy. Moreover, none of the interactions between multilingualism or type of language variables and atrophy were statistically significant, and the stratified models did not provide significant evidence for the presence of a floor effect in cognitive resilience.

6.1.4 Research question 4: Does education (an indicator of cognitive reserve) modify the association of cognitive resilience with multilingualism or type of language spoken?

When the models assessing the association between multilingualism or type of language and cognitive resilience were adjusted for education in order to explore the possibility of a ceiling effect, no substantial changes were observed in the results for either CERAD or NIA-RI samples. The presence of a ceiling effect would indicate that factors that influence cognitive reserve, such as education, could reduce the strength of the association between multilingualism or type of language and cognitive resilience by outcompeting the ability of multilingualism or type of language to contribute to cognitive resilience. In this

study, if there was a ceiling effect in cognitive resilience, the presence of education (i.e., an established strong promoter of cognitive resilience) should weaken the association between cognitive resilience and multilingualism or type of language (hypothesized to be a weaker influence than education). Based on the study findings, however, no statistically significant interactions were observed between multilingualism or type of language variables and education. The results from stratified analyses showed that speaking two or more languages (versus one language) did not have a statistically significant association with cognitive resilience in any of the education strata. Similarly, no statistically significant associations were observed between the type of language and cognitive resilience when stratified by education. The results from stratified analyses could not be used as evidence for or against a possible ceiling effect in cognitive resilience, because the estimates had low precision as indicated by the wide confidence intervals. However, since education is a well-established promoter of cognitive resilience and because the majority of participants in this study were highly educated, this may have reduced the ability to detect a benefit of speaking two or three languages on cognitive resilience (i.e., a ceiling effect), while only the stronger exposure of speaking four or more languages was able to produce significant benefits. Overall, since no significant interaction was observed between multilingualism or type of language and education as well as no significant trends supporting a ceiling effect were observed in the stratified analyses, this study did not provide strong supportive evidence for the "ceiling

effect" hypothesis between multilingualism or type of language, education and cognitive resilience.

From previous research studies, there has been some support for a ceiling effect in cognitive resilience. For example, previous work in the Nun Study showed that larger brain size significantly reduced the risk of dementia, but only when the participants also had lower levels of education (Mortimer, Snowdon, & Markesbery, 2003). Recall that cognitive reserve refers to an 'active' process of using neural networks efficiently to compensate for brain damage, while brain reserve relies on structural advantages, such as greater synaptic connections between neurons, which can increase the capacity to tolerate more brain damage. Thus, education is known to be a strong contributor to cognitive reserve, while having a larger brain size (i.e., a structural advantage) is known to be contributor to brain reserve. However, in the study by Mortimer et al. (2003), having a larger brain size did not reduce the risk of dementia when education was high, thereby indicating that education (i.e., an established strong promoter of cognitive reserve) outcompeted the ability of larger brain size (suggested to have a weaker influence than education) to contribute to cognitive resilience. This implies a ceiling effect, where the level of cognitive resilience was already maximized by high levels of education and no further gains from a larger brain size were observed. Similarly, another study found that low education influenced the association between bilingualism and age at AD diagnosis (Gollan et al., 2011). For example, when participants had low levels of education (2-11 years), bilingualism delayed the age at AD diagnosis.

Conversely, when the participants had high levels of education (12-20 years), no association was observed between bilingualism and the age at diagnosis of AD (Gollan et al., 2011). Moreover, studies that had observed a protective effect from bilingualism against dementia have reported that their study participants had low levels of education (Bialystok et al., 2007; Craik et al., 2010).

In this study, adjusting for education did not substantially change the association between multilingualism or type of language and cognitive resilience. One reason might be that there were few participants who had low levels of education (i.e., up to high school or less), as the majority of Nun Study participants were highly educated. Therefore, the effect of low education on the association between multilingualism or type of language and cognitive resilience might not have been apparent due to lack of power from the smaller sample of participants with low education. Conversely, based on the results from samples restricted to university-educated teachers, the presence of high educational levels may have reduced the ability to detect an association between speaking two or three languages on cognitive resilience (i.e., a ceiling effect), while only speaking four or more languages was able to produce significant benefits on cognitive resilience. Because no significant interactions were observed between multilingualism or type of language and education as well as no significant results were observed in models stratified by education in both CERAD and NIA-RI samples, the current study could not provide strong supportive evidence for a ceiling effect in cognitive resilience.

6.2 Strengths

One of the major strengths of the Nun Study is the homogeneity of the study population. All the religious sisters had a similar diet, tobacco and alcohol use, access to healthcare services, and marital and reproductive status, which helped minimize the potential for confounding. Previous studies have shown that socioeconomic status can influence the association between multilingualism and cognitive resilience. Since the participants in the Nun Study had similar incomes, this study could better control for socioeconomic status than many other studies. In addition, the Nun Study had access to archival records, including a survey conducted in 1983 by the School Sisters of Notre Dame religious congregation and used for assigning teaching placements. These records provided data on language proficiency, educational attainment, occupation, and immigration status of the sisters. Because of the longitudinal nature of the Nun Study, temporality could be maintained between exposure and outcome, since language proficiency of sisters was assessed through the 1983 questionnaire prior to the assessment of dementia status.

Moreover, in the 1983 questionnaire of the religious sisters, the level of language proficiency was recorded through self-report of the number and the types of languages spoken (e.g., English, French, Spanish). According to the language proficiency data, a significant proportion of religious sisters spoke more than two languages, and there was diversity in the types of languages spoken by them. Since it can be challenging to obtain samples of non-immigrant participants who speak more than two languages (i.e., multilinguals), the Nun Study is a valuable resource, providing a relatively large sample of

multilingual participants born in the United States that could be used to determine the effect of multilingualism on cognitive resilience among non-immigrants. As the religious sisters spoke up to five languages, the dose-response effect of multilingualism on cognitive resilience was examined as well. Moreover, this study was also able to explore whether the type of language spoken influenced the odds of cognitive resilience, which was a topic that had not been thoroughly studied in previous research. In addition, the Nun Study had access to data on *APOE* genetic information, education, occupation, primary language spoken, immigration status, and the presence of cortical atrophy that were used to determine their influence on the relationship between multilingualism and cognitive resilience.

Lastly, the Nun Study also had access to data, such as dementia status at the last cognitive assessment before death and the presence of Alzheimer neuropathology through post-mortem examination. As a result, using both the data on dementia status coupled with the presence of Alzheimer neuropathology helped to operationalize the concept of cognitive resilience. For example, if participants did not exhibit any clinical symptoms of AD prior to death, but neuropathological assessments showed high levels of Alzheimer neuropathology, then the participants were classified as having cognitive resilience. Most studies on multilingualism and dementia/AD research had not been able to operationalize cognitive resilience as was done in this current study. Some studies have used the age at onset of dementia as an indirect assessment of cognitive resilience without directly examining the presence of Alzheimer neuropathology, while this study explored whether cognitive

resilience had prevented dementia in participants who had evidence of Alzheimer neuropathology based on post-mortem examinations. A few studies have used other diagnostic methods; rCBF and neuroimaging studies, such as computerized tomography scans, have been used to detect the presence of neuropathology. However, above all diagnostic methods that are available, a post-mortem examination remains the gold-standard diagnostic method for assessing Alzheimer neuropathology, such as NPs and NFTs. In addition, this research study presented findings on cognitive resilience, based on both CERAD (measured only NPs) and NIA-RI (measured both NPs and NFTs) criteria. Thus, the assessment of cognitive resilience in this study had high validity.

6.3 Limitations

In this current study, multilingualism was defined as speaking more than one language and could not consider other factors relating to multilingualism, such as reading ability, language comprehension, and the frequency and intensity of language use, and age at language acquisition. In the Nun Study, data on multilingualism were collected through self-report and therefore, the religious sisters may have over- or underestimated their level of language proficiency. Moreover, the number and the type of languages spoken and whether the participants spoke English as the primary language were the only measures available on multilingualism among the Nun Study participants.

Secondly, cognitive resilience was based on two types of diagnostic criteria for Alzheimer neuropathology (CERAD and NIA-RI criteria). CERAD criteria assessed only the presence of NPs. On the other hand, the NIA-RI criteria included both the distribution of NPs

and NFTs; however, a significant number of "unclassified subjects" (i.e., those with a higher score for NP count and a lower score for NFT count, or vice versa) were present, thereby reducing the size of the samples. Therefore, given the specific limitations of both CERAD and NIA-RI criteria, performing the analyses on both CERAD and NIA-RI samples helped to compare and validate the results.

Small sample sizes were a limitation for some of the analyses in this study. For example, for the analyses on the type of languages and cognitive resilience, some languages such as Latin and Italian were spoken by very few participants within the study sample. Because of the smaller sample size of those proficient in Latin, the results were not consistent across different analytic samples. In terms of Italian, there were very few Italian speakers present in the sample, also limiting those analyses. In addition, those who spoke Italian were combined with those who spoke Spanish, or other romance languages to analyze the effects of speaking specific types of languages on cognitive resilience. Moreover, excluding participants with missing data on atrophy reduced the sample sizes, such that previous statistically significant associations (between multilingualism and cognitive resilience), became nonsignificant (in research question 3). Also, in the analyses stratified by atrophy, the presence of a floor effect for cognitive resilience could not be adequately addressed as the sample sizes within some of the atrophy strata were very small and affected the precision of the estimates by widening the confidence intervals. Furthermore, because the majority of Nun Study participants were highly educated (i.e., had attained at least an undergraduate

degree), there were few who had attained low levels of education (i.e., had completed up to high school or less) within the analytic samples. Therefore, due to less variability in the educational levels of participants, this study may have been unable to detect a ceiling effect in cognitive resilience.

Although the Nun Study population was homogeneous in many factors as discussed in section 6.2, which helped to control for confounders and to maintain a high internal validity, this study population was all females and was from a religious order, thereby causing challenges in generalizability of findings to the public. However, to date there is no evidence from previous literature stating that Alzheimer neuropathology affects females and males differently, and therefore, given the nature of the outcome of this study, generalizability would not be a significant limitation. Lastly, the Nun Study only recruited participants who were 75 years of age or older. As a result, participants who had died earlier were not included in the Nun Study, and it is unknown whether these participants were significantly different from those who survived to the age of 75, which could lead to survival bias. For example, the participants who did not survive to the age of 75 (i.e., participants who were not included in the study) may have had low levels of education, may have spoken only one language, or were not teachers and had died from AD because of low levels of cognitive resilience. Therefore, excluding participants younger than the age of 75 could have implications on generalizability of the study findings.

6.4 Implications and Future Directions

Since no specific cure is available for AD, research has increasingly focused on preventative strategies. Early to mid-life factors, such as multilingualism, may help prevent the onset of AD, while late-life factors, such as cortical atrophy, may reduce the ability to buffer the adverse effects of Alzheimer neuropathology. Thus, improving early to mid-life factors and taking measures to minimize the risks of brain damage can be used as preventative strategies for AD. The main purpose of this study was to find out whether multilingualism and the type of language spoken were associated with cognitive resilience, and whether factors that influence cognitive reserve, such as education, as well as factors that influence brain reserve, such as cortical atrophy, could modify the association between multilingualism or type of language and cognitive resilience.

The results showed that multilingualism significantly contributed to cognitive resilience only in participants who spoke four or more languages. Further, speaking linguistically similar languages (English and German), significantly reduced the likelihood of cognitive resilience, but this association became nonsignificant when the models were adjusted for cortical atrophy, which indicated that it was the presence of atrophy that reduced the likelihood of cognitive resilience in German speakers. Since these findings were inconsistent with previous research, where speaking typologically similar languages had more cognitive benefits than speaking dissimilar languages, further research will be needed to clarify findings, particularly on the effects of speaking German and cognitive resilience. Speaking dissimilar languages, such as Korean and English, has been shown to benefit

executive function through activation of additional brain regions involved in visuospatial processing (Yang & Yang, 2016). Similarly, it may be possible that speaking linguistically dissimilar languages could enhance cognitive resilience by the activation of efficient and multiple neuronal networks. Therefore, future research should focus on how other type of languages, such as those that are orthographically different from English (e.g., Japanese, Chinese, and Korean) would influence the likelihood of cognitive resilience. Because the current study could not incorporate various aspects of multilingualism, such as the frequency of multiple language use, age at language acquisition, reading ability, and language comprehension skills in the assessment of multilingualism or type of language use, future studies should consider incorporating these measures when using multilingualism as an exposure in studies, in order to fully investigate the impact of multilingualism.

Even though those who spoke German initially had a reduced likelihood of cognitive resilience, subsequent analyses indicated that the German speakers in this sample also were more likely to have atrophy present, which reduces the odds of cognitive resilience. Thus, this current study supported that cortical atrophy itself was a significant independent predictor of cognitive resilience as well as weakened the association between speaking German and cognitive resilience. This illustrates the importance of including indicators of brain reserve in studies of multilingualism. In addition, this finding emphasized the importance of minimizing cortical atrophy through healthy eating and lifestyle in order to preserve both brain and cognitive reserve. To date, one study conducted on Nun Study

participants has found that intake of healthy nutrients such as folate can protect against atrophy (Snowdon et al., 2000). Therefore, healthy nutrient intake can be used as a strategy to minimize the risk of atrophy and help to preserve brain reserve. Although the current study did not provide strong evidence for the presence of a ceiling or floor effect for cognitive resilience, future research should focus on analyses with a larger sample size with factors, such as education, atrophy, and stroke to verify whether there is a ceiling or floor effect influencing the association between multilingualism and cognitive resilience. Moreover, survival bias would have influenced the study findings if the participants who died before the age of 75 were significantly different (e.g., they were less likely to be cognitively resilient because of lower education or monolingualism) than those who were not. Therefore, in order to minimize survival bias, future research should consider using participants younger than 75 years and establish a study sample that has more variability in education and multilingualism and is more representative of the general population. In addition, because older populations are more likely to have brain damage from various comorbidities other than Alzheimer neuropathology, future studies should use younger populations to ensure that the presence of dementia is an actual consequence of pure Alzheimer neuropathology instead of from other forms of brain damage.

Overall, multilingualism contributed to cognitive resilience only when four or more languages were spoken, and no evidence of benefit of bilingualism on cognitive resilience was observed. Also, this research project did not find any evidence on type of language being

important for contributing to cognitive resilience. Today, improving cognitive resilience has become an appealing and feasible preventative strategy against AD/dementia, as more people are able to build up cognitive resilience through higher educational attainment, and by engaging in other cognitively stimulating activities such as leisure activities and by learning a second language. Based on the results of this current study, it may seem that one needs to learn at least four or more languages in order to significantly build up cognitive resilience. However, the context within which the languages were spoken must also be considered. For example, in this study no protective effect from bilingualism was observed, perhaps because being bilingual was the norm in this population; thus, monolinguals in this study may have been unusual, affecting the results on bilingualism. However, results are consistent with other population-based, longitudinal studies that found no association between bilingualism and AD. Few studies have looked at the impact of four or more languages. Greater levels of cognitive stimulation beyond the most common category of speaking two languages might have been required to achieve significant benefits. Furthermore, given that learning four or more languages is a very challenging task that requires greater levels of interest, motivation and dedication, it is also possible that in this study, those who spoke four or more languages were particularly different in that they had higher levels of intelligence or a relatively greater tendency to engage in higher levels of intellectual stimulation than those who spoke fewer languages. It may also be the case that those speaking four or more languages were capable of learning multiple languages because they were born with superior executive function,

instead of improving executive function from learning multiple languages (see review by Valian, 2015). Overall, the study findings highlight the importance of engaging in activities that enhance higher levels of cognitive stimulation in order to build up cognitive resilience. Thus, enhanced cognitive stimulation is the underlying key contributor to cognitive resilience, and learning multiple languages is one method by which one could increase cognitive stimulation and build up cognitive resilience. As our society is becoming more multilingual with greater cultural diversity, there are now more opportunities available for people to learn to speak four or more languages and also to practice speaking them. Further, multilingualism can enhance cognitive flexibility and creativity skills as well as promote effective cross-cultural communication skills and create cultural awareness in a society (Okal, 2014). Thus, multilingualism can be considered as one modifiable way to enhance cognitive stimulation in order to build up cognitive resilience and thus reduce the impact of AD, thereby improving the quality of life of aging populations.

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8.0 Appendices

8.1 Appendix A: Literature Search Templates

Table A1: PubMed Search Strategy Template

Concept	Multilingualism	Aged	Cognitive resilience	Alzheimer's disease
Author Keywords	Multilingual* [tw] Bilingual* [tw] Multi-lingual* [tw] Dual language [tw] Second language* [tw] Language proficienc* [tw] Languages [tw]	Older Elder *	Cognitive resilience [tw] Cognitive function [tw] Cognitive reserve [tw] Brain reserve [tw] Neural compensation [tw] Neural reserve [tw] Neuronal plasticity [tw] Mental performance [tw] Neurobiologic* [tw] Neuroprotect* [tw]	Alzheimer* [tw] Dementia [tw]
Subject Headings: MEDLINE MeSH	Multilingualism [MeSH] Language[MeSH:noexp]	Aged Aging	Cognitive reserve [MeSH] Cognition [MeSH:noexp] Executive function [MeSH] Higher nervous activity [MeSH]	Alzheimer disease [MeSH] Dementia [MeSH] Mild cognitive impairment [MeSH] Alzheimer disease/epidemiology [MeSH] Dementia/ epidemiology [MeSH]

Search performed September, 2017 [#1 AND #4 (#2 OR #3)] and retrieved 1179 records.

Complete search strategy: #1 AND #4 AND (#2 OR #3)

#4 Older [tw] OR elder* [tw] OR seniors [tw] OR aged [MeSH] OR aging [MeSH]

#3 Alzheimer* [tw] OR dementia [tw] OR Alzheimer disease [MeSH] OR dementia [MeSH] OR mild cognitive impairment [MeSH] OR Alzheimer disease/epidemiology [MeSH] OR Dementia/epidemiology [MeSH]

#2 Cognitive resilience [tw] OR cognitive function [tw] OR cognitive reserve [tw] OR brain reserve [tw] OR neural compensation [tw] OR neural reserve [tw] OR neuronal plasticity [tw] OR mental performance [tw] OR neurobiologic* [tw] OR neuroprotect* [tw] OR cognitive reserve [MeSH] OR cognition [MeSH:noexp] OR executive function [MeSH] OR higher nervous activity [MeSH]

#1 multilingual* [tw] OR bilingual* [tw] OR multi-lingual* [tw] OR dual language [tw] OR second language* [tw] OR language proficienc* [tw] OR languages [tw] OR language [MeSH:noexp] OR multilingualism [MeSH]

Table A2: PsycINFO Search Strategy Template

Concept	Multilingualism	Cognitive resilience	Alzheimer's disease
Author Keywords	Multilingual* Bilingual* Multi-lingual* Dual language Second language* Language proficienc*	Cognitive resilience Cognitive function Cognitive reserve Brain reserve Neural compensation Neural reserve Neuronal plasticity Mental performance Neurobiologic* Neuroprotect*	Alzheimer* Dementia
Subject Headings Index terms	Bilingualism Language proficiency English as a second language Foreign language learning	Cognitive reserve Cognitive ability Cognitive development	Mild cognitive impairment Alzheimer's disease Dementia

Search performed September, 2017 and retrieved 68 records

Overall search strategy: #1 AND #2 AND #3

#3 Alzheimer* OR dementia OR “Alzheimer’s disease” OR “mild cognitive impairment”

#2 “Cognitive res*“OR “cognitive function” OR “cognitive reserve” OR “brain reserve” OR “neural compensation” OR “neural reserve” OR “neuronal plasticity” OR neurobiologic* OR neuroprotect* OR “cognitive ability” OR “cognitive development”

#1 multilingual* OR bilingual* OR “dual language” OR “second language*” OR “language proficienc*” OR bilingualism OR “language proficiency” OR “English as a second language” OR “foreign language learning”

8.2 Appendix B: Summary of Relevant Literature

Table B1: Literature summary table for findings on the association of multilingualism with AD or dementia

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
Alladi et al. (2013). Bilingualism delays age at onset of dementia, independent of education and immigration status	People with dementia were recruited from a specialist Memory Clinic of a university hospital in Hyderabad, India. Sample: 648 participants Men/women ratio: 424:224. Mean age: 66.2 years 60.3% were multilinguals, of whom 26.2% were bilinguals, 25% were trilinguals and 9.1% spoke more than four languages.	Bilingualism Assessed for possible interactions between bilingualism and literacy, education, occupation, dementia subtypes, sex, vascular factors, rural/urban dwelling, family history, and dementia severity. Confounders: education, sex, occupation, cardiovascular risk factors, and urban versus rural dwelling. Since both bilinguals and monolinguals were obtained from the same environment, immigration	Age at onset of dementia including the different subtypes of dementia, such as AD, frontotemporal dementia, vascular dementia, dementia with Lewy bodies, and mixed dementia.	Independent samples *t*-tests and ANOVAs were used for descriptive analysis. Univariate general linear model was used to assess the relationship between bilingualism and age at onset of dementia.	Bilinguals were mostly men, and were literate and educated individuals living in urban areas with higher levels of skilled occupations compared to monolinguals. Bilinguals developed dementia 4.5 years later than monolinguals. When analyzed separately, a 3.2-year delay was observed in participants with dementia of AD type, 6-year delay with frontotemporal dementia, and a 3.7-year delay with vascular dementia. Also, a 6-year delay was observed among those that were illiterate compared to monolinguals. No additional benefit was

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
		status was not a confounder. Language history was assessed by family caregivers. However, this study did not specify the bilingual participants' proficiency and age at second language acquisition. The sample was heterogeneous and included different minority groups that spoke dominant languages different from the dominant language spoken in the environment.			found with speaking more than two languages. Since older populations have higher levels of comorbidities and lower life expectancies compared to younger populations, the referral rates to the clinic were low from the older groups, which could influence the study findings.
Bak et al. (2014). Does bilingualism	Included 853 participants from the Lothian Birth	Bilingualism was assessed by self-report (had to specify the number of	Later-life cognition assessed	Multiple linear regression.	Bilinguals had significant cognitive effects on reading, verbal fluency,

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
influence cognitive aging?	Cohort 1936 that had completed the Scottish Mental Survey in 1947 at the age of 11. These participants were reassessed in 2008-2010. There were 410 females and 443 males in this study. The participants were obtained from a homogeneous cohort, where all were of European origin and spoke English as their native language.	languages spoken, age of second language acquisition, and frequency of second language use). Participants who reported their ability to communicate in their second language were classified as bilinguals. Adjusted for childhood intelligence, sex, social class of both the participant and the participant's father's, and age at cognitive testing.	through cognitive performanc e in various tests, general fluid-type intelligence, memory, speed of information processing, moray house test, and vocabulary/ reading tests.		and general intelligence. Strong protective effect of bilingualism in late-life cognition, independently of childhood intelligence. Participants with high intelligence had a greater bilingual benefit if they had an earlier acquisition of second language, while those with low levels of intelligence had a greater benefit from a later acquisition of second language. Moreover, proficiency in >three languages had stronger effects than speaking two languages. The frequency of second language use did not have significant effects.
Bialystok et al. (2014). Effects of bilingualism on	Recruited 149 participants from the Sam and Ida Ross	Bilingualism (measured by the Language and	Onset of symptoms (measured	ANOVA and logistic regression	Bilinguals had a delayed onset of MCI (4.7 years)

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
the age of onset and progression of MCI and AD: Evidence from executive function tests	Memory Clinic at Baycrest, Toronto, Canada. All participants had a diagnosis of AD or mild cognitive impairment (MCI). The participants were excluded if they had any neurological or psychiatric condition.	Social Background Questionnaire). Participants were classified as bilinguals if they had an early age of acquisition of their second language with a high frequency of use of both languages. The sample had 74 participants with MCI and 75 participants with probable AD. Covariates: Diet, alcohol, smoking, physical and social activity	by an interview questionnaire that included subjective reporting from participants or caregivers). Participants had to complete three of the Delis-Kaplan Executive Function System Tests.		and AD (7.3 years) compared to monolinguals. With respect to the previous studies, this study had a larger delay in the number of years from AD (more than five) likely to smaller sample size. The performance in the executive function system tests declined over the 3 assessments, but the rate of decline was not different between monolinguals and bilinguals. However, only a smaller number of participants were able to complete all three assessments that measured cognitive decline. Immigration status did not influence the association

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
					between bilingualism and the onset of AD/MCI.
Bialystok et al. (2007). Bilingualism as a protection against the onset of symptoms of dementia.	228 participants admitted with cognitive complaints to the memory clinic at Baycrest, Toronto, Canada between 2002-2005 were examined. This study selected participants with a probable AD diagnosis. There were184 participants included in the final sample (91 were monolinguals and 93 were bilinguals). There were 48 females in the monolingual group	Bilingualism Bilinguals were classified as those that regularly speak at least two languages since early adulthood. Covariates: years of education, MMSE scores at the initial appointment, occupation	Age at onset of dementia symptoms	ANOVA and regression analysis	Bilinguals had a significant 4.1-year delay in the age at onset of dementia than monolinguals. Bilinguals were also 3.2 years older than monolinguals in their first appointment to the memory clinic, and they had a shorter interval between their first appointment at the clinic and the onset of dementia. Bilinguals had a 4.3-year delayed onset of AD symptoms and a 3.5-year delayed onset of symptoms for other dementia types, compared to monolinguals. Bilingualism delayed the onset of dementia even after taking into account other factors, such as

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
	and 55 females in the bilingual group. The sample of bilinguals in this study have spoken 25 different languages.				immigration, formal education and occupation. Both bilinguals and monolinguals underwent cognitive decline at the same rate.
• Chertkow et al. (2010). Multilingualism (but not always bilingualism) delays the onset of Alzheimer disease: Evidence from a bilingual	632 individuals were recruited from the memory clinic of the Jewish General Hospital in Montreal, Canada, who had memory complaints and were diagnosed with AD. The participants were followed up for one year. There were 253 multilinguals and 379 unilinguals.	Speaking more than one language. Age of second language acquisition and age of immigration were not taken into account when defining bi-or multilingualism. Unilinguals: only French or English speakers. Native bilinguals: Both French and English speakers only. Non-native (immigrant) bilinguals/multilinguals: Those whose primary language was not	Age at diagnosis of AD or age at symptom onset.	ANOVA and linear regression analyses	No significant benefit was observed among bilinguals in their age at diagnosis of AD or age at symptom onset. Speaking more than two languages was slightly protective. When restricted to native Canadians, speaking more than two languages had a significant delayed onset of symptoms and diagnosis of AD only in the native French group, but not in the native English group. In the immigrant group, a dose-response effect was

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
community.	Among multilinguals, 135 were immigrants. Among unilinguals, 66 were native French and 290 were native English.	English/French and were born and educated outside of Canada. Covariates: Occupation (as a proxy measure for socioeconomic status), education, sex, and immigrant/native status. This study assumed that participants whose first language was native to Canada were native born Canadians, while those who spoke other languages were considered immigrants. However, there can be participants whose first language was either English or French, if they were immigrants from English or French-			observed where immigrant bilinguals had a five-year delay, trilinguals had a 6.4-year delay, and those speaking ≥4 languages had a 9.5-year delay in the diagnosis of AD. A smaller sample size of native bilinguals could have influenced the results.

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
		speaking countries. Conversely, there can be individuals who were born in Canada but whose first language was not native to Canada, if their parents recently immigrated from another country. Thus, the classification of native born Canadians and immigrants might not have been clear cut in this study.			
Clare et al. (2014). Bilingualism, executive control, and age at diagnosis among people with early-stage Alzheimer's disease in Wales.	Welsh/English bilingual and monolingual English-speaking participants with an AD diagnosis were recruited from memory clinics. There were 86 participants in this	Bilingualism Covariates: Age, gender, education, and socioeconomic status. Language was assessed using a "Language Questionnaire" and standardized language tests.	Age at AD diagnosis and performanc e on executive control tasks Age at AD diagnosis	ANOVA and ANCOVA Regression analyses	Bilinguals were 3 years older than monolinguals, but this difference was non-significant. However, bilinguals had a significantly greater level of cognitive impairment at diagnosis as indicated by MMSE scores. There was no clear evidence for a delay in the

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
	study. According to the power analysis, a sample of 42 participants was required in each language group. From the BANC study, 49 monolinguals and 24 bilinguals were used. However, due to the smaller bilingual sample size, 13 additional participants had to be recruited from an earlier MIDAS study. The MIDAS study only had information on the age at AD onset and no data on performance in		was obtained from clinical records and MMSE scores.		onset of AD among bilinguals. Also, no significant difference was shown in the performance of executive function tests between bilinguals and monolinguals; however, bilinguals demonstrated better performance on inhibition and conflict resolution skills than monolinguals.

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
	neuropsychological tests were available.				
Craik et al. (2010). Delaying the onset of Alzheimer disease: Bilingualism as a form of cognitive reserve.	Total of 211 participants (102 bilinguals and 109 monolinguals) diagnosed with probable AD were used in this study. The participants were recruited from the Sam and Ida Ross memory clinic at Baycrest, Toronto, Canada. There were 60 bilingual females and 60 monolinguals females. The study only included participants diagnosed with probable AD.	Bilingualism Covariates: occupational history, education, language history, birth place, fluency in English or other languages, date of immigration.	Age of AD diagnosis and the onset of symptoms. Age at diagnosis was completed by physicians and a neuropsychologist. Age at symptom onset was reported by participants or their caregivers.	ANOVA	Bilinguals had a 4.3-year delayed diagnosis of AD and a 5.1-year delayed onset of dementia symptoms compared to monolinguals. No effect of immigration status, education or occupational status was observed on the relationship between bilingualism and AD.

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
Crane et al. (2010). Use of spoken and written Japanese did not protect Japanese-American men from cognitive decline in late life	Second-generation Japanese-American men born in 1900-1919 were recruited from the Hawaiian Island of Oahu in 1965. They had to be free of dementia at baseline. There were 2520 participants in the analytic samples. Of those, 465 did not speak or read Japanese, 1495 only spoke Japanese, and 560 both spoke and read Japanese.	Midlife use of spoken and written Japanese (based on self-reported data). Covariates: age, income, education, smoking status, *APOE*-ε4 status, and head circumference.	Cognitive functioning (measured by the Cognitive Abilities Screening Instrument).	Mixed effects modelling	Midlife spoken or written Japanese was not associated with the rate of cognitive decline. Use of self-reported data and the presence of missing data may have influenced the findings.
Gollan et al. (2011). Degree of bilingualism predicts age of diagnosis of	Sample: 44 Spanish-English bilinguals from the UCSD Alzheimer's Disease Research Center.	Bilingualism (objectively measured using Boston Naming Test scores for each language)	Onset of symptoms and AD diagnosis	Regression analyses	Bilingualism was associated with a delayed age of symptom onset and diagnosis of AD, but this effect was only observed

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
Alzheimer's disease in low-education but not in highly educated Hispanics		Covariates: Education, MMSE scores at diagnosis, Dementia Rating Scale scores at diagnosis.			when bilingualism was objectively measured and when the education level was low (i.e., a significant interaction was observed between bilingualism and education). For example, when bilinguals had 2-11 years of education, the age at diagnosis of AD increased with bilingualism, while having 12-20 years of education showed no association between bilingualism and age at diagnosis of AD.
Jafari et al. (2015). Bilingual proficiency and cognitive reserve in Persian-English bilingual older adults	Sample: 26 educated older adults who were all university teachers (8 females). All participants had post-secondary education.	Bilingualism (proficient in both Persian and English from an eary stage in life)	Cognitive reserve (indirectly measured by the performanc e in lexical memory	Parametric statistical tests, such as independent *t*-test, paired *t* test, and Pearson	Significant correlations were observed between the level of bilingual proficiency versus lexical memory score ($p < 0.043$) and dichotic listening scores ($p \leq 0.045$). Therefore, bilinguals

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
	Mean age: 67.52 years Age range: 60-75 years		and Bergen dichotic listening tests).	correlation test.	underwent "linguistic experience-dependent neuroplasticity."
Kave et al. (2008). Multilingualism and cognitive state in the oldest old.	Sample: Oldest Israeli Jewish population (n=814). Mean age=83.0 years Interviewed in 1989 and assessed twice within 12 years.	Multilingualism (bilingual, trilingual, and speaking more than three languages). Measured by self-report. Details on language proficiency, frequency of language use, or the age of language acquisition were not collected in this study. Covariates: age, gender, birth place, age at immigration, and education.	Cognitive performance (based on Katzman cognitive screening test and Folstein MMSE scores)	Regression analyses	Multilingualism (speaking three or more languages) was associated with cognitive state among individuals with no formal education. Speaking multiple languages might have prevented cognitive deterioration despite having low levels of education. Participants who were fluent in a language other than their mother tongue had a higher cognitive score than those who were fluent only in their mother tongue.
Lawton et al. (2015). Age of dementia	Sample: 91 bilingual or monolingual participants were	Bilingualism	Age of clinically diagnosed	ANOVA	Mean age of incident dementia diagnosis was higher among

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
diagnosis in community dwelling bilingual and monolingual Hispanic Americans.	used from a community dwelling sample from the Sacramento Area Latino Study on Aging. The sample included both immigrant, and Hispanic American participants (born in the United States).	Covariates: immigrant status	AD and vascular dementia		monolinguals than bilinguals. Immigrant bilinguals were more educated than monolinguals; however, bilinguals/monolinguals (born in the United States) did not differ by education.
Ljungberg et al. (2016). The effect of language skills on dementia in a Swedish longitudinal cohort	Sample: 835 non-demented participants, aged 60 years or older, were followed up for 10 years. Data for this study was used from the Betula prospective cohort study in Umea, Sweden.	Bilingualism The participants were asked to self-report their proficiency in speaking a second language based on a Likert scale. All with a score of four or higher were considered as bilinguals, while participants speaking only Swedish (one language)	Incidence of dementia diagnosis (yes/no) Dementia cases (n=112) during follow-up included AD,	Cox proportional hazards regression analysis. The models were adjusted for age, sex, and *APOE*-ε4 status.	Of the total population, 112 participants developed dementia. In the Cox regression analyses, when adjusted for age and sex, bilinguals did not have a lower hazard ratio for developing all types of dementia (HR=1.43, 95% CI = 0.73-2.85, p=.29), or AD alone

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
	Participants were selected by using a population registry of Umea municipality through random sampling. Inclusion criteria: Participants with a Swedish native tongue were selected. Those who were lost to follow-up or were eventually diagnosed with dementia were removed from the study, leaving a final sample of 818 participants at baseline.	were considered as monolinguals.	vascular dementia, Lewy body dementia, frontal lobe dementia, Parkinson dementia, and unspecified dementia.		(HR: 1.52, 95% CI = 0.62-3.71, p.36). Further adjusting for *APOE*-ε4 status did not cause substantial changes to the findings. However, the frequency of language use among the bilinguals in this study was reported to be low (e.g., 60% of the participants only used their second language while travelling). Moreover, of the total population that developed dementia (112), 102 were monolinguals while only 10 participants were bilingual.

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
	Mean age of participants: 73.6 Total men: 403 Total women:415				
Mukadam et al. (2017). The relationship of bilingualism to cognitive decline: The Australian Longitudinal Study of Ageing	Sample: 2087 participants were used from the Australian Longitudinal Study of Ageing, which had data collected for more than 20 years. Age: 65 or over. The bilinguals in this study were younger, born outside of Australia, and had emigrated from Italy, Poland, Hungary, Germany, and other European countries.	Bilingualism (assessed by self-report). Bilinguals were classified by whether they spoke another language (except English) at home or not, and reassured that the other language spoken at home was their native language.	Cognitive function (based on the MMSE scores and executive function tests, such as verbal fluency, describing similarities, and the Boston naming test.	Chi-squared tests and *t*-tests Linear mixed models were used to investigate the association between bilingualism and MMSE scores, with time. Linear regression investigated	The mean MMSE score of bilinguals at baseline was 2.23 points lower than the monolinguals. However, when adjusted for education and the National Reading Test scores, no significant differences were observed between bilinguals and monolinguals. No significant differences were found between bilinguals and monolinguals with respect to the decline in MMSE scores or in baseline tests of executive function over time.

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
				the effect of bilingualism on baseline MMSE scores. The participants' physical and mental health, demographic factors, their social networks were examined.	Had a large sample size and a long follow-up. However, participants with lower MMSE scores were lost to follow-up, and this may have influenced the results. Performance on the tests might have been influenced by the participants' fluency in English. This study did not have any data available on dementia diagnosis.
Olsen et al. (2015). The effect of lifelong bilingualism on regional grey and white matter volume	Sample: 14 Lifelong bilingual older adults with a mean age of 70.4, and 14 older monolinguals with a mean age	Lifelong bilingualism	Structural differences in the brain	ANOVA	Bilinguals had a higher amount of white matter in the frontal lobe of the brain than monolinguals. Frontal lobe white matter was positively correlated with

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
	70.6 were included in the sample.				the performance on Stroop task.
Ossher et al. (2013). The effect of bilingualism on amnestic mild cognitive impairment	Sample: Recruited 111 older adults from physician referrals and newspaper advertisements.	Bilingualism Covariates: age, duration of symptoms, education, sex, MMSE scores	Age of diagnosis for those with single or multiple-domain amnestic mild cognitive impairment (aMCI)	Two-way ANOVA	Among bilinguals, those with single domain aMCI had a delayed diagnosis of AD (mean = 79.4 years) compared to monolinguals (mean = 74.9 years).
Perquin et al. (2013). Lifelong exposure to multilingualism: new evidence to support cognitive reserve hypothesis - Missing	Sample: 232 non-demented participants (44 CIND and 188 with intact cognition) were recruited from the Luxembourg general population (from the MemoVie study).	Multilingualism Participants were asked to self-report on the number of languages spoken throughout life as well as the languages spoken concomitantly. Also, for each language the participants were asked to specify their age	CIND	Univariate analyses and mixed models	Participants who spoke more than two languages had a lower risk of CIND (OR=0.30, 95% CI=0.10-0.92). The same trend was observed between trilinguals versus bilinguals, and those speaking four languages versus bilinguals. However, in comparison to

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
		of language acquisition, number of languages spoken, the current practice of the language, and the duration of practice for each language learned (in years) until the time of the study Participants spoke two to seven languages. As there were no lifelong monolinguals in the sample, bilinguals were used as the reference group. Covariates: Age, education, leisure and sociocultural factors			trilinguals, those speaking four languages had similar risk of CIND as the trilinguals (i.e., no dose-response effect was observed). Similarly, speaking four or more languages versus speaking four languages had a similar risk of CIND as well. Participants who progressed from speaking two languages to three languages had a seven-fold protection against CIND. A delay of one year in becoming a multilingual (defined as speaking three or more languages) multiplied the risk of CIND by 1.02 (OR=1.02, 95% CI=1.01-1.04).

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
Sanders et al. (2012). Non-native language use and risk of incident dementia in the elderly	Sample: 1779 participants (70 years of age) recruited from the Einstein Aging Study. Non-native English speakers were considered as bilinguals.	Non-native English speakers Data on language proficiency, the number of languages spoken other than English, and where the languages were learned (setting) were not collected in this study. Also, only non-native English speakers were asked to specify whether they spoke additional languages or not. As a result, this could have underestimated the classification of bilinguals in the data. Covariates: gender, race, education, immigrant and marital status	Risk of incident dementia /AD	Cox proportional hazards models	There was no significant association observed between non-native English speakers and incident dementia (HR 1.26; 95% CI 0.76–2.09; $p = 0.36$). When stratified by education, the absolute dementia incidence among the non-native English speakers was high when education was low, and when education was high (≥16 years) the absolute dementia incidence was still high. It is possible that when stratified by education, the samples were small and had reduced power, which might have influenced the results.

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
Schweizer et al. (2012). Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in AD.	Sample: Recruited 40 participants with a diagnosis of AD from the memory clinic at St. Michael's Hospital in Toronto. The two language groups were comparable by the years of education and gender.	Bilingualism Covariates: Age, education, occupational status, MMSE, CDR	Degree of brain atrophy (as an indirect measure of cognitive reserve)	Bivariate analysis	Bilinguals diagnosed with AD had higher levels of brain atrophy in the temporal horn and the temporal horn ratio (regions that are used to differentiate AD patients from healthy individuals) than monolinguals
Woumans et al. (2015). Bilingualism delays clinical manifestation of Alzheimer's disease	Sample: 69 monolinguals and 65 bilinguals with a diagnosis of probable AD were recruited from two university hospitals	Bilingualism (assessed by participant and caregiver interviews based on proficiency and frequency of use of the second language). All bilinguals in this study spoke same language combination (Dutch-French) and spoke each	Time for clinical AD manifestation and diagnosis	Linear regression models	Bilinguals had a delayed manifestation (4.6 years) and diagnosis (4.8 years) of AD. Also, no significant effects from education, occupation, or gender were observed on the association between bilingualism and the manifestation of

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
		language in a specific context with minimal language mixing. Also, all bilinguals lived in an environment where their first language was the dominant language used in the public. Covariates: Age, initial MMSE, education, gender			symptoms, or AD diagnosis.
Yeung et al. (2014). Is bilingualism associated with a lower risk of dementia in community-living older adults? Cross-sectional and prospective analyses	Sample: 1616 community-living older adults Follow-up: 5 years Cross-sectional and prospective cohort study	Exposures: Monolingual English, bilingual English and English as a second language (ESL) Covariates: Age, sex, education, subjective memory loss, modified MMSE (3MS)	Dementia	Bivariate and multivariate analyses	No significant association was observed between bilingualism (when using either the bilingual English or ESL group) and dementia at time 1 (cross-sectional analysis). At follow-up, no association was observed between bilingualism and dementia at time 2 (prospective cohort analysis).

Study	Study population, sample characteristics	Exposure and covariates	Outcome	Analysis	Results
					Since the cognitive assessments were done in English, the participant's level of fluency in English might have influenced their performance in the tests.
Zahodne et al. (2014). Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants.	Sample: 1067 participants recruited from the Washington/Hamilton Heights Inwood Columbia Aging Project (used a community-based sample). Follow-up: 18-24-month intervals for 23 years.	Bilingualism (spoke Spanish-English language combination). The primary language spoken by the participants was Spanish. The bilinguals had learned English after migrating to United States. Used self-reports with an objective measure (English reading level) to assess language proficiency. Covariates: country of origin, gender, education, time spent in the United States, recruitment cohort, and age at enrollment.	Cognitive decline and age of dementia diagnosis (determined through comprehensive neuropsychological testing)	Cox regression analyses	Spanish-English bilinguals who learned English after they migrated to United States, did not show any protective effect from bilingualism against cognitive decline or the onset of dementia. However, bilingualism was associated with better executive function and memory. Also, this study could not assess the frequency of language use, or the age of language acquisition among bilinguals.

8.3 Appendix C: Additional results for research question 1

Table C1: Educational level by occupation, CERAD sample A[1] (n=199)

	Occupation* (%)		
Education (%)	**Teacher**	**Other**	**Total**
High school or less	43.5	56.5	11.6
Undergraduate degree	100.0	0	42.2
Graduate degree	100.0	0	46.2

*Association between education and occupation: $p<0.0001$ [1]CERAD main sample. **Abbreviations:** CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria

Table C2: Educational level by occupation, NIA-RI sample A[1] (n=147)

	Occupation* (%)		
Education (%)	**Teacher**	**Other**	**Total**
High school or less	37.5	62.5	10.9
Undergraduate degree	100.0	0	44.2
Graduate degree	100.0	0	44.9

*Association between education and occupation ($p<0.0001$**)** [1]NIA-RI main sample. **Abbreviations:** NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria

Table C3: Primary language by immigration status, CERAD sample A[1] (n=199)

	Immigration status* (%)		
Primary language (%)	**Born in United States**	**Not born in United States**	**Total**
English	98.3	1.7	87.4
Not English	60.0	40.0	12.6

*Association between primary language and immigration status ($p<0.0001$**)** [1]CERAD main sample. **Abbreviations:** CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria

Table C4: Primary language by immigration status, NIA-RI sample A[1] (n=147)

	Immigration status* (%)		
Primary language (%)	**Born in United States**	**Not born in United States**	**Total**
English	97.7	2.3	87.1
Not English	68.4	31.6	12.9

*Association between primary language and immigration status ($p<0.0001$**)** [1]NIA-RI main sample. **Abbreviations:** NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria

Table C5: Sample characteristics by cognitive resilience status in CERAD and NIA-RI samples B[1]

Variables	Cognitive resilience (CERAD criteria) (n=176)			Cognitive resilience (NIA-RI criteria) (n=131)		
	Yes	No	Total	Yes	No	Total
Exposure						
Number of languages spoken (%)						
1	33.3	25.5	29.0	35.0	33.0	33.6
2	47.4	54.1	51.1	42.5	48.4	46.6
3	12.8	17.4	15.3	10.0	15.4	13.7
4	3.9	2.0	2.8	7.5	2.2	3.8
5	2.6	1.0	1.7	5.0	1.1	2.3
Speaking two or more languages (%)	33.3	25.5	29.0	35.0	33.0	33.6
Speaking four or more languages (%)	6.4	3.1	4.6	12.5	3.3	6.1
Covariates						
Age at death, years (SD)	91.10 (4.59)	91.95 (4.95)	91.57 (4.80)	91.06 (4.29)	91.41 (4.80)	91.31 (4.64)
Education (%)						
Undergraduate degree	47.4	48.0	47.7	47.5	50.6	49.6
Graduate degree	52.6	52.0	52.3	52.5	49.5	50.4
Presence of *APOE*-ε4 allele (%)	21.8	40.8*	32.4	30.0	44.0	39.7
Primary language (%)						
English	91.0	90.8	90.9	92.5	89.0	90.1
Immigration status (%)						
Born in the United States	44.1	55.9	96.6	31.0	69.1	96.2

*Significantly associated with cognitive resilience ($p<0.05$). [1]CERAD or NIA-RI restricted samples. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; SD = Standard deviation

Table C6a: The association between a four-level multilingualism variable (speaking two, three, or four or more languages versus one) and cognitive resilience, CERAD sample B[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=176) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals)										
Speaking two languages	0.67 (0.34-1.34)	-	0.66 (0.32-1.34)	-	0.66 (0.33-1.33)	-	0.66 (0.33-1.34)	-	0.67 (0.33-1.34)	0.65 (0.31-1.34)
Speaking three languages	0.57 (0.21-1.45)	-	0.52 (0.19-1.35)	-	0.55 (0.21-1.43)	-	0.55 (0.20-1.45)	-	0.55 (0.20-1.45)	0.50 (0.17-1.39)
Speaking four or more languages	1.60 (0.36-8.48)	-	1.71 (0.37-9.41)	-	1.79 (0.39-9.62)	-	1.58 (0.35-8.39)	-	1.57 (0.34-8.40)	2.00 (0.40-11.61)
Presence of *APOE*-ε4 allele	-	**0.40 (0.20-0.78)**	**0.39 (0.19-0.75)**	-	-	-	-	-	-	**0.37 (0.18-0.72)**
Age at death (in years)	-	-	-	0.96 (0.90-1.03)	0.96 (0.90-1.02)	-	-	-	-	0.95 (0.88-1.01)
Primary language (English versus other)	-	-	-	-	-	1.03 (0.36-3.00)	0.88 (0.30-2.67)	-	-	0.92 (0.30-2.88)

	Cognitive resilience based on CERAD neuropathologic criteria (n=176) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Education (Graduate degree versus undergraduate degree)	-	-	-	-	-	-	-	1.02 (0.56-1.86)	1.07 (0.58-1.98)	0.96 (0.49-1.87)

Statistically significant values are **bolded** ($p<0.05$). [1] CERAD restricted sample. **Abbreviations:** *APOE-ε4*=Apolipoprotein E-*ε4*; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table C6b: The association between a four-level multilingualism variable (speaking two, three, or four or more languages versus one) and cognitive resilience, NIA-RI sample B[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=131) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals)										
Speaking two languages	0.83 (0.36-1.95)	-	0.81 (0.34-1.91)	-	0.85 (0.36-2.01)	-	0.87 (0.37-2.09)	-	0.82 (0.35-1.93)	0.89 (0.37-2.17)
Speaking three languages	0.61 (0.15-2.08)	-	0.57 (0.14-1.96)	-	0.59 (0.15-2.03)	-	0.65 (0.16-2.25)	-	0.59 (0.14-2.08)	0.58 (0.14-2.13)
Speaking four or more languages	3.57 (0.77-19.47)	-	3.55 (0.75-19.67)	-	3.99 (0.83-22.42)	-	3.76 (0.80-20.78)	-	3.44 (0.72-19.16)	4.29 (0.82-26.19)
Presence of *APOE*-ε4 allele	-	0.55 (0.24-1.19)	0.53 (0.23-1.17)	-	-	-	-	-	-	0.49 (0.21-1.11)
Age at death (in years)	-	-	-	0.98 (0.91-1.07)	0.97 (0.89-1.05)	-	-	-	-	0.96 (0.87-1.05)
Primary language (English versus other)	-	-	-	-	-	1.52 (0.44-7.08)	1.48 (0.39-7.28)	-	-	1.61 (0.42-8.18)

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=131) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Education (Graduate degree versus undergraduate degree)	-	-	-	-	-	-	-	1.13 (0.54-2.39)	1.11 (0.50-2.45)	1.05 (0.45-2.43)

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI restricted sample. **Abbreviations:** *APOE-ε4*=Apolipoprotein E-*ε4*; CI=Confidence Interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

Table C7a: The association between speaking two or more languages (versus one language) and cognitive resilience, CERAD sample B[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=176) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals) Speaking two languages	0.69 (0.36-1.32)	-	0.67 (0.34-1.30)	-	0.68 (0.35-1.31)	-	0.68 (0.35-1.32)	-	0.68 (0.35-1.31)	0.66 (0.33-1.32)
Presence of *APOE*-ε4 allele	-	**0.40 (0.20-0.78)**	**0.40 (0.20-0.77)**	-	-	-	-	-	-	**0.38 (0.19-0.74)**
Age at death (in years)	-	-	-	0.96 (0.90-1.03)	0.96 (0.90-1.03)	-	-	-	-	0.95 (0.89-1.02)
Primary language (English versus other)	-	-	-	-	-	1.03 (0.36-3.00)	0.90 (0.31-2.70)	-	-	0.94 (0.32-2.88)
Education (Graduate degree versus undergraduate degree)	-	-	-	-	-	-	-	1.02 (0.56-1.86)	1.08 (0.59-1.97)	0.99 (0.52-1.88)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD restricted sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table C7b: The association between speaking two or more languages (versus one language) and cognitive resilience, NIA-RI sample B[1]

	Cognitive resilience based on NIA-RI neuropathologic criteria (n=131) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus monolinguals) Speaking two languages	0.91 (0.42-2.03)	-	0.88 (0.40-1.98)	-	0.92 (0.42-2.06)	-	0.97 (0.44-2.19)	-	0.89 (0.41-2.00)	0.93 (0.41-2.18)
Presence of *APOE*-ε4 allele	-	0.55 (0.24-1.19)	0.54 (0.24-1.18)	-	-	-	-	-	-	0.52 (0.22-1.14)
Age at death (in years)	-	-	-	0.98 (0.91-1.07)	0.98 (0.91-1.07)	-	-	-	-	0.98 (0.90-1.07)
Primary language (English versus other)	-	-	-	-	-	1.52 (0.44-7.08)	1.50 (0.41-7.17)	-	-	1.59 (0.43-7.70)
Education (Graduate degree versus undergraduate degree)	-	-	-	-	-	-	-	1.13 (0.54-2.39)	1.15 (0.54-2.47)	1.15 (0.52-2.56)

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI restricted sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CI=Confidence Interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

Table C8a: The association between speaking four or more languages (versus fewer languages) and cognitive resilience, CERAD sample B[1]

	Cognitive resilience based on CERAD neuropathologic criteria (n=176) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus one to three languages) Speaking four or more languages	2.17 (0.52-10.85)	-	2.37 (0.54-12.27)	-	2.44 (0.57-12.38)	-	2.17 (0.52-10.87)	-	2.18 (0.51-10.94)	2.90 (0.64-15.66)
Presence of *APOE*-ε4 allele	-	**0.40 (0.20-0.78)**	**0.40 (0.20-0.77)**	-	-	-	-	-	-	**0.38 (0.19-0.73)**
Age at death (in years)	-	-	-	0.96 (0.90-1.03)	0.96 (0.90-1.02)	-	-	-	-	0.94 (0.88-1.01)
Primary language (English versus other)	-	-	-	-	-	1.03 (0.36-3.00)	1.04 (0.37-3.06)	-	-	1.11 (0.38-3.37)
Education (Graduate degree versus undergraduate degree)	-	-	-	-	-	-	-	1.02 (0.56-1.86)	0.99 (0.54-1.80)	0.87 (0.46-1.66)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD restricted sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI=Confidence Interval; OR=Odds Ratio

Table C8b: The association between speaking four or more languages (versus fewer languages) and cognitive resilience, NIA-RI sample B[1]

	Cognitive resilience based on NIA-RI criteria (n=131) (OR, 95% CI)									
	Model a	**Model b**	**Model c**	**Model d**	**Model e**	**Model f**	**Model g**	**Model h**	**Model i**	**Model j**
Multilingualism (versus one to three languages) Speaking four or more languages	4.19 (0.98-21.32)	-	4.26 (0.98-21.99)	-	**4.61 (1.05-24.08)**	-	4.27 (0.99-21.88)	-	4.16 (0.96-21.41)	**5.01 (1.08-27.55)**
Presence of *APOE*-ε4 allele	-	0.55 (0.24-1.19)	0.54 (0.24-1.19)	-	-	-	-	-	-	0.51 (0.22-1.13)
Age at death (in years)	-	-	-	0.98 (0.91-1.07)	0.97 (0.89-1.05)	-	-	-	-	0.96 (0.88-1.05)
Primary language (English versus other)	-	-	-	-	-	1.52 (0.44-7.08)	1.60 (0.45-7.65)	-	-	1.76 (0.48-8.70)
Education (Graduate degree versus undergraduate degree)	-	-	-	-	-	-	-	1.13 (0.54-2.39)	1.03 (0.48-2.21)	0.97 (0.43-2.18)

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI restricted sample. **Abbreviations:** *APOE*-ε4=Apolipoprotein E-ε4; CI=Confidence Interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR=Odds Ratio

8.4 Appendix D: Additional results for research question 2

Table D1a: The distribution of type of language by cognitive resilience status, CERAD sample B[1]

Exposure variables[2]	Cognitive resilience (CERAD criteria) (n=176)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	34.7* (25)	65.3* (47)	40.9 (72)
Speaking French	57.1 (20)	42.9 (15)	19.9 (35)
Speaking Spanish	42.1 (8)	57.9 (11)	10.8 (19)
Speaking Spanish or Italian	45.8 (11)	54.2 (13)	13.6 (24)
Speaking romance languages[3]	51.0 (25)	49.0 (24)	27.8 (49)
Proficiency in Latin	38.5 (5)	61.5 (8)	7.4 (13)
Speaking Polish	57.1 (12)	42.9 (9)	11.9 (21)

*Significantly associated with cognitive resilience (p<0.05). [1]CERAD restricted sample. [2]All participants spoke English**.** [3]Spoke French, Spanish, or Italian. **Abbreviations:** CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria.

Table D1b: The distribution of type of language by cognitive resilience status, NIA-RI sample B[1]

Variables[2]	Cognitive resilience (NIA-RI criteria) (n=131)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	25.0 (12)	75.0 (36)	36.6 (48)
Speaking French	42.3 (11)	57.7 (15)	19.9 (26)
Speaking Spanish	35.7 (5)	64.3 (9)	10.7 (14)
Speaking Spanish or Italian	35.3 (6)	64.7 (11)	13.0 (17)
Speaking romance languages[3]	37.1 (13)	62.9 (22)	26.7 (35)
Speaking Latin	38.5 (5)	61.5 (8)	9.9 (13)
Speaking Polish	46.7 (7)	53.3 (8)	11.5 (15)

*Significantly associated with cognitive resilience (p<0.05). [1]NIA-RI restricted sample. [2]All participants spoke English**.** [3]Spoke French, Spanish, or Italian. **Abbreviations:** NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria.

Table D2: The association between type of language and cognitive resilience, CERAD sample B*

Variables**	Cognitive resilience (n=176) (OR, 95% CI)							
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**
Speaking German	**0.51 (0.27-0.95)**	**0.47 (0.25-0.88)**	**0.53 (0.28-0.99)**	**0.51 (0.27-0.94)**	**0.51 (0.27-0.94)**	**0.49 (0.26-0.92)**	**0.48 (0.24-0.91)**	**0.48 (0.25-0.92)**
Speaking French	1.91 (0.91-4.09)	2.09 (0.97-4.61)	1.85 (0.87-3.98)	1.98 (0.92-4.36)	1.91 (0.91-4.10)	1.94 (0.92-4.17)	2.21 (0.99-5.08)	2.21 (0.99-5.07)
Speaking Spanish	0.90 (0.33-2.36)	0.89 (0.32-2.37)	0.86 (0.32-2.26)	0.90 (0.33-2.35)	0.90 (0.33-2.35)	0.91 (0.34-2.38)	0.86 (0.31-2.31)	0.86 (0.31-2.30)
Speaking Spanish or Italian	1.07 (0.45-2.55)	1.04 (0.42-2.52)	1.07 (0.44-2.55)	1.07 (0.44-2.55)	1.07 (0.45-2.55)	1.08 (0.45-2.58)	1.06 (0.43-2.59)	1.06 (0.43-2.59)
Speaking romance languages***	1.45 (0.75-2.83)	1.53 (0.77-3.02)	1.40 (0.72-2.74)	1.47 (0.75-2.92)	1.45 (0.75-2.83)	1.48 (0.76-2.89)	1.55 (0.76-3.15)	1.55 (0.77-3.16)
Proficiency in Latin	0.77 (0.23-2.41)	0.75 (0.22-2.40)	0.80 (0.23-2.53)	0.76 (0.22-2.41)	0.77 (0.22-2.43)	0.76 (0.22-2.39)	0.79 (0.22-2.61)	0.80 (0.22-2.67)
Speaking Polish	1.80 (0.72-4.64)	1.69 (0.66-4.43)	1.70 (0.67-4.42)	1.80 (0.72-4.64)	1.94 (0.74-5.31)	1.78 (0.71-4.64)	1.55 (0.59-4.15)	1.68 (0.61-4.76)

Statistically significant values are **bolded** ($p<0.05$). *CERAD restricted sample. **All participants spoke English. ***Spoke French or Spanish or Italian. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (graduate degree versus undergraduate degree). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education, and immigration status only. [7]Adjusted for *APOE*-ε4 status, age at death, education, immigration status, and primary language. **Abbreviations**: *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table D3: The association between type of language and cognitive resilience, NIA-RI sample B*

Variables**	Cognitive resilience (n=131) (OR, 95% CI)							
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**
Speaking German	0.66 (0.29-1.43)	0.65 (0.28-1.43)	0.67 (0.29-1.48)	0.65 (0.28-1.41)	0.66 (0.29-1.45)	0.67 (0.29-1.46)	0.66 (0.28-1.49)	0.66 (0.28-1.51)
Speaking French	1.92 (0.78-4.66)	1.99 (0.80-4.89)	1.92 (0.78-4.66)	1.92 (0.76-4.80)	1.91 (0.77-4.63)	1.89 (0.76-4.59)	1.91 (0.74-4.86)	1.91 (0.74-4.88)
Speaking Spanish	1.30 (0.38-4.05)	1.34 (0.38-4.22)	1.29 (0.37-4.02)	1.28 (0.37-4.01)	1.25 (0.36-3.92)	1.28 (0.37-3.98)	1.28 (0.36-4.07)	1.23 (0.35-3.94)
Speaking Spanish or Italian	1.28 (0.41-3.66)	1.30 (0.42-3.76)	1.28 (0.41-3.67)	1.26 (0.40-3.63)	1.26 (0.41-3.61)	1.26 (0.40-3.60)	1.26 (0.40-3.69)	1.25 (0.39-3.66)
Speaking romance languages***	1.51 (0.66-3.40)	1.56 (0.67-3.57)	1.49 (0.65-3.37)	1.49 (0.64-3.42)	1.50 (0.65-3.39)	1.48 (0.64-3.35)	1.49 (0.63-3.48)	1.51 (0.64-3.52)
Proficiency in Latin	1.48 (0.42-4.76)	1.41 (0.40-4.58)	1.53 (0.43-4.96)	1.45 (0.41-4.75)	1.59 (0.45-5.25)	1.52 (0.43-4.93)	1.46 (0.40-4.97)	1.56 (0.42-5.46)
Speaking Polish	2.20 (0.72-6.62)	1.91 (0.61-5.86)	2.17 (0.70-6.56)	2.19 (0.72-6.60)	2.70 (0.83-9.06)	2.42 (0.77-7.58)	2.04 (0.62-6.64)	2.45 (0.71-8.72)

Significant values were **bolded** in the table. *NIA-RI restricted sample. **All participants spoke English. ***Spoke French or Spanish or Italian. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (graduate degree versus undergraduate degree). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education, and immigration status only. [7]Adjusted for *APOE*-ε4 status, age at death, education, immigration status, and primary language. **Abbreviations**: CI = Confidence intervals; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

8.5 Appendix E: Additional results for research question 3

Table E1: Sample characteristics by cognitive resilience status, CERAD and NIA-RI samples C[1]

Variables	Cognitive resilience (CERAD criteria) (n=180)			Cognitive resilience (NIA-RI criteria) (n=135)		
	Yes	No	Total	Yes	No	Total
Exposure						
Number of languages spoken (%)						
1	32.0	23.8	27.2	35.9	31.3	32.6
2	50.7	55.2	53.3	43.6	50.0	48.2
3	13.3	18.1	16.1	12.8	15.6	14.8
4	2.7	1.9	2.2	5.1	2.1	3.0
5	1.3	1.0	1.1	2.6	1.0	1.5
Speaking two or more languages (%)	68.0	76.2	72.8	64.1	68.8	67.4
Speaking four or more languages (%)	4.0	2.9	3.3	7.7	3.1	4.4
Covariates						
Age at death, years (SD)	91.14 (4.78)	92.38 (5.29)	91.86 (5.11)	90.78 (4.12)	91.98 (4.87)	91.64 (4.68)
Education (%)						
High school or less	6.7	14.3	11.1	2.6	13.5	10.4
Undergraduate degree	45.3	43.8	44.4	48.7	46.9	47.4
Graduate degree	48.0	41.9	44.4	48.7	39.6	42.2
Presence of *APOE*-ε4 allele (%)	21.3	39.1*	31.7	30.8	41.7	38.5
Occupation (%)						
Teacher	94.7	92.4	93.3	97.4	91.7	93.3
Primary language (%)						
English	86.7	86.7	86.7	89.7	85.4	86.7
Immigration status (%)						
Born in the United States	93.3	93.3	93.3	94.9	92.7	93.3
Atrophy (%)						
Present	33.1	66.9*	77.2	22.4	77.6*	79.3

*Significantly associated with cognitive resilience ($p<0.05$). [1]CERAD or NIA-RI atrophy samples. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; SD = Standard deviation

Table E2: Sample characteristics by cognitive resilience status, CERAD and NIA-RI samples D[1]

Variables	Cognitive resilience (CERAD criteria) (n=160)			Cognitive resilience (NIA-RI criteria) (n=121)		
	Yes	No	Total	Yes	No	Total
Exposure						
Number of languages spoken (%)						
1	52.2	47.8	28.8	34.2	65.9	33.9
2	41.0	59.0	51.9	29.8	70.2	47.1
3	36.0	64.0	15.6	23.5	76.5	14.1
4	50.0	50.0	2.5	50.0	50.0	3.3
5	50.0	50.0	1.3	50.0	50.0	1.7
Speaking two or more languages (%)	40.4	59.7	71.3	30.0	70.0	66.1
Speaking four or more languages (%)	4.3	3.3	3.8	7.9	3.6	5.0
Covariates						
Age at death, years (SD)	90.84 (4.49)	92.08 (5.11)	91.54 (4.88)	90.75 (4.17)	91.65 (4.76)	91.37 (4.58)
Education (%)						
Undergraduate degree	42.5	57.5	50.0	29.7	70.3	52.9
Graduate degree	45.0	55.0	50.0	33.3	66.7	47.1
Presence of *APOE*-ε4 allele (%)	30.8	69.2*	32.5	25.5	74.5	38.8
Primary language (%)						
English	43.8	56.3	90.0	32.4	67.6	89.3
Immigration status (%)						
Born in the United States	43.5	56.5	96.3	31.9	68.1	95.9
Atrophy (%)						
Present	34.7	65.3*	75.6	24.7	75.3*	76.9

*Significantly associated with cognitive resilience ($p<0.05$). [1]CERAD or NIA-RI restricted atrophy samples. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; SD = Standard deviation

Table E3: The association between a four-level multilingualism variable (speaking two, three, or four or more languages versus one) and cognitive resilience stratified by the presence of atrophy, CERAD sample C[1]

	Cognitive resilience		
	Unstratified model (n=180) OR (95% CI)	**Atrophy present (n=139) OR (95% CI)**	**Atrophy absent (n=41) OR (95% CI)**
Multilingualism (versus monolinguals) Speaking two languages	0.65 (0.31-1.36)	0.59 (0.24-1.42)	1.27 (0.25-6.47)
Speaking three languages	0.47 (0.16-1.31)	0.63 (0.20-2.00)	1.07 (0.03-43.50)
Speaking four or more languages	1.15 (0.18-7.65)	0.54 (0.05-5.72)	9.12 (0.13-645.451)
Presence of *APOE*-ε4 allele	**0.37 (0.18-0.73)**	**0.41 (0.18-0.92)**	0.62 (0.09-4.19)
Age at death (years)	0.95 (0.89-1.02)	0.98 (0.92-1.06)	0.85 (0.70-1.05)
Primary language (English versus. other)	0.68 (0.25-1.84)	0.57 (0.16-2.09)	2.50 (0.30-21.07)
Education (versus high school or less) Undergraduate degree	2.28 (0.73-8.13)	1.89 (0.51-7.07)	0.95 (0.01-109.01)
Graduate degree	2.46 (0.76-9.07)	2.33 (0.58-9.39)	0.86 (0.01-93.63)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table E4: The association between a four-level multilingualism variable (speaking two, three, or four or more languages versus one) and cognitive resilience stratified by the presence of atrophy, CERAD sample D[1]

	Cognitive resilience		
	Unstratified model (n=160) OR (95% CI)	**Atrophy present (n=121) OR (95% CI)**	**Atrophy absent (n=39) OR (95% CI)**
Multilingualism (versus monolinguals) Speaking two languages	0.59 (0.27-1.27)	0.55 (0.22-1.38)	1.39 (0.26-7.48)
Speaking three languages	0.43 (0.14-1.26)	0.59 (0.18-1.99)	0.96 (0.02-41.44)
Speaking four or more languages	1.12 (0.17-7.46)	0.50 (0.05-5.32)	11.81 (0.15-942.54)
Presence of *APOE*-ε4 allele	**0.39 (0.19-0.79)**	0.46 (0.20-1.07)	0.59 (0.09-4.13)
Age at death (years)	0.94 (0.87-1.01)	0.96 (0.89-1.04)	0.83 (0.65-1.05)
Primary language (English versus other)	0.86 (0.28-2.70)	1.00 (0.19-5.39)	2.82 (0.31-25.54)
Education (Graduate degree versus undergraduate degree)	1.05 (0.52-2.12)	1.15 (0.50-2.68)	0.90 (0.19-4.23)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD restricted atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table E5: The association between speaking two or more languages (versus one language) and cognitive resilience stratified by the presence of atrophy, CERAD sample C[1]

	Cognitive resilience		
	Unstratified model (n=180) OR (95% CI)	**Atrophy present (n=139) OR (95% CI)**	**Atrophy absent (n=41) OR (95% CI)**
Multilingualism (versus one language) Speaking two or more languages	0.63 (0.30-1.28)	0.58 (0.25-1.38)	1.45 (0.29-7.32)
Presence of *APOE*-ε4 allele	**0.38 (0.19-0.75)**	**0.40 (0.18-0.90)**	0.84 (0.13-5.53)
Age at death (years)	0.95 (0.89-1.02)	0.98 (0.92-1.06)	0.88 (0.73-1.06)
Primary language (English versus other)	0.70 (0.26-1.89)	0.56 (0.15-2.02)	2.10 (0.34-13.05)
Education (versus high school or less) Undergraduate degree	2.32 (0.75-8.24)	1.92 (0.51-7.18)	1.52 (0.03-78.77)
Graduate degree	2.44 (0.77-8.83)	2.35 (0.59-9.26)	1.11 (0.02-59.83)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table E6: The association between speaking two or more languages (versus one language) and cognitive resilience stratified by the presence of atrophy, CERAD sample D[1]

	Cognitive resilience		
	Unstratified model (n=160) OR (95% CI)	**Atrophy present (n=121) OR (95% CI)**	**Atrophy absent (n=39) OR (95% CI)**
Multilingualism (versus one language) Speaking two or more languages	0.58 (0.27-1.21)	0.55 (0.23-1.33)	1.48 (0.28-7.76)
Presence of *APOE*-ε4 allele	**0.41 (0.19-0.82)**	0.45 (0.19-1.04)	0.84 (0.13-5.53)
Age at death (years)	0.94 (0.87-1.01)	0.96 (0.89-1.04)	0.87 (0.70-1.08)
Primary language (English versus other)	0.88 (0.29-2.73)	0.97 (0.18-5.16)	2.19 (0.32-14.90)
Education (Graduate degree versus undergraduate degree)	1.03 (0.51-2.03)	1.14 (0.50-2.59)	0.72 (0.16-3.22)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD restricted atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table E7: The association between speaking four or more languages (versus fewer languages) and cognitive resilience stratified by the presence of atrophy, CERAD sample C[1]

	Cognitive resilience		
	Unstratified model (n=180) OR (95% CI)	**Atrophy present (n=139) OR (95% CI)**	**Atrophy absent (n=41) OR (95% CI)**
Multilingualism (versus one to three languages) Speaking four or more languages	1.70 (0.28-10.46)	0.81 (0.08-7.79)	8.10 (0.14-469.48)
Presence of *APOE*-ε4 allele	**0.38 (0.19-0.75)**	**0.42 (0.19-0.94)**	0.59 (0.09-4.00)
Age at death (years)	0.95 (0.89-1.01)	0.98 (0.91-1.06)	0.85 (0.70-1.04)
Primary language (English versus other)	0.82 (0.32-2.17)	0.66 (0.19-2.32)	2.42 (0.42-13.85)
Education (versus high school or less) Undergraduate degree	2.38 (0.77-8.41)	1.97 (0.53-7.31)	0.97 (0.01-87.04)
Graduate degree	2.30 (0.72-8.31)	2.22 (0.57-8.67)	0.86 (0.01-78.41)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table E8: The association between speaking four or more languages (versus fewer languages) and cognitive resilience stratified by the presence of atrophy, CERAD sample D[1]

	Cognitive resilience		
	Unstratified model (n=160) OR (95% CI)	**Atrophy present (n=121) OR (95% CI)**	**Atrophy absent (n=39) OR (95% CI)**
Multilingualism (versus one to three languages) Speaking four or more languages	1.76 (0.29-10.80)	0.79 (0.082-7.56)	9.72 (0.15-613.19)
Presence of *APOE*-ε4 allele	**0.41 (0.19-0.82)**	0.47 (0.21-1.09)	0.57 (0.082-3.91)
Age at death (years)	0.94 (0.87-1.00)	0.96 (0.89-1.04)	0.83 (0.66-1.04)
Primary language (English versus other)	1.08 (0.37-3.27)	1.20 (0.23-6.16)	2.74 (0.44-17.02)
Education (Graduate degree versus undergraduate degree)	0.93 (0.47-1.82)	1.04 (0.47-2.31)	0.86 (0.19-4.00)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD restricted atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table E9: The association between speaking two or more languages (versus one language) and cognitive resilience stratified by the presence of atrophy, NIA-RI sample C[1]

	Cognitive resilience		
	Unstratified model (n=135) OR (95% CI)	**Atrophy present (n=93) OR (95% CI)**	**Atrophy absent (n=28) OR (95% CI)**
Multilingualism (versus one language) Speaking two or more languages	0.87 (0.38-2.05)	0.70 (0.26-1.87)	5.14 (0.53-49.94)
Presence of *APOE*-ε4 allele	0.57 (0.25-1.27)	0.57 (0.22-1.46)	1.39 (0.15-12.98)
Age at death (years)	0.95 (0.87-1.04)	0.99 (0.90-1.09)	0.76 (0.56-1.03)
Primary language (English versus other)	1.20 (0.35-4.82)	1.37 (0.20-9.27)	4.14 (0.38-45.04)
Education (versus undergraduate degree High school or less	4.94 (0.85-94.45)	0.46 (0.07-3.01)	0.52 (0.09-3.21)
Graduate degree	5.51 (0.91-106.69)	1.41 (0.53-3.78)	-

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CI = Confidence intervals; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio.

Table E10: The association between speaking two or more languages (versus one language) and cognitive resilience stratified by the presence of atrophy, NIA-RI sample D[1]

	Cognitive resilience		
	Unstratified model (n=121) OR (95% CI)	**Atrophy present (n=93) OR (95% CI)**	**Atrophy absent (n=28) OR (95% CI)**
Multilingualism (versus one language) Speaking two or more languages	0.87 (0.37-2.06)	0.69 (0.25-1.89)	5.14 (0.53-49.94)
Presence of *APOE*-ε4 allele	0.59 (0.25-1.32)	0.62 (0.24-1.65)	1.39 (0.15-12.98)
Age at death (years)	0.96 (0.87-1.04)	0.99 (0.89-1.09)	0.76 (0.56-1.03)
Primary language (English versus other)	1.61 (0.43-7.88)	3.79 (0.17-83.99)	4.14 (0.38-45.04)
Education (Graduate degree versus undergraduate degree)	1.12 (0.49-2.55)	1.43 (0.53-3.84)	0.52 (0.085-3.21)

Statistically significant values are **bolded** ($p<0.05$). [1]NIA-RI restricted atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CI = Confidence intervals; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Table E11a: The distribution of type of language by cognitive resilience status, CERAD sample D[1]

Variables[2]	Cognitive resilience (CERAD criteria) (n=160)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	32.4 (22)	67.7* (46)	42.5 (68)
Speaking French	56.7 (17)	43.3 (13)	18.8 (30)
Speaking Spanish	31.3 (5)	68.8 (11)	10.0 (16)
Speaking Spanish and Italian	40.0 (8)	60.0 (12)	12.5 (20)
Speaking romance languages[3]	48.8 (21)	51.2 (22)	26.9 (43)
Proficiency in Latin	30.0 (3)	70.0 (7)	6.3 (10)
Speaking Polish	57.9 (11)	42.1 (8)	11.9 (19)

*Significantly associated with cognitive resilience ($p<0.05$). [1]CERAD restricted atrophy sample. [2]All participants spoke English. [3]Spoke French, Spanish, or Italian. **Abbreviations:** CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria.

Table E11b: The distribution of type of language by cognitive resilience status, NIA-RI sample D[1]

Variables[2]	Cognitive resilience (NIA-RI criteria) (n=121)		
	Yes % (n)	No % (n)	Total % (n)
Speaking German	23.9 (11)	76.1 (35)	38.0 (46)
Speaking French	40.9 (9)	59.1 (13)	18.2 (22)
Speaking Spanish	25.0 (3)	75.0 (9)	9.9 (12)
Speaking Spanish or Italian	28.6 (4)	71.4 (10)	11.6 (14)
Speaking romance languages[3]	35.5 (11)	64.5 (20)	25.6 (31)
Speaking Latin	30.0 (3)	70.0 (7)	8.3 (10)
Speaking Polish	50.0 (7)	50.0 (7)	11.6 (14)

*Significantly associated with cognitive resilience ($p<0.05$). [1]NIA-RI restricted atrophy sample. [2]All participants spoke English. [3]Spoke French, Spanish, or Italian. **Abbreviations:** NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria.

Table E12: The association between speaking German and cognitive resilience, CERAD sample D*

Exposure variables**	Cognitive resilience (n=160) (OR, 95% CI)								
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**	**Model 8-adjusted[8]**
Speaking German	**0.44 (0.23-0.84)**	**0.40 (0.20-0.78)**	**0.47 (0.24-0.90)**	**0.44 (0.22-0.83)**	**0.44 (0.23-0.83)**	**0.42 (0.21-0.81)**	**0.42 (0.20-0.83)**	0.51 (0.25-1.00)	**0.48 (0.23-0.99)**

Statistically significant values are **bolded** (p<0.05). *CERAD restricted atrophy sample. **All participants spoke English. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (undergraduate degree versus high school or less, and graduate degree versus high school or less). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education, primary language, and immigration status. [7]Adjusted for atrophy (atrophy present versus absent) [8]Adjusted for *APOE*-ε4 status, age at death, education, primary language, immigration status, and atrophy. **Abbreviations**: CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

Table E13: The association between speaking German and cognitive resilience, NIA-RI sample D*

Exposure variables**	Cognitive resilience (n=121) (OR, 95% CI)								
	Model-Crude	**Model 1-adjusted[1]**	**Model 2-adjusted[2]**	**Model 3-adjusted[3]**	**Model 4-adjusted[4]**	**Model 5-adjusted[5]**	**Model 6-adjusted[6]**	**Model 7-adjusted[7]**	**Model 8-adjusted[8]**
Speaking German	0.56 (0.24-1.25)	0.57 (0.24-1.27)	0.59 (0.25-1.35)	0.54 (0.23-1.22)	0.57 (0.24-1.27)	0.57 (0.24-1.28)	0.60 (0.25-1.41)	0.64 (0.27-1.49)	0.73 (0.29-1.78)

Statistically significant values are **bolded** (p<0.05). *NIA-RI restricted atrophy sample. **All participants spoke English. [1]Adjusted for *APOE*-ε4 status. [2]Adjusted for age at death. [3]Adjusted for education (undergraduate degree versus high school or less, and graduate degree versus high school or less). [4]Adjusted for primary language (English versus other). [5]Adjusted for immigration status (born in the United States or not). [6]Adjusted for *APOE*-ε4 status, age at death, education, primary language, and immigration status. [7]Adjusted for atrophy (atrophy present versus absent) [8]Adjusted for *APOE*-ε4 status, age at death, education, primary language, immigration status, and atrophy. **Abbreviations:** CI = Confidence intervals; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Table E14: The association between speaking German and cognitive resilience stratified by the presence of atrophy, CERAD sample D[1]

	Cognitive resilience		
	Unstratified model (n=160) OR (95% CI)	**Atrophy present (n=121) OR (95% CI)**	**Atrophy absent (n=39) OR (95% CI)**
Speaking German (Yes versus no)	**0.43 (0.22-0.85)**	0.44 (0.19-1.00)	0.72 (0.14-4.03)
Presence of *APOE*-ε4 allele	**0.39 (0.19-0.79)**	**0.40 (0.16-0.92)**	0.88 (0.13-7.87)
Age at death (years)	0.95 (0.88-1.02)	0.97 (0.90-1.06)	0.86 (0.68-1.06)
Education (Graduate degree versus undergraduate degree)	1.03 (0.52-2.06)	1.20 (0.52-2.77)	0.64 (0.12-3.01)
Primary language (English versus other)	0.98 (0.32-3.04)	1.13 (0.22-8.50)	1.86 (0.29-11.00)

Statistically significant values are **bolded** ($p<0.05$). [1]CERAD restricted atrophy sample. **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = Confidence intervals; OR = Odds ratio

8.6 Appendix F: Assessment of selection bias in analytic samples

Tables F1 through F4 have summarized the results assessing selection bias in the four sets of analytic samples. Table F1 has compared the excluded participants from CERAD (n=479) or NIA-RI (n=531) samples A with those who were included in the CERAD (n=199) or NIA-RI (n=147) samples A (see Figure 3a). Table F2 shows the comparison between CERAD (n=176) or NIA-RI (n=131) samples B (see Figure 3b) and those who were excluded from CERAD (n=23) or NIA-RI (n=16) samples B. Table F3 has compared CERAD (n=180) or NIA-RI (n=135) samples C (see Figure 3b) with those who were excluded because of having missing data on atrophy (CERAD: n=19; NIA-RI n=12). Lastly, Table F4 shows the comparison between CERAD (n=160) or NIA-RI (n=121) samples D and those who were excluded from CERAD (n=20) or NIA-RI (n=14) samples D.

When comparing the excluded participants from the CERAD or NIA-RI samples A with those who were included in CERAD or NIA-RI samples A, Tables F1 and F3 show that the presence of an *APOE*-ε4 allele ($p<0.001$) and atrophy ($p<0.01$) were significantly less common in participants who were excluded from samples A than those who were included in samples A. Since the presence of *APOE*-ε4 allele is a strong predictor of the likelihood of AD, and atrophy has a strong correlation with Alzheimer neuropathology, these findings were not surprising as the analytic samples A were restricted to participants with substantial Alzheimer neuropathology. Also, age at death was significantly different between the included and excluded participants, where those who were included in either CERAD or NIA-RI samples A were older than those who were excluded from samples A. Again, this would be expected as older participants would

be more likely to have Alzheimer neuropathology and also more likely to have died and thus had undergone neuropathologic assessment.

When comparing the CERAD or NIA-RI samples B or D (restricted to university-educated teachers) (see Figure 3b) with those who were excluded from samples B or D, respectively, the results showed that being born in the United States and speaking English as the primary language were significantly less common in those who completed up to high school or less and were not teachers ($p<0.001$), compared to those who had attained at least an undergraduate degree or higher and had served as teachers. It may be possible that immigrants in this study were exposed to more early-life challenges than those who were born in the United States and so, they perhaps had difficulties in performing well in high school. Consequently, these participants might have been unable to attain higher levels of education and to serve as teachers. Moreover, there were significant differences in age at death among those who were excluded versus those who were included in the CERAD or NIA-RI samples B or D, where the excluded participants were significantly older at death than the university-educated participants ($p<0.05$). It is expected that university-educated participants would live longer than those who only completed up to high school or less. However, the results were contradictory to the expected results, and it may be possible that the university-educated participants in these analytic samples had more comorbidities than the excluded participants, which could have resulted in shorter survival.

When the CERAD or NIA-RI samples C (see Figure 3b) were compared to the excluded participants with missing data on atrophy, there were no significant differences observed in the variables listed in the Tables (Table F2 and F4) between the CERAD sample C and the excluded

participants (Table F2). However, within the NIA-RI sample C, attaining a graduate degree was more common among the excluded participants than those who were included in sample C. Further, speaking English as the primary language was also more common in participants who were excluded than in those who were not ($p<0.05$) (Table F4).

Finally, in terms of multilingualism (the exposure), no significant differences were observed between each analytic sample and the excluded participants. Similarly, cognitive resilience (the outcome) also did not significantly differ in the CERAD or NIA-RI analytic samples B, C, and D when compared with the excluded participants.

Table F1: Assessment of selection bias: comparisons of CERAD samples A[1] or B[2] with excluded participants

	Sample A versus excluded subjects		Sample B versus excluded subjects	
Variable	**Excluded participants from sample A (n=479)[3]**	**Sample A (n=199)[4]**	**Excluded participants from sample B (n=23)[5]**	**Sample B (n=176)[6]**
Multilingualism				
1	30.8	27.6	17.4	29.0
2	49.0	52.8	65.2	51.1
3	15.6	15.6	17.4	15.3
4+	4.6	4.0	0.0	4.6
Presence of *APOE*-ε4 allele (%)	18.8	31.2***	21.7	32.4
Age at death, years (SD)	89.69 (5.4)	91.87 (5.0)***	94.15 (5.9)	91.57 (4.8)*
Education				
High school or less	17.1	11.6	100.0	0.0
Undergraduate degree	38.8	42.2	0.0	47.7***
Graduate degree	44.1	46.2	0.0	52.3***
Primary language spoken				
English	91.2	87.4	60.9	90.9***
Immigration status				
Born in the United States	94.2	93.5	69.6	96.6***
Occupation				
Teacher	87.8	93.5*	43.5	100.0***
Atrophy				
Present	65.4	77.2**	90.0	75.6
Cognitive resilience	-	-	26.1	44.3

*p<0.05, **p<0.01, ***p<0.001 [1]CERAD main analytic sample. [2]CERAD sample restricted to university-educated teachers. Following variables had different sample sizes because of missing data. [3]Multilingualism (n=308); *APOE*-ε4 status (n=420); primary language (n-307); occupation (n=477); and atrophy (n=295). [4]Atrophy (n=180). [5]Atrophy

(n=20), [6]Atrophy (n=160). **Abbreviations:** *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; SD = Standard deviation

Table F2: Assessment of selection bias: comparisons of CERAD samples C[1] or D[2] with excluded participants

	Sample C versus excluded subjects		Sample D versus excluded subjects	
Variable	**Sample C (n=180)**	**Excluded participants from sample C (n=19)**	**Sample D (n=160)**	**Excluded participants from sample D (n=20)**
Multilingualism				
1	27.2	31.6	28.8	15.0
2	53.3	47.4	51.9	65.0
3	16.1	10.5	15.6	20.0
4+	3.3	10.5	3.8	0.0
Presence of *APOE*-ε4 allele (%)	31.7	26.3	32.5	25.0
Age at death, years (SD)	91.86 (5.1)	91.96 (3.8)	91.54 (4.9)	94.47 (6.2)*
Education				
High school or less	11.1	15.8	0.0	100.0***
Undergraduate degree	44.4	21.1	50.0	0.0
Graduate degree	44.4	63.2	50.0	0.0
Primary language spoken				
English	86.7	94.7	90.0	60.0**
Immigration status				
Born in the United States	93.3	94.7	96.3	70.0***
Occupation				
Teacher	93.3	94.7	100.0	40.0***
Atrophy				
Present	-	-	75.6	90.0
Cognitive resilience	41.7	47.4	43.8	25.0

*p<0.05, **p<0.01, ***p<0.001. [1]CERAD atrophy sample. [2]CERAD atrophy sample restricted to university-educated teachers.

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; SD = Standard deviation

Table F3: Assessment of selection bias: comparisons of NIA-RI samples A[1] or B[2] with excluded participants

Variable	Sample A versus excluded subjects		Sample B versus excluded subjects	
	Excluded participants from sample A (n=531)[3]	Sample A (n=147)[4]	Excluded participants from sample B (n=16)[5]	Sample B (n=131)[6]
Multilingualism				
1	28.3	32.7	25.0	33.6
2	51.7	47.6	56.3	46.6
3	16.1	14.3	18.8	13.7
4+	3.9	5.4	0.0	6.1
Presence of *APOE*-ε4 allele (%)	17.8	38.8***	31.3	39.7
Age at death, years (SD)	90.02 (5.5)	91.59 (4.7)***	93.89 (4.8)	91.31 (4.6)*
Education	16.8	10.9	100.0	0.0
High school or less	38.6	44.2	0.0	49.6***
Undergraduate degree				
Graduate degree	44.6	44.9	0.0	50.4***
Primary language spoken				
English	90.8	87.1	62.5	90.1**
Immigration status				
Born in the United States	94.0	93.9	75.0	96.2**
Occupation				
Teacher	88.5	93.2	37.5	100.0***
Atrophy				
Present	66.2	79.3**	100.0	76.9*
Cognitive resilience	-	-	18.8	30.5

*p<0.05, **p<0.01, ***p<0.001 [1]NIA-RI main analytic sample. [2]NIA-RI sample restricted to university-educated teachers. Following variables had different sample sizes because of missing data. [3]Multilingualism (n=360); *APOE*-ε4 status (n=472); age at death (n=459); primary language (n-359); occupation (n=529); and atrophy (n=340). [4]Atrophy (n=135). [5]Atrophy (n=14). [6]Atrophy (n=121).

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; SD = Standard deviation

Table F4: Assessment of selection bias: comparisons of NIA-RI samples C[1] or D[2] with excluded participants

	Sample C versus excluded subjects		Sample D versus excluded subjects	
Variable	**Sample C (n=135)**	**Excluded participants from sample C (n=12)**	**Sample D (n=121)**	**Excluded participants from sample D (n=14)**
Multilingualism	32.6	33.3	33.9	21.4
1	48.2	41.7	47.1	57.1
2	14.8	8.3	14.1	21.4
3				
4+	4.4	16.7	5.0	0.0
Presence of *APOE*-ε4 allele (%)	38.5	41.7	38.8	35.7
Age at death, years (SD)	91.64 (4.7)	91.02 (5.1)	91.37 (4.6)	93.98 (5.1)*
Education	10.4	16.7*	0.0	100.0***
High school or less	47.4	8.3*	52.9	0.0
Undergraduate degree				
Graduate degree	42.2	75.0*	47.1	0.0
Primary language spoken				
English	86.7	91.7*	89.3	64.3*
Immigration status				
Born in the United States	93.3	100.0	95.9	71.4**
Occupation				
Teacher	93.3	91.7	100.0	35.7***
Atrophy				
Present	-	-	76.9	100.0*
Cognitive resilience	28.9	33.3	31.4	7.1

*p<0.05, **p<0.01, ***p<0.001 [1]NIA-RI atrophy sample. [2]NIA-RI atrophy sample restricted to university-educated teachers.

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; SD = Standard deviation