The Association of Multilingualism and Written Linguistic Ability with Mild Cognitive Impairment in the Nun Study

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: Multilingualism may be associated with enhanced cognitive function and reduced risk of mild cognitive impairment (MCI) due to enhanced cognitive reserve.

Objectives: To investigate the association of multilingualism with overall MCI and MCI subtypes (non-amnestic versus amnestic).

Methods: Participants from the Nun Study, a longitudinal study of 678 Catholic sisters in the U.S. aged 75+ years, were assessed for MCI in late life using standard neuropsychological tests and activities of daily living. Convent archives provided data on self-reported multilingualism from midlife and written linguistic ability (idea density and grammatical complexity) from early adulthood. Logistic regression models controlled for age, apolipoprotein E (a genetic risk factor), country of birth and education (n=384); sensitivity analyses (n=122) additionally controlled for written linguistic ability.

Results: Speaking 4+ languages (but not 2 or 3) was associated with a significantly lower risk of overall MCI (OR: 0.32; 95% CI: 0.11-0.96) compared to monolinguals. However, this association weakened to non-significance after controlling for education. In the sensitivity analyses, multilingualism did not reduce the risk of overall MCI and its subtypes; however, written linguistic ability (specifically idea density) was significantly associated with a reduced risk of amnestic MCI, even after adjusting for education.

Conclusion: By examining the number of languages spoken, in addition to examining written linguistic ability and controlling for education, this study contributes to the understanding of how these cognitively stimulating activities can act individually as well as in combination and how this may lead to a ceiling effect in their protective impact on MCI.

(250 words)

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I can do all things through Christ who strengthens me. – Philippians 4:13

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List of Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
aMCI	Amnestic mild cognitive impairment
APOE	Apolipoprotein E
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence interval
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
naMCI	Non-amnestic mild cognitive impairment
OR	Odds ratio

1.0 Introduction

Globally, the number of older adults is steadily increasing. The world's population aged 60 years and older is predicted to reach 2 billion by 2050, doubling from 900 million in 2015 (Prince et al., 2015). With the growing aging population, rates of age-related diseases, such as dementia and other neurodegenerative disorders, are projected to increase (Prince et al., 2015). Worldwide, around 44.3 million people are living with dementia and the yearly total cost of dementia is $604 billion (Langa, 2015). Although population-based studies suggest that the age-specific risk of dementia and its subtype Alzheimer's disease (AD) may be declining because of falling levels of cardiovascular disease and rising levels of education, which may be contributing to an improvement in brain health (Gregg et al., 2014; Becker et al., 2010; Schrijvers et al, 2012; Matthews et al., 2013), population aging means that the total number of people with dementia will continue to rise. The number of people living with dementia currently and in the future emphasizes the need for more research related to healthy aging and ways to maintain cognitive function in older age.

Dementia is an umbrella term for memory loss and other types of cognitive impairment that are severe enough to interfere with activities of daily living, with AD being the most common cause of dementia (Cumming, 2019). MCI is defined by a measurable decline in cognitive domain abilities that is less severe than dementia (Petersen, 2004). MCI can be subdivided into: 1) amnestic MCI, where memory is significantly impaired, and 2) non-amnestic MCI, where memory remains intact, but other cognitive domains (e.g., executive function, visual-spatial skills, language, attention) are significantly impaired (Petersen et al., 2001; Petersen, 2004).

To maintain cognitive health, investigating modifiable factors that have the potential to prevent cognitive impairment is crucial. Cognitively stimulating factors (e.g., education) are hypothesized to reduce the risk of cognitive impairment through building and maintaining cognitive reserve. Individuals with high cognitive reserve may be able to process tasks in a manner that allows them to better cope with the presence of brain pathology and thus they can sustain greater degrees of brain damage before showing clinical symptoms of AD (Stern, 2009; Stern, 2012).

Similar to education, multilingualism (speaking more than one language) is a cognitively stimulating activity that may reduce the risk of dementia and other cognitive impairments. Current estimates suggest that over half of the world's population is bilingual *(*Marian & Shook, 2012; Bialystok, Poarch, et al., 2014). Speaking more than one language has been shown to enhance mental engagement and cognitive flexibility, which may play a role in reducing the risk of MCI and increasing cognitive reserve (Bialystok et al., 2004). However, current studies on multilingualism have mostly been restricted to examining its association with dementia or AD rather than with MCI or its subtypes. Notable gaps in the literature include whether multilingualism is protective against earlier stages of cognitive impairment such as MCI, if the effect differs for amnestic and non-amnestic MCI, and analyses that fully consider potential confounders, such as apolipoprotein E-ε4 (*APOE*-ε4), a genetic risk factor for AD.

This study uses secondary data from the Nun Study, a population-based longitudinal study of 678 religious sisters. This homogeneous population presents a unique opportunity to investigate the impact of early and mid-life multilingualism on late-life MCI and its subtypes by controlling for socioeconomic status, *APOE*-ε4, and linguistic ability measures in addition to multilingualism. Cognitively stimulating factors may work together to protect against cognitive

impairment. For example, previous studies have found that the association between bilingualism and AD was only significant when educational attainment was low (Gollan et al., 2011). However, the impact of language on MCI may extend beyond the number of languages spoken to include other factors of linguistic ability measures, more specifically written ability. This has been supported in previous reports from the Nun Study, where early written linguistic performance had a strong influence on late-life cognition (Snowdon et al., 1996; Riley et al., 2005). By investigating the number of languages spoken, in addition to examining written linguistic ability and controlling for education, this study contributes to the understanding of how language skills and other cognitively stimulating activities can act individually as well as in combination and how this may lead to a ceiling effect of the protective impact of cognitively stimulating activities on MCI. Cognitively stimulating activities may be one important strategy, among other strategies such as social and physical activities, that could play a role in reducing the risk of MCI.

2.0 Literature Review

2.1 Cognitive Function

2.1.1 Normal Cognitive Aging

There is a lot of variability and heterogeneity in cognitive changes among older adults. Maintaining cognitive ability in later life is associated with better quality of life and well-being (Anstey & Low, 2004). Normal cognitive aging refers to maintaining cognitive ability in older age with minimal decline (Harada et al., 2013). The normal aging process is associated with slight deterioration in certain cognitive domain abilities, such as memory, language, visuospatial skills, processing speed, and executive function (Grundman et al., 2004; Harada et al., 2013). However, this decline is not severe enough to interfere with everyday activities (Petersen et al., 1999). When cognitive decline goes beyond a typical age-related threshold of impairment, it is no longer normal aging but MCI, which can subsequently progress to dementia (Petersen et al., 1999; Petersen, 2004). However, the majority of older adults will not go on to develop MCI or dementia (Anstey & Low, 2004; Harada et al., 2013).

2.1.2 Mild Cognitive Impairment (MCI)

MCI is defined as an intermediate state between normal cognitive aging and dementia (Gauthier et al., 2006; Petersen et al., 1999; Petersen et al., 2001). Like dementia, MCI is a syndrome with one or more underlying causes (Hughes et al., 2011). MCI is referred to as cognitive impairment that is greater than expected for an individual's age, but not severe enough to interfere with activities of daily living (ADLs) (Gauthier et al., 2006). ADLs are the fundamental skills required to independently care for oneself, such as bathing, toileting and eating (Rockwood, 2007). They are used as an indicator of a person's functional status. Cognitive function in individuals with MCI can remain stable or even revert to normal cognition.

A recent study from the Nun Study discovered that in this highly educated population, 30% of participants reverted from MCI to normal cognition (Iraniparast et al., 2022). Reverse transition rates from MCI to normal cognition increased with higher educational levels and other indicators of cognitive reserve (Iraniparast et al., 2022). Most importantly, those with greater levels of cognitive reserve indicators (higher educational level and stronger language skills, measured both as written linguistic skills in early adulthood and as academic performance in high school English) had a significantly greater chance of reversion from MCI to normal cognition than progression from MCI to dementia (Iraniparast et al., 2022).

MCI can be subdivided into amnestic MCI (aMCI) and non-amnestic MCI (naMCI) (Hughes et al., 2011; Petersen et al., 2001). In aMCI, memory is significantly impaired whereas in naMCI memory remains intact, but other cognitive abilities (e.g., executive function, visuospatial skills) are significantly impaired (Calderon et al., 2001; Bennett et al., 2002).

aMCI and naMCI are different entities based on brain structures as well as neuropsychological tests (Costumero et al., 2020). Major structural differences consist of a decrease in the size of the amygdala, hippocampus and the entorhinal cortex in aMCI compared to naMCI and to healthy controls, leading to poorer performance on memory tests (Csukly et al., 2016; Serra et al., 2013). Furthermore, the thickness of the fusiform gyrus, the entorhinal cortex, the precuneus, and the cingulate gyrus are also significantly decreased in aMCI compared to naMCI and healthy controls (Csukly et al., 2016; Costumero et al., 2020). On the other hand, the volume of the precuneus is the only structure that is decreased in naMCI compared to healthy controls (Costumero et al., 2020; Csukly et al., 2016).

Moreover, significant differences are found in neuropsychological test results between aMCI and naMCI (Csukly et al., 2016). aMCI participants have decreased anterograde and

retrograde memory function as well as poorer performance on category fluency relative to participants with naMCI and controls. However, naMCI participants show a decreased performance on letter fluency compared to healthy controls. Additionally, both MCI groups have decreased executive functioning compared to controls (measured by the Trail Making test) (Csukly et al., 2016).

Subtypes of MCI also differ in their risk of subsequent disease, with aMCI more likely to progress to AD than naMCI. For instance, aMCI is associated with biomarkers for AD, whereas individuals with naMCI are more likely to develop non-Alzheimer's dementia (e.g., Lewy body dementia) as well as cerebrovascular disease (e.g., stroke and aneurysm) (Grundman et al., 2004; Hughes et al., 2011; Killiany et al., 2000; Morris et al., 2001; Petersen & Negash, 2008; Petersen et al., 1999). For those whose MCI progressed to Lewy body dementia, the baseline MCI diagnosis typically includes attention or visuospatial deficits, while for those who developed AD, the baseline MCI diagnosis includes memory and naming impairment (Csukly et al., 2016; Calderon et al., 2001).

2.1.2.1 Relevance of the MCI stage: MCI, the intermediate stage between normal cognition and dementia, is important to study because there are many benefits to intervening at an earlier stage of cognitive impairment. This is supported by evidence of reverse transitions from MCI to normal cognition, but the absence of any such transitions from dementia to MCI (Iraniparast et al., 2022), suggesting that intervening earlier may lead to better outcomes. Since MCI is a precursor for dementia, it is crucial to study MCI and determine whether it is possible to reduce the risk of progressing to dementia. For example, in dementia, some medications are only approved for earlier stages of dementia because that is where there is evidence of a benefit. Early multilingual or cognitive stimulation (i.e., written language) could enhance a person's

ability to carry out basic everyday tasks and maintain independence, leading to a better quality of life in later life.

2.1.3 Dementia and Alzheimer's Disease

It is estimated that approximately 50 million people around the world have dementia and this number is predicted to triple by 2050 (Livingston et al., 2020; Prince et al., 2015). Dementia is characterized by the loss of cognitive functioning in multiple domains that is severe enough to interfere with ADLs (see review by Tyas & Gutmanis, 2015). Dementia is defined by many symptoms, such as memory loss, difficulties with problem-solving, thinking, orientation, processing language, and planning and reasoning skills, as well as behavioural changes in mood and personality (Schrijvers et al, 2012). Moreover, dementia is associated with an increased risk for institutionalization, urinary incontinence, falls, and early death (Chang et al., 2015). Ultimately, quality of life becomes compromised due to the loss of independence (Chang et al., 2015).

Dementia is a heterogeneous condition. AD is the most common type of dementia, accounting for approximately two-thirds of all cases and vascular dementia is the second most common type (5 to 10% of cases) (Prince et al., 2015). AD diagnosis requires both the pathology of AD—neurofibrillary tangles and amyloid plaques—and clinical symptoms of dementia (Jack et al., 2013). It is suggested that these AD pathologies are present 20 to 30 years before the presence of symptoms of dementia (Mattsson et al., 2009). Similarly, the pathology of vascular dementia—arteriosclerosis in cerebral vasculature—is also present before any clinical symptoms of dementia (Tyas & Gutmanis, 2015). Other forms of dementia include frontotemporal dementia, Lewy body dementia, Parkinson's disease, and Creutzfeldt-Jakob disease (Mattsson et al., 2009). Aside from the above degenerative pathologic conditions, factors such as depression,

head traumas, infections and side effects of some medications can also lead to dementia (Tyas & Gutmanis, 2015).

2.1.4 Factors that Influence Cognitive Function

Cognitive function is influenced by various modifiable and non-modifiable risk factors. Some common examples of non-modifiable factors include sex, age, and genetics, whereas examples of modifiable factors include cognitively stimulating activities and lifestyle behaviours (Tyas & Gutmanis, 2015) (see the concept map in Appendix D).

2.1.4.1 Non-Modifiable Factors. Age is the major risk factor for cognitive decline and dementia. Since age is a primary and unmodifiable risk factor for dementia, there will be a rapidly growing public health problem as the population ages. Dementia incidence for Canadians 65+ years is expected to increase to 250,000 new cases by 2038 (Prince et al., 2015).

In addition to age, sex also has an impact on the risk of cognitive impairment. Males and females show differences in cognitive impairment because of differences in biological sex (Li & Singh, 2014). Female sex has been associated with a higher prevalence of dementia in some (Bachman et al., 1993; Fratiglioni et al., 2000; Snyder et al., 2016), but not all studies (Khondoker et al., 2017; Rocca et al., 1998). Researchers had previously attributed this higher prevalence to the greater longevity of females compared to males, but more recent findings suggest that there may be other contributing factors, such as sex differences in head circumference, hormonal changes, chromosomes, and expression of genes (Snyder et al., 2016). Furthermore, there are also gender differences between men and women that may impact the risk of cognitive impairment, including lifestyle behaviours (e.g., alcohol use and smoking), socioeconomic status (i.e., education, income, occupation, family roles), and psychosocial indicators (i.e., coping with stress, social engagement) (Gannon et al., 2019). For example, the

current higher prevalence of dementia among women may be due to women having lower levels of education compared to men, in the past (Snyder et al., 2016). This is consistent with previous literature that high educational attainment exerts a protective effect on cognitive impairment, and low education is a strong risk factor for dementia (Crimmins et al., 2018). However, with the recent increase in women pursuing higher education, it is possible that the risk of dementia may change in the future, as the gender differences decrease in educational attainment. Moreover, women drink less alcohol, have fewer alcohol-related problems than men and are less likely to manifest certain risk factors for alcohol problems (Nolen-Hoeksema, 2004). There are also gender differences in perceived stress and coping strategies. For example, women are more likely than men to seek social support as a coping strategy (Eisenbarth, 2019).

Genetics plays a significant role in the development of dementia. *APOE*-ε4 is the most widely accepted genetic risk factor for dementia and AD (Ali et al, 2018; Flowers & Rebeck, 2020; Holtzman et al, 2012; Liu et al., 2015; Tyas et al., 2007). The ApoE protein is responsible for carrying cholesterol from the brain extracellular matrix to the bloodstream (Bagyinszky et al., 2014); however, this mechanism is impaired for individuals who have an *APOE*-ε4 allele (Shobab et al., 2005). Having an *APOE*-ε4 allele leads to an increase in the accumulation of amyloid plaques and neurofibrillary tangles in the brain, which results in more brain inflammation as well as hippocampal atrophy (Poirier et al., 1995; Shobab et al., 2005; Egensperger et al., 1998). Individuals who have one copy of the *APOE*-ε4 allele (heterozygous) have a three times greater likelihood of developing dementia, whereas those with two ε4 alleles (homozygous) have a 12 times greater risk (Shobab et al., 2005). Moreover, individuals with MCI who carry an *APOE*-ε4 allele have a higher risk of developing dementia compared to those without the allele (Smith et al., 1996). In contrast, the *APOE*-ε2 allele is thought to be protective

against cognitive decline (Shobab et al., 2005). Having an *APOE*-ε4 allele predicts individuals with MCI who will progress to dementia in 2 to 4 years from those who will remain free from dementia (MCI stable) (Shobab et al., 2005). *APOE*-ε4 has also been shown to decrease reversion from MCI to normal cognition and increase progression from MCI to dementia (Iraniparast et al., 2022).

2.1.4.2 Modifiable Factors. There are many modifiable factors that can impact the development and course of MCI and dementia. Although some of the variation in older people's health is based on genetics, much is due to people's lifestyles and social environments. The major modifiable risk factors for cognitive decline include low educational attainment, diabetes, obesity, depression, smoking, physical inactivity, hypertension, hearing impairment, and social isolation (Livingston et al., 2020). New evidence added three additional modifiable risk factors—air pollution, excessive alcohol consumption, and head injury (Livingston et al., 2022). The above modifiable risk factors are currently seen as the greatest contributors to dementia prevalence (Livingston et al., 2022). Modifying those 12 risk factors might prevent or delay up to 40% of dementia cases (Livingston et al., 2022).

Higher educational attainment has been associated with a reduced risk of dementia and AD (Fritsch et al., 2002; Gatz et al., 2001; Khondoker et al., 2017; Mortimer et al., 2003; Mortimer & Graves, 1993). The cognitive reserve hypothesis suggests that education increases cognitive stimulation, which increases the capacity of an individual to withstand damage from brain pathology, thus delaying dementia symptoms and compressing cognitive impairment closer to the end of life (Stern, 2009; Valenzuela & Sachdev, 2006). As well, cognitively stimulating occupations are associated with a decreased risk of dementia later in life (Scazufca et al., 2010; Zhu et al., 2012). Intellectual factors work together to change the brain via neuroplasticity.

Neuroplasticity is the brain's ability to adapt or change through neural pathways and synapses: the brain engages in synaptic pruning by eliminating synapses that are no longer necessary or useful (Baum & Titone, 20014). A study by Kumar et al. (2017) found that brain plasticity is significantly lower in people with MCI and AD than in healthy individuals of the same age. Therefore, engaging in cognitively stimulating activities (e.g., education and multilingualism) may influence cognitive function in later life (Li et al., 2014).

Lifestyle factors such as social activities, physical activities, and mental health influence cognitive function in late life (Fratiglioni et al., 2004; Paillard-Borg et al, 2012). Epidemiological studies show a relationship between mild to moderate physical activity and improved cognition in older adults (Ahlskog et al., 2011; Baumgart et al., 2015; Sofi et al., 2011). Older adults with dementia who are physically active daily can delay deterioration of ADL performance (Burge et al., 2012). Heavy smoking in mid-life was linked to a greater than 100% increase in the risk of dementia compared to non-smokers, after adjusting for age, sex, educational attainment, alcohol use, hypertension, BMI, diabetes, heart disease, and stroke (Rusanen et al., 2011). Likewise, smoking and lack of physical activity are risk factors for other health conditions, such as diabetes and hypertension, which in turn are also risk factors for dementia. Previous research suggests that 3% of worldwide cases of AD are attributed to diabetes, 5% to hypertension, and 13% to physical inactivity (Norton et al, 2014). Therefore, better prevention strategies and management of these modifiable risk factors could help reduce the risk of dementia.

Some mental health conditions (e.g., depression) are associated with lower cognitive function and performance (Byers & Yaffe, 2011; Korczyn & Halperin, 2009). Biological mechanisms associating depression with dementia include vascular disease, hippocampal atrophy, brain inflammation and accumulation of amyloid plaques in the brain (Byers & Yaffe,

2011). Depression increases the risk for cognitive impairment across several domains, including memory and executive function (Butters et al., 2022; Trivedi & Greer, 2014). Depression can impact executive function directly by causing hippocampus atrophy (Butters et al., 2022). Other mechanisms for the association between depression and dementia include less physical activity and social interaction (Bourassa et al., 2017; Brown et al., 2016).

2.1.5 Cognitive Reserve: Protection Against Cognitive Impairment

In addition to the modifiable and non-modifiable factors, the risk of MCI and dementia can be influenced by cognitive reserve capacity (Stern, 2012). Cognitive reserve is a hypothetical construct designed to explain the differences in cognitive performance due to age or brain pathology (Stern, 2009). In other words, cognitive reserve is the brain's ability to buffer against the clinical symptoms of neuropathology via compensatory strategies (Stern, 2002). Individuals with greater levels of cognitive reserve capacity have the ability to function at a normal or higher than expected level given the amount of brain damage (Stern, 2012; Stern, 2009). Therefore, cognitive reserve reduces the risk of dementia by buffering against clinical symptoms and thereby reducing the likelihood of a diagnosis of dementia (Stern, 2012).

Cognitive reserve is shown to increase with lifetime cognitive stimulation (Stern, 2009). Many epidemiological studies suggest that frequent cognitive stimulation throughout life can prevent symptoms of dementia or delay the onset of dementia (Klimova et al., 2017; Valenzuela et al., 2008). Factors suggested to increase cognitive reserve include education, occupation, physical activity, and multilingualism.

Education is the most studied cognitively stimulating factor, and many longitudinal studies have found that higher educational attainment is linked to cognitive reserve (Le Carret et al., 2003; Mungas et al., 2018; Wilson et al., 2019). It is suggested that those with higher

education do better on cognitive performance tests in older age and delay cognitive impairment until the very end of life (Alley et al., 2007; Wattmo et al, 2014; Wilson et al., 2019; Zahodne et al., 2015). Additionally, higher education has been linked to an increased odds of reverse transition from MCI to intact cognition or to a less impaired state (Iraniparast et al., 2022; Xue et al., 2019). Cognitively stimulating occupations, physical activity and multilingualism have also been shown to increase cognitive reserve and maintain cognitive functioning later in life (Ihle, Oris, Fagot, & Kliegel, 2016).

2.2 Multilingualism

Investigating factors that build cognitive reserve capacity (e.g., multilingualism) is key to developing interventions and strategies that will preserve cognitive function in later life. Various studies have found that speaking two or more languages has cognitive benefits and contributes to cognitive reserve (e.g., Bialystok et al., 2007; Perani et al., 2017; Kowoll et al., 2016). This evidence concerning the number of languages spoken and cognitive function has primarily focused on the influence of speaking two languages (bilingualism). However, language research is inconsistent due to the different definitions and measures of multilingualism. To bring clarity to this research field, multilingualism will be defined here as speaking two or more languages. While multilingualism is commonly defined as the ability to speak multiple languages, the experience of multilingualism goes beyond a simple definition of the number of languages spoken. The complex conceptualization of multilingualism also encompasses the frequency and intensity of language use, age of language acquisition, and the context in which the language was learned. For example, lifelong bilingualism, in which an individual frequently uses both languages throughout their lifetime, is associated with a delayed age of onset of dementia, indicating that speaking two or more languages is relevant to brain health in aging (Atkinson,

2016; DeLuca et al., 2019; Gold, 2016; Kowoll et al., 2015; Olsen et al., 2015). Furthermore, a greater degree of lifelong bilingualism (i.e., low, moderate, or high use) has been found to be significantly protective against AD (Gold et al, 2013; Jafari et al., 2015; Perani et al., 2017). Before exploring the literature of the association between the number of languages spoken and cognitive status (dementia and MCI), cognitive advantages and disadvantages of multilingualism as well as the potential mechanism of multilingualism to influence cognition will be discussed.

2.2.1 Cognitive Advantages of Multilingualism: "The Multilingual Advantage"

Language is a complex ability of the human brain that requires a great amount of cognitive flexibility and switching. Full knowledge of a language requires lexicon (remembering the words), phenology (sound system), orthography (writing system), syntax (grammar), and pragmatics (expressing oneself) (Pennington, 2014). The ability to speak many languages is associated with a greater cognitive control function in language-related and language-unrelated task performances (Bialystok, 2015; Kroll & Bialystok, 2013).

A growing body of literature has suggested that multilingualism leads to greater performance on a range of executive function tasks (reviews by Bialystok et al., 2009; Hilchey & Klein, 2011). These enhanced executive function tasks include task-switching, conflict-resolution skills, attention control, and inhibitory control (Bialystok, 2017; Prior & Gollan, 2011; Suchy, 2009; Valian, 2015). The effect of multilingualism on executive function in older adults is assessed via various cognitive performance tests, including the Stroop test, Trail making test, Verbal fluency test, and Clock drawing test (Faria et al., 2015; Valian, 2015). Multilinguals have outperformed monolinguals on tasks of inhibition, such as Simon tasks (Cox et al., 2016), Stroop (Bialystok, Craik, et al., 2014), and Flanker (Abutalebi et al., 2015). In addition, multilinguals also perform better on task-switching tests (Gold, Kim, et al., 2013) and working memory

(Bialystok et al., 2004; Zahodne et al., 2014). The multilingual advantage in executive function has been reported across the lifespan, including in infants (Brito & Barr, 2012), children (Bialystok & Martin, 2004; Diaz & Klingler, 1991), and young adults (Costa et al., 2008; Prior & MacWhinney, 2010) as well as older adults (Bialystok, Craik, et al., 2014; Gold, Johnson, & Powell, 2013). These cognitive benefits are also seen in people who learn a second language later in life (Linck et al., 2008; Craik et al., 2010).

Moreover, those who speak more than one language have a higher metalinguistic awareness, which is the ability to identify language as a system that can be manipulated and changed (e.g., code switching) (Gold, Johnson, & Powell, 2013). Older multilinguals are also said to have improved memory, visual-spatial skills, and even creativity compared to older monolinguals (Schroeder & Marian, 2012). Besides cognitive benefits, there are also social benefits from being multilingual, as it facilitates cross-cultural communication and brings greater cultural awareness (Krizman et al., 2012).

In addition to performing differently on cognitive tests, the brain anatomy of multilinguals is also different from that of monolinguals (Luk et al, 2012). Neuroanatomical differences in lifelong bilingualism support these findings, with structural differences in the brains of lifelong bilingual older adults compared to monolinguals (Olsen et al., 2015; review by Bialystok et al., 2016). Olsen and colleagues (2015) found that lifelong bilinguals exhibited greater grey and white matter volume in regions related to executive and language functions (frontal lobe and temporal lobe) compared to monolinguals. Additionally, higher proficiency in languages is correlated with a higher grey matter volume in the left lateral frontal cortex and the anterior cingulate cortex, the parts of the brain that control language switching (Gold, Johnson, & Powell, 2013; Duncan et al., 2018). Multilinguals have high levels of activation in brain

regions—left prefrontal cortex, temporal context, and inferior parietal lobule—associated with executive function, making the bilingual brain more resistant to brain atrophy or disease pathology (Bak et al., 2014; Bialystok et al., 2016; Olsen et al., 2015).

Multilingualism has been suggested to have a protective effect against cognitive impairment through the mechanism of task-switching and language inhibition (Bialystok, 2017; Hernandez et al., 2013). Multilingualism involves consistent cognitive effort, mental juggling, and cognitive control. A multilingual individual must inhibit the other spoken language(s) to speak that one required language in a situation (Prior & Macwhinney, 2010). A bilingual individual's ability to control which language they speak and to constantly switch between languages continually exercises executive function abilities and may confer a broader cognitive advantage (Bialystok, 2017; Weissberger et al., 2015; Wiseheart et al., 2016). Cognitive reserve capacity is increased in bilinguals, as a result of this constant task-switching and cognitive stimulation (Bak, 2016). Given this greater cognitive reserve, bilinguals would thus be expected to require more severe AD neuropathology before showing any clinical symptoms (Anderson et al., 2020).

2.2.2 Cognitive Disadvantages of Multilingualism: "The Multilingual Disadvantage"

Even though there are more cognitive advantages than disadvantages to being multilingual, there are still some negative effects. Overall, monolinguals have a larger vocabulary in that one single language they speak compared to multilinguals, although multilinguals have a larger total vocabulary combined across all of their languages (Bialystok et al., 2008). For example, it takes longer for multilinguals to retrieve individual words on average (i.e., poorer performance on verbal fluency tasks) due to a conflict between cross-language words: this phenomenon is called tip-of-the-tongue word retrieval (Bialystok, 2009).

Monolinguals can outperform multilinguals in retrieving low frequency words, which is measured by the accuracy of naming and speed (Gasquoine, 2016). During the Peabody Picture Vocabulary Test III, monolinguals had higher vocabulary test scores compared to multilinguals (Bialystok et al., 2008). In multilinguals, language processing becomes more effortful because of reduced linguistic representation (vocabulary) in each language compared to monolinguals (Bialystok et al., 2008). Monolinguals score higher on letter and category fluency tests compared to multilinguals, perhaps related to cross-language interference (Bialystok et al., 2008). During the Boston naming task, multilinguals have increased naming difficulty with slower speed in naming pictures (Gollan et al., 2005).

2.3 Multilingualism and MCI/Dementia

Studies on the association between multilingualism and dementia are fairly common, whereas they are very limited for the association between multilingualism and MCI, particularly aMCI and naMCI. Thus, the following literature review summarizes evidence for both dementia and MCI. Some studies have associated multilingualism with a later onset or reduced risk of MCI and dementia. However, not all studies have observed such relationships. These differences in results may be due to confounding factors, such as level of education, *APOE*, socioeconomic factors, and immigrant status, in addition to other methodological differences.

2.3.1 Association Between Multilingualism and Dementia

Considerable inconsistency in the literature remains regarding the protective effect of the number of languages spoken on dementia. These inconclusive findings across studies may be explained as a result of differences in populations (clinic-based vs. population-based samples), differences in the definition of multilingualism, differences in measurement of outcomes (MCI, dementia, cognitive test scores, overall domain-specific scores, or global cognitive function),

type of outcome (age at onset vs. risk of dementia), and study designs (cross-sectional vs. longitudinal studies).

Previous studies investigating multilingualism and dementia/AD have found a significant association between bilingualism and the delay in the age of onset of dementia or AD (Alladi et al., 2013; Bialystok et al., 2007; Chertkow et al., 2010; Craik et al., 2010; Woumans et al., 2015). However, evidence of a protective effect of bilingualism on dementia (a four to five-year delay in the age of onset) has primarily been based on cross-sectional studies of clinic-based populations. For example, in a retrospective review of patient charts, Bialystok et al. (2007) found that, among Canadians, there was on average a four-year delay in the age of onset of dementia among bilinguals (measured as fluently speaking two languages since early adulthood) compared to monolinguals, although onset of dementia was self-reported, which might have led to recall bias and inaccuracy (Bialystok et al., 2007). Furthermore, other clinic-based studies have found similar delays of 4.5 years (Alladi et al., 2013) and 5.1 years (Craik et al., 2010) in the onset of dementia among bilinguals compared to monolinguals. Many clinic-based studies have also found that this protective effect of multilingualism persisted even after accounting for other cognitively stimulating activities, such as education and occupation (Alladi et al., 2013; Bialystok, Craik, et al., 2014; Craik et al., 2010; Gollan et al., 2011; Kave et al., 2008; Perquin et al., 2013; Schweizer et al., 2012). Further studies have shown that SES (Chertkow et al., 2010; Gollan et al., 2011) acts as a confounder and may also play a role in delaying the onset of clinical symptoms.

In contrast to clinic-based studies, population-based studies have not generally supported an association between bilingualism and dementia/AD (Crane et al, 2010; Hack et al., 2019; Lawton et al., 2015; Ljungberg et al., 2016; Mukadam et al., 2018; Yeung et al., 2014; Zahodne

et al., 2014). For example, Crane et al. (2010) found no association between speaking two languages and cognitive impairment in Japanese-American older men. Studies across diverse population-based samples found similar null results between bilingualism and onset of dementia or risk of dementia in community-dwelling older adults (Yeung et al., 2014; Mukadam et al., 2018; Ljungberg et al., 2016).

However, some population-based studies have reported a protective effect of multilingualism on dementia when the measure of multilingualism focuses on those speaking more than two languages (Chertkow et al., 2010; Perquin et al., 2013; Kave et al., 2008). For example, Chertkow et al. (2010) found that speaking three or more languages was protective against dementia, but there was no significant benefit in bilingual individuals (those speaking two languages). Greater number of languages spoken provided additional years of delay in the age of onset of dementia in immigrant participants, suggesting a dose-response (Chertkow et al., 2010). As well, Perquin et al. (2013) found that only individuals who spoke more than two languages showed a lower risk of dementia and delayed age of onset of dementia compared to bilinguals. Furthermore, a study conducted by Kave et al. (2008) found that cognitive test scores significantly differed among Israeli participants speaking two versus three versus four languages, after accounting for the effects of age, gender, immigration status and educational level. Those speaking more than four languages were more likely to be cognitively intact compared to bilinguals or trilinguals (Kave et al., 2008). A study conducted by Hack and colleagues in the Nun Study (2019) found that only 6% of individuals speaking four or more languages developed dementia compared to 31% of monolinguals. A significant protective effect of the number of languages spoken on the risk of dementia was observed only in participants speaking four or more languages. However, these findings were attenuated by other linguistic ability

characteristics, such as written language skills, specifically idea density (Hack et al., 2019). See Section 2.4 for a summary of the evidence on the association between other measures of language and cognitive function.

2.3.2 Association Between Multilingualism and MCI

Evidence regarding an association between multilingualism and overall MCI is very limited and to date is based on only a few clinic-based studies and one population-based study. Evidence suggests that bilingualism is protective against MCI, delaying the age of onset of clinical symptoms and date of first clinic visit compared to monolinguals (Berkes et al., 2020; Bialystok, Craik, et al., 2014; Calabria et al., 2020; Li et al., 2021; Ramakrishnan et al., 2017) as well as reducing the risk of MCI (Wilson et al., 2015). For instance, Bialystok et al. (2014) found that bilinguals with MCI had an onset of symptoms 4.7 years later, and bilinguals with AD had an onset of symptoms 7.3 years later compared to monolinguals with MCI and AD, respectively. Ramakrishnan et al. (2017) found that the onset of MCI in bilinguals was 7.4 years later than in monolinguals, after adjusting for education. Another clinic-based study found that bilingual patients were diagnosed with MCI two years later than monolingual patients (77.8 years vs. 75.5 years, respectively), after controlling for sex, immigration status, and education (Berkes et al., 2020). Moreover, a more recent study by Calabria and colleagues (2020) found that active bilinguals (high proficiency in both languages with a balanced usage of both languages) had a two-year delay in the age of onset of MCI compared to passive bilinguals (being able to understand a second language, but with little or no usage of the language), even after controlling for other intellectual factors (occupation and educational level) across the lifespan. The above clinic-based studies reported a significant protective effect of bilingualism on later onset of symptoms for overall MCI, but they differed with respect to the length of delay in symptoms of

MCI (Berkes et al., 2020; Bialystok et al., 2014; Calabria et al., 2020; Ramakrishnan et al., 2017). However, another clinic-based study from the U.S. found no significant difference between the age of onset of MCI in bilinguals and monolinguals within the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (Li et al., 2021). Furthermore, a population-based study found that second language instruction during youth (i.e., at least 5 years of instruction by age 18) was associated with a lower risk of developing overall MCI, after models were adjusted for age, sex, and education (Wilson et al., 2015). The results suggest that cognitively stimulating experiences during childhood are associated with better cognitive health in later life.

The association between multilingualism and MCI subtypes has rarely been investigated. To my knowledge, only two clinic-based studies investigated the potential influence of bilingualism on the age at onset of MCI subtypes (Ossher et al., 2013; Ramakrishnan et al., 2017), and one population-based study examined the risk of developing aMCI and naMCI (Wilson et al, 2015). The study conducted by Ossher and colleagues (2013) found that bilinguals with single-domain aMCI demonstrated a later age of diagnosis of four years (mean = 79.4 years) than monolinguals (mean = 74.9 years). This protective advantage was not observed in multiple-domain aMCI, suggesting that the protective advantage of lifelong bilingualism may be specific to single-domain aMCI (Ossher et al, 2013). Previous studies have found that lifelong bilingualism was associated with a delayed age of onset of AD rather than other dementias (Bialystok et al., 2007). Thus, it might be that lifelong bilingualism (measured as speaking two languages daily at least in early adulthood) leads to a delayed age of onset of single-domain aMCI (Ossher et al, 2013). Since single-domain MCI is characterized only by memory impairment, it may be that lifelong bilingualism plays a role in preserving memory. Ramakrishnan et al. (2017) found that bilinguals with aMCI had a later age at onset than

monolinguals (mean = 63.6.vs. 55.3 years), while this was not seen for naMCI. However, Wilson and colleagues (2015) found that early-life language instruction was associated with a lower incidence of naMCI but not aMCI.

Overall, evidence of an association between multilingualism and overall MCI as well as its subtypes is very limited. The evidence of a protective effect of bilingualism on delaying the age of onset of MCI in clinic-based samples is unclear and inconsistent. The evidence of an association between bilingualism and risk of overall MCI in a population-based sample is limited to one study. Evidence of a stronger protective multilingual effect for aMCI vs. naMCI is limited and inconclusive.

2.3.3 Covariates for Multilingualism and MCI/dementia

Covariates (confounding variables and effect modifiers), such as age, genetic factors, immigration status, primary language spoken, education, and occupation, may play an important role in the association between multilingualism and cognitive status (see Appendix D).

As age is a key risk factor for cognitive impairment, many studies have investigated the role of age and whether it confounds or modifies the association between multilingualism and cognition. In addition, previous studies have shown that carrying an *APOE*-ε4 allele is strongly associated with an increased risk of developing dementia (Ungar et al., 2014) (see Section 2.1.4.1 for a more detailed discussion of *APOE*-ε4 as a risk factor for cognitive impairment). However, this established genetic risk factor has rarely been controlled for in previous studies looking at the association between multilingualism and cognitive status, and thus reflects an important gap in current evidence.

Immigration status is another common covariate in language studies. Because immigrants have a higher probability of speaking multiple languages, they are over-represented in

multilingual samples (Woumans et al., 2015). Most immigrants will learn the new language to a high level of proficiency as the environment will force them to quickly learn the language and place a greater demand on their cognition (Kave et al., 2008). Furthermore, a selection bias, called the healthy immigrant effect, could confound the association between language and MCI/dementia. This happens when an immigrant population is healthier than the non-immigrant population of a country and could lead to a reduced risk of MCI and dementia in these immigrant populations (Fuller-Thomson, 2015). Chertkow and colleagues (2010) found that Canadian multilinguals, of which 50% were immigrants, had a five-year delay in the onset of AD compared to Canadian-born monolinguals. However, other studies did not find an effect of immigration status on the relationship between the number of languages spoken and dementia or AD (Bialystok, Caik, et al., 2014; Craik et al., 2010; Lawton et al., 2015). On the other hand, an opposite, unhealthy immigrant effect could also cause selection bias, where the immigrant population could face greater health disparities related to trauma and stress before and after immigration compared to non-immigrants, leading to their increased risk of MCI. This might be explained by higher stress levels related to fleeing war or conflict, leading to unhealthy behaviours such as substance use and unhealthy diets; in addition, they are more likely to be affected by poverty, unemployment, and difficulty accessing services due to language barriers (McDonald & Kennedy, 2004). In summary, immigrant status or country of birth may play a role in influencing the association between multilingualism and cognitive status.

Furthermore, cognitive performance on tasks can be impacted by the participant's primary language. Participants who speak English as a second language may perform worse on language-based cognitive tasks than those who speak English as a first language (Yeung et al., 2014). Highly language-based cognitive tasks include Verbal Fluency tests (i.e., category and

letter fluency), tests typically included in cognitive assessments to diagnose MCI and other cognitive states.

Additionally, education is a well-established protective factor against cognitive impairment in old age. A few studies have found that individuals who have lower educational attainment are less likely to improve from MCI to intact cognition (Iraniparast et al., 2022; Wei et al., 2016). Likewise, occupation has also been shown to influence the relationship between multilingualism and dementia (Woumans et al., 2015). Stressful and non-cognitively stimulating occupations modified the protective effect of multilingualism, leading to an earlier diagnosis of dementia and AD (Woumans et al., 2015). See section 2.1.4.2 for further details on education and occupation as risk factors for cognitive impairment.

Besides the number of languages spoken, other measures of linguistic abilities also have the potential to influence the association between multilingualism and cognitive status.

2.4 Association between Linguistic Ability and Cognitive Function

The impact of language on dementia may extend beyond the number of languages spoken to encompass writing abilities. The cognitive demand of writing requires great amounts of processing capacity and working memory (Olive, 2012; McCutchen, 2000). Working memory is a limited cognitive system that can hold temporary information. When learning a new language, working memory is particularly relevant. For example, individuals who are learning English may not have automatized spelling and grammar, thus a large amount of their working memory will be engaged with those aspects, at the expense of written content or even adaptation to the reader (Olive, 2012; McCutchen, 2000). Similarly, learners who have not yet automatized the mechanics of writing (i.e., holding the pen or typing on the keyboard) are likely to use the majority of their working memory capacity for the mechanics (Olive, 2012; McCutchen, 2000).

Consequently, they would not be able to focus as much on content or grammar due to competing demands on their cognitive resources. An individual's writing skills depend on their cognitive resources. In writing, we must juggle motor skills, content, ideas, language, spelling, grammar, and the reader, while simultaneously writing a text (Olive, 2012; McCutchen, 2000). Thus, building cognitive reserve through writing skills via the mechanism of increasing working memory capacity may be one way to decrease cognitive impairment later in life.

In a longitudinal community aging study, illiterate (not being able to read or write) participants were almost three times as likely to have dementia compared to literate participants (Rentería et al., 2019). In another longitudinal population-based study, the Nun Study, written linguistic measures (idea density and grammatical complexity) were collected in early adulthood from autobiographies written at a mean age of 22 years (Snowdon et al., 1996). Low idea density was also associated with an increased risk of MCI, lower brain weight, higher degree of cerebral atrophy, more severe neurofibrillary pathology (Riley et al., 2005), decline in global cognition, poor cognitive function, and premature death in late life (Snowdon et al., 2000). Low idea density in early life had a stronger association with poor cognitive function than did low grammatical complexity (Snowdon et al., 1996; Riley et al., 2005). Furthermore, AD was confirmed in all of those with low idea density and in none of those with high idea density (Snowdon et al., 1996). Hack and colleagues (2019) found that written linguistic ability (specifically idea density) was a stronger predictor of dementia than multilingualism, rendering the impact of number of languages on dementia non-significant. This suggests that there may be a ceiling effect, where a maximum level of protection may have already been achieved through written linguistic ability, with no further benefit from additional language skills such as multilingualism.

These studies suggest that the impact of language on the risk of cognitive impairment may extend beyond the number of languages spoken to encompass writing and reading abilities, and show the importance of controlling for other linguistic abilities besides the number of languages spoken when investigating the association between multilingualism and cognitive impairment. Further research is needed to identify language characteristics most salient for predicting the risk of cognitive impairment, which could be useful in the design of strategies to promote multilingualism and other linguistic training to reduce the risk of cognitive impairment.

2.5 Conclusion

Targeting modifiable factors is key to the prevention of cognitive impairment. Thus, it is important to understand how cognitively stimulating factors (e.g., education, multilingualism, and other linguistic measures) affect the brain and have the potential to increase or maintain cognitive function in late life. Evidence concerning the association between multilingualism and MCI as well as its subtypes is limited and warrants further investigation. Multilingual speakers are highly variable, differing with respect to various characteristics that can impact their cognitive status. The complex association between multilingualism and cognitive status can be influenced by factors such as age, genetics, immigrant status, education, and other linguistic measures, such as written ability. A better understanding of the impact of multilingualism and other linguistic measures could provide a foundation for the development of language-based strategies to reduce the risk of MCI or its subtypes to promote healthy cognitive aging.

3.0 Study Rationale and Research Questions

3.1 Study Rationale

The association of multilingualism with cognitive impairment is complex and unclear. Very few studies have examined the link between multilingualism and MCI and even fewer studies have investigated the different subtypes of MCI, as most studies have focused on dementia and AD as their outcomes. In addition to differences in measures of multilingualism and cognitive states, previous studies have focused on clinic-based samples rather than population-based samples, which are less prone to sampling bias and more representative of the general population. Population-based samples generate important findings regarding the risk of cognitive impairment, whereas clinic-based samples can only assess age of onset of cognitive impairment among those who already have memory concerns. Moreover, most previous studies do not account for important confounders (i.e., genetic factors and SES) or other measures of language ability.

The current study uses secondary data from the Nun Study, a longitudinal study of 678 Roman Catholic religious sisters from the School Sisters of Notre Dame in the US. This study fills the gaps in the literature regarding the association between multilingualism and MCI as well as its subtypes using a population-based sample. More specifically, this study adds knowledge on the number of languages spoken as a predictor of MCI and its subtypes in older women. As well, past literature has been criticized for lack of control for key covariates. This study minimizes the effect of confounders seen in other studies because the Nun Study provides a homogeneous sample of participants who have had similar lifestyles, housing conditions, incomes, medical access, social lives, marital and reproductive histories, smoking status, and alcohol use, as well as SES. It is particularly important to adequately control for the effect of social and income

inequalities, such as SES, when conducting studies with languages and cultural diversity (e.g., immigrant status). Furthermore, this study assessed the effect of *APOE*-ε4 allele status on MCI. *APOE* status has rarely been controlled for in other studies of multilingualism and dementia, and has not been addressed in the limited studies of multilingualism and MCI. In addition, this study evaluated the influence of written linguistic measures (specifically, idea density and grammatical complexity) on cognitive status, to provide a broader assessment of the impact of linguistic ability on MCI beyond the simple definition of number of languages. By addressing these gaps in the literature, this thesis contributes to our understanding of the complex association between linguistic ability and MCI, providing evidence that may be used to inform language-based strategies aimed at reducing the risk of MCI or its subtypes.

The objectives of this study are: 1) to investigate the relationship between multilingualism and overall MCI; 2) to determine if the association between multilingualism and MCI varies by subtypes of MCI (non-amnestic MCI vs. amnestic MCI); and 3) to determine if the association between multilingualism and MCI (overall, naMCI, and aMCI) persists after controlling for key covariates (demographic, SES, genetic, and other linguistic measures).

3.2 Research Questions

1. Is multilingualism (speaking more than one language) associated with a reduced risk of overall MCI, after adjusting for key covariates (age, *APOE*, country of birth, education, idea density, and grammatical complexity)?
2. Does the association of multilingualism with MCI vary by subtype (amnestic MCI vs. non-amnestic MCI), after adjusting for key covariates (age, *APOE*, country of birth, education, idea density, and grammatical complexity)?

4.0 Methods

4.1 Literature Search Strategy

To investigate the literature on the relationship between multilingualism and MCI, a systematic literature search was conducted using PubMed Medline and PsycINFO in April 2021 and updated in April 2022.The first search was conducted using the PubMed database (1950 to present). Specific keywords (see Appendix A - Table A1) were used relating to multilingualism (as the exposure) and MCI (as the outcome). After conducting the first search, additional keywords related to "age" and 'time" were included (e.g., aged, aging, prospective study) to narrow the research strategy to the most relevant results. Medical Subject Heading (MeSH) terms were used to conduct the most exhaustive search of relevant studies. The literature search strategy was further restricted to articles written in French or English and that used human participants. Refer to Appendix A, Table A1, for a full summary of the literature search used in PubMed. The search strategy from PubMed retrieved 1069 records to be screened manually for relevant articles.

A second search was conducted using the PsycINFO database (1840 to present) in April 2021 and updated in April 2022. The same search concepts from the PubMed database were used to retrieve relevant literature in PsycINFO. The search was limited to peer-reviewed articles and a date limit was not set in the search strategy. Refer to Appendix A, Table A2 for a full list and description of the search strategy. In the PsycINFO search, 1662 articles were retrieved. After adding both the results from PubMed and PsycINFO, a total of 2731 articles were screened and assessed for inclusion.

After all duplicate articles were removed (n=498), the remaining 2233 articles were screened in three steps. First, all articles were screened on their title alone based on the exposure,

outcome, and sample of interest. Only those that remained after the preceding step continued to the next step. In this next step, articles were screened based on the title and abstract. Last, the remaining articles underwent a full-text assessment for eligibility. During the screening process, articles were excluded if: i) the exposure was not multilingualism; ii) the outcome was not MCI, non-amnestic MCI, amnestic MCI, dementia, or AD; or iii) the sample only included participants under the age of 65 years. Once all articles were screened and exclusion criteria were applied, a total of 32 articles remained. Refer to Appendix A, Figure A, for a flowchart of the systematic literature search strategy. A summary of each of the final 32 articles can be found in Appendix B.

4.2 Data Source: The Nun Study

4.2.1 Nun Study Design and Population

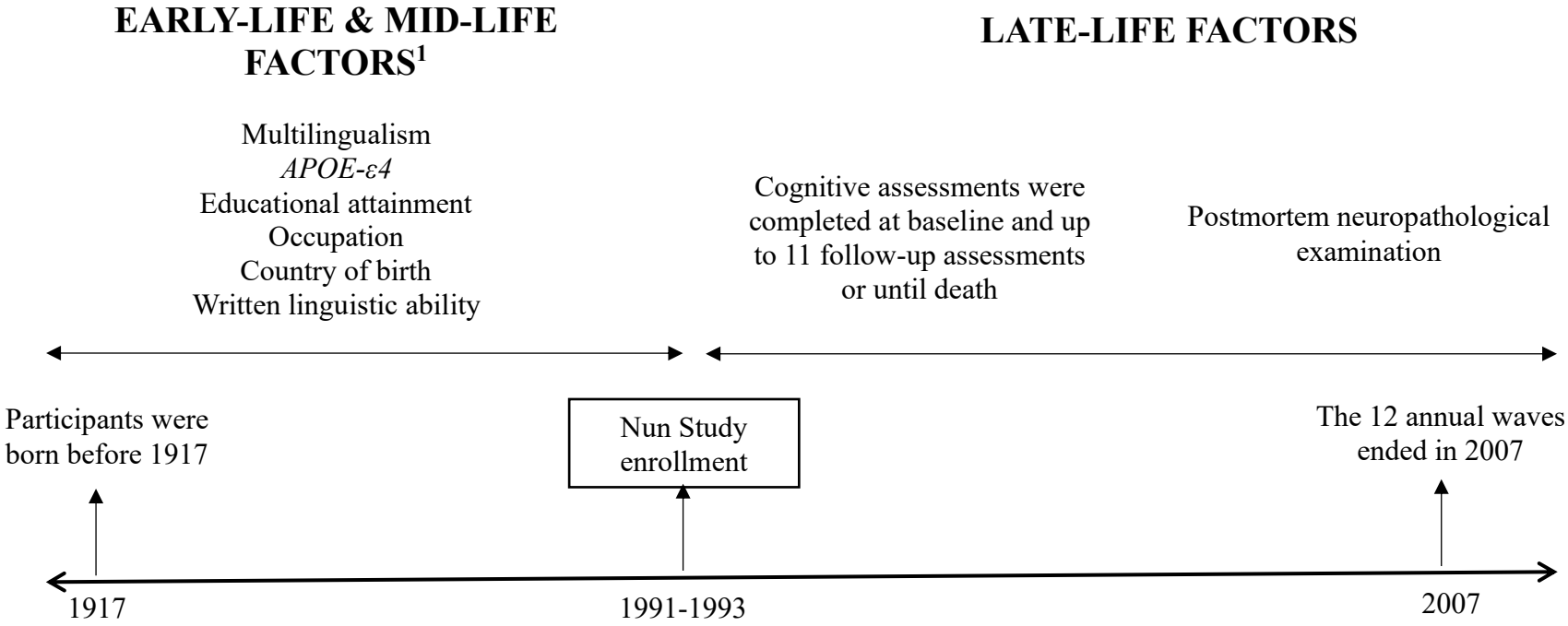
The Nun Study is a longitudinal study related to aging with a focus on cognitive decline and risk factors for AD and dementia. In 1986, Dr. David Snowdon proposed his research on aging to the School Sisters of Notre Dame congregation in Minnesota and began a pilot study (Snowdon, 2002). Between 1991 and 1993, a full-scale study recruited members of the School Sisters of Notre Dame from across the United States (Snowdon, 2002). Eligible participants were those who were born before 1917 and living in religious communities in the midwestern, eastern, and southern United States (n=1031); of these, 678 (66%) consented to participate (Snowdon et al., 1996). This led to the beginning of what is now called the Nun Study, which included 678 sisters between the ages of 75 to 106 years at baseline, with an average age of 83 (Snowdon et al., 1996). The sisters gave permission for investigators to have access to their medical and archival records and agreed to annual cognitive and physical testing as well as donation of their brain after death for examination (Snowdon, 2002). The 678 participants did not differ

significantly from the 353 non-participants in their average age at baseline, rate of mortality, race, or country of birth (Snowdon et al., 1996).

The Nun Study is unique since it reduces many potential confounders by studying a relatively homogeneous group. All participants are women. The religious sisters lived different lives before entering the convent (childhood and adolescence), but when they joined the convent in adulthood, they became a relatively homogenous group in terms of social activities, social support, drug and alcohol use, housing, income, and access to health care services as well as reproductive histories and marital status (Snowdon et al., 1996). Additionally, the sisters had similar occupations, since the majority served as teachers; a small number were domestic workers and nurse aides (Snowdon et al., 1996). This homogeneity in adulthood allows us to control for many potential confounders and provides an ideal population in which to examine how early-life factors can impact cognition later in life.

4.2.2 Data Collection

Longitudinal data were collected starting in 1991 and included baseline and up to 11 follow-up cognitive and physical assessments that were performed approximately every year. Cognitive function was measured through the CERAD neuropsychological battery (Morris et al., 1989) and ADL measures (Kuriansky & Gurland, 1976). The Nun Study also had access to convent archival records, which included information on early-life and mid-life factors from hand-written autobiographies and a survey administered in 1983 by the School Sisters of Notre Dame (Patzwald & Wildt, 2004) (see Section 4.4 for further details on measures). The timeline of data collection for the Nun Study is presented in Figure 1.



[1]Early-life and mid-life factors were either collected during the study (e.g., *APOE*-ε4), obtained retrospectively from the 1983 survey questionnaire (e.g., multilingualism, country of birth) and written autobiographies (idea density and grammatical complexity), or extracted from archival records (e.g., educational attainment, occupation).

Figure 1. Timeline of Data Collection of the Nun Study

4.3 Analytic Sample and Subsample

To assess the association between multilingualism and MCI in older adults from the Nun Study, two different samples were analyzed. The analytic samples were restricted to the main analytic sample (n=384) and the linguistic ability subsample (n=122).

In the main analytic sample, participants with complete data available on multilingualism (n=507) were included. Participants were excluded if they had missing data on MCI at first cognitive assessment (n=1), which requires data from the CERAD neuropsychological battery (Delayed Word Recall, Boston Naming, Verbal Fluency, Constructional Praxis) and MMSE as well as ADLs. Participants with dementia at the first cognitive assessment were excluded (n=85) as they do not contribute to the analysis, which compared MCI vs normal cognition. In addition, individuals were excluded from the main analytic sample if they had missing data on key covariates (age at baseline, *APOE,* country of birth, and education). The main analytic sample included 384 participants. Refer to **Figure 2** for a detailed description.

For sensitivity analyses, the main analytic sample was further restricted to university-educated teachers born in the US (n=335) to stringently adjust for the effect of occupation, education, and country of birth beyond what could be controlled in multivariable analyses. See **Appendix F** for the derivation of university-educated teachers subsample.

In the linguistic ability subsample, participants were excluded if they had missing data on multilingualism (n=171), MCI at first cognitive assessment (n=1), age at first cognitive assessment (n=0) and *APOE*-ε4 (n=15). Participants were also excluded if they had dementia at first cognitive assessment (n=85). For the linguistic ability sensitivity analyses, participants were further excluded if they had missing data on idea density or grammatical complexity (n=280). In

addition, this subsample was restricted to university-educated participants because of the few participants with less than a university education. The resultant sample (n=122) only included participants born in the U.S. Refer to **Figure 3** for a detailed description.

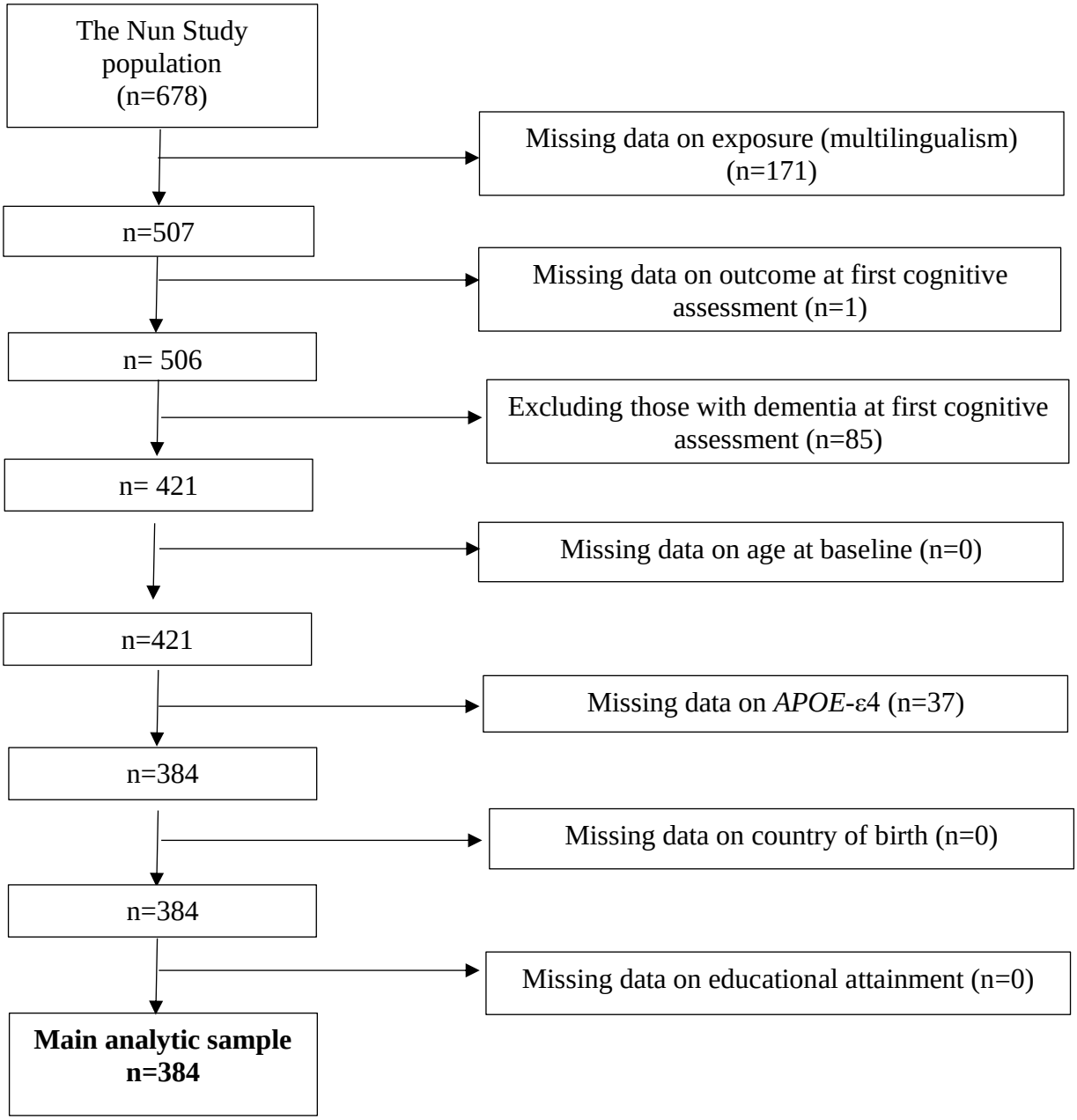


Figure 2. Derivation of the Main Analytic Sample

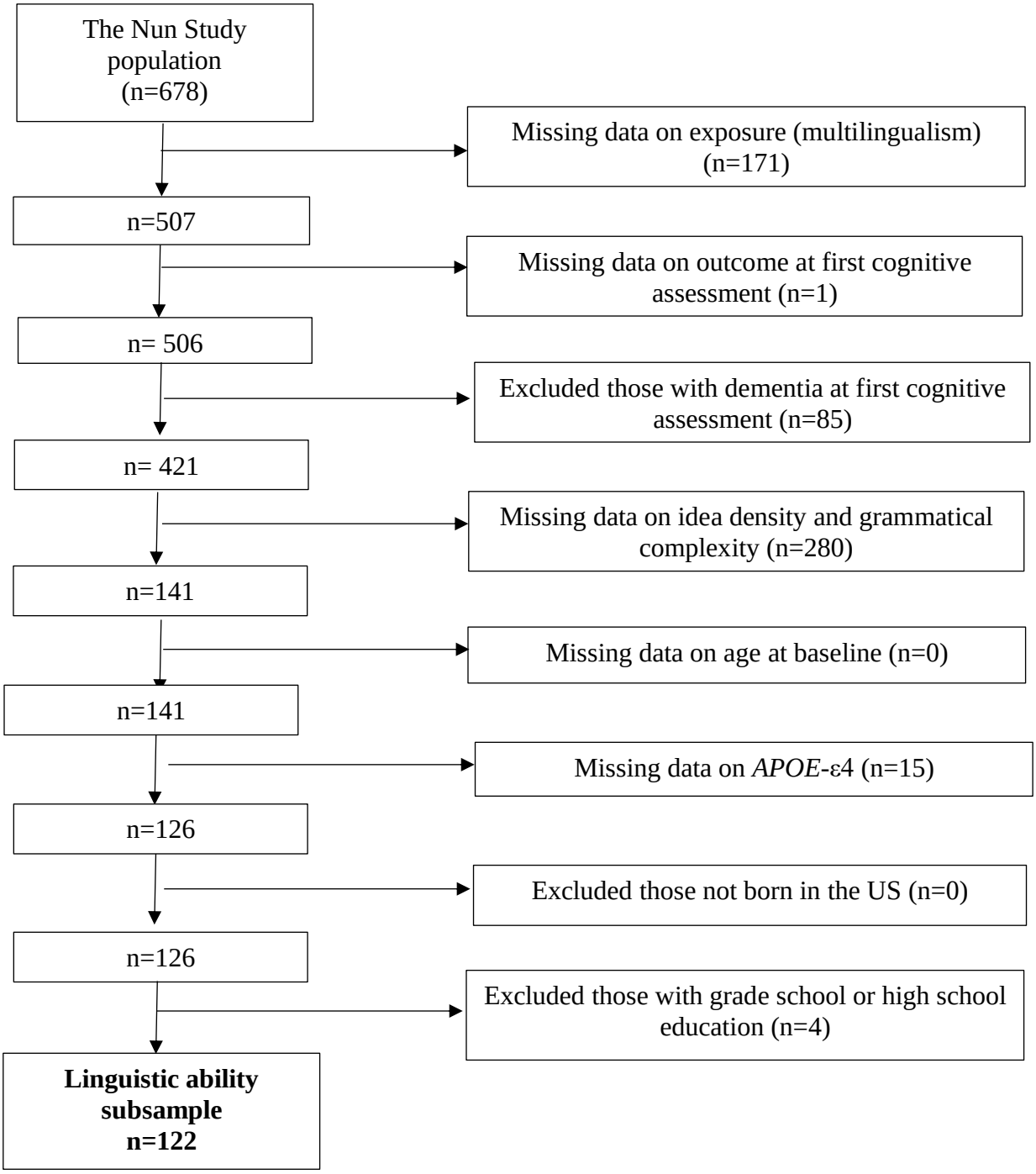


Figure 3. Derivation of the Linguistic Ability Subsample

4.4 Measures

4.4.1 Multilingualism

Data on multilingualism (number of languages) was obtained from the School Sisters of Notre Dame survey conducted in 1983, which was before the start of the Nun Study. The responses for multilingualism were used to help match sisters to foreign missionary work. The survey asked sisters to specify the first, second, third, and other languages they were proficient in (Patzwald & Wildt, 2004). Participants reported speaking from one to five languages; however, since speaking four or five languages was less frequently reported, these responses were collapsed into one category. Multilingualism (exposure) was investigated as both a four-level variable (2, 3, 4+ languages vs. 1 language as the reference category) and a two-level variable (2+ vs. 1 language as the reference category, and 4+ vs. fewer languages as the reference category). Supplementary analyses also assessed an exposure variable dichotomized as 4+ vs 1 language (Appendix J).

4.4.2 Cognitive States

Cognitive states were assessed at baseline and approximately every year for up to 11 follow-up assessments. Categories for cognition were classified into cognitive states including normal cognition, MCI, and dementia (Riley et al., 2002). Cognitive performance in the Nun Study was assessed using five measures from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery: Delayed Word Recall, Verbal Fluency, Boston Naming, Constructional Praxis, and the Mini-Mental State Examination (MMSE) (Riley et al., 2002), as well as performance on ADLs. Cut points on these tests for each cognitive status were based on CERAD normative data, which included women with comparable age and educational attainment (Morris et al., 1989). The CERAD neuropsychological battery

was used to evaluate cognitive domains such as attention, executive function, memory, visuospatial function, and language (Morris et al., 1989). Basic ADLs included feeding, dressing, walking, standing, and toileting. These were performance-based measures with the exception of toileting, which was reported by participants or health care staff.

MCI is the intermediate cognitive state between intact cognition and dementia, and participants with MCI did not meet criteria for intact cognition or dementia. MCI status was investigated at baseline assessment (cross-sectional data) as overall MCI and MCI subtypes (amnestic and non-amnestic MCI).

The diagnostic criteria for normal cognition, MCI, and dementia have been described previously and are summarized below (Morris et al., 1989). Refer to Table 1 for a detailed description of the diagnostic criteria for cognitive states in the Nun Study.

Intact cognition. Criteria for intact cognition were based on scores for Delayed Word Recall (≥5), Boston Naming (≥14), Verbal Fluency (≥12), and Constructional Praxis (≥9) tests, MMSE for global cognition (≥24), and ADLs ((Folstein et al., 1975; Kuriansky & Gurland, 1976). ADLs were defined as the ability to independently perform at least four of the five activities.

Mild cognitive impairment (MCI). Individuals with MCI did not meet criteria for intact cognition or dementia. MCI was diagnosed based on having at least one specific area of impaired cognitive function and could include impairment in global cognition based on the MMSE or in function based on ADLs (Riley et al., 2005; Kuriansky & Gurland, 1976). The MCI diagnosis combines the categories of mild impairment and global impairment previously described in the Nun Study (Riley et al., 2005). Individuals with mild impairment had: i) impairment in memory or another area of cognitive function; ii) intact global cognitive function, as measured by the MMSE; iii)

intact physical function as measured by ADLs; and iv) did not have dementia (Riley et al., 2005). The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean (<5 for Delayed Word Recall, <14 for Boston Naming, <12 for Verbal Fluency, and <9 for Constructional Praxis) (Morris et al., 1989). In contrast, those assessed with global impairment had an impaired score on the MMSE or ADLs. They may also have had additional impairments in other areas of cognitive function, but this was not required. None of the participants with global impairment had dementia (Riley et al., 2005).

Non-amnestic MCI and Amnestic MCI. MCI was further categorized into naMCI and aMCI subtypes. Participants with naMCI were diagnosed based on having intact memory (based on Delayed Word Recall performance) but impairment in at least one of the other three cognitive tests (Boston Naming, Verbal Fluency, Constructional Praxis). Participants with aMCI were diagnosed based on having impaired Delayed Word Recall regardless of performance on any of the other tests. For both naMCI and aMCI, individuals could be cognitively impaired based on the MMSE or ADLs, but impaired performance in the MMSE or ADLs was not required for an MCI diagnosis.

Dementia. Participants diagnosed with dementia showed impairment in memory and in at least one other cognitive domain, as well as impairment in ADLs (< 4) and decline from a previous cognitive level (Riley et al., 2005). The threshold used for cognitive impairment in each test for a diagnosis of dementia was below the 5^{th} percentile of the age-appropriate means (<4 for Delayed Word Recall, <13 for Boston Naming, <11for Verbal Fluency, and <8 for Constructional Praxis) (Morris et al., 1989). MMSE scores for global cognition were not used for a diagnosis of dementia.

Table 1. Diagnostic Criteria for Cognitive States in the Nun Study

CRITERIA	Intact Cognition	Overall MCI		Non-Amnestic MCI		Amnestic MCI		Dementia	
ADLs[1]	≥ 4	Impaired in MMSE (< 24) or ADLs (< 4) or neither						Impaired in ADLs (< 4)	
CERAD Neuropsychological battery:									
MMSE	≥ 24							Not used	
Delayed Work Recall	≥ 5	< 5	Impaired in at least one	≥ 5	Intact	< 5	Impaired	Impaired (< 4)	
Boston Naming	≥ 14	< 14		< 14	Impaired in 1-3 tests	< 14	Impaired in 0-3 tests	< 13	Impaired in 1-3 tests
Verbal Fluency	≥ 12	< 12		< 12		< 12		< 11	
Constructional Praxis	≥ 9	< 9		< 9		< 9		< 8	
Decline in function from a previous level	Absent	Absent		Absent		Absent		Present	

[1] The number of activities that can be performed independently (maximum of 5 ADLs)

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; MMSE = Mini-Mental State Examination; ADL = Activities of daily living; MCI = Mild Cognitive Impairment; Non-amnestic MCI = Non-amnestic Mild Cognitive Impairment; Amnestic MCI = Amnestic Mild Cognitive Impairment

4.4.3 Covariates

Age at baseline was measured based on date of birth from convent archives. ***APOE*-ε4** genotype was obtained from buccal cells of living participants or from brain tissue at autopsy of deceased participants (Patzwald & Wildt, 2004). *APOE*-ε4 genotyping was performed according to standard methods and blinded to cognitive status (Riley et al., 2002). *APOE*-ε4 status was defined as the presence of at least one *APOE*-ε4 allele and coded as a dichotomous variable (yes/no). Sensitivity analyses assessed the impact of including participants with the *APOE*-ε2ε4 genotype among the *APOE*-ε4 carriers, given the potential protective effect of *APOE*-ε2. Data on **country of birth** (whether the participant was born in the United States: yes/no), **primary language** (English spoken as the primary language spoken: yes/no) and **educational attainment** were collected from the 1983 survey questionnaire (Patswald & Wildt, 2004). Educational attainment was categorized as grade school, high school, bachelor's degree, and master's degree or higher. Information on **occupation** was obtained from mission cards, which had data on the employment of each participant after entering the convent (Patzwald & Wildt, 2004). A dichotomous variable for occupation was derived, where one category included all teachers while the other category included all other occupations (domestic work and nurse aids).

Measures of written language skills (**idea density and grammatical complexity)** were based on handwritten autobiographies available from the convent archives (Patzwald & Wildt, 2004). Idea density was defined as the average of ideas expressed every ten words in the autobiographies (Kintsch & Keenan, 1973). Grammatical complexity scores ranged from zero (simple one-clause sentences) to seven (complex sentences of multiples clauses) (Cheung & Kemper, 1992). Idea density and grammatical complexity measures were ranked within convents and were categorized into quartiles (Snowdon et al., 1996). These linguistic measures were

available for only a subsample of participants (180 autobiographies) and sensitivity analyses were conducted on the subsample with these measures.

4.5 Data Analysis

All analyses were conducted using SAS Studio Enterprise Edition 3.6 (SAS Institute Inc., Cary, North Carolina).

4.5.1 Descriptive Analysis

To provide an overall description of the main analytic sample and subsamples, univariate and bivariate analyses were conducted on all variables (exposures, outcomes, and covariates). Univariate analyses (i.e., means and proportions) were performed for the exposure, outcome, and covariates. Bivariate analyses cross-tabulated the exposure and covariates with the outcome. Pearson chi-square tests were used to assess the significance of associations between categorical variables when the sample sizes were large enough (i.e., cell counts greater than or equal to five). Fisher's exact tests were used for small cell counts (less than five). Furthermore, t-tests were used for bivariate analyses assessing continuous variables across two outcome categories (i.e., intact cognition vs. overall MCI). The Satterthwaite method was used for unequal variances and the pooled method was used for equal variances. ANOVA tests were used for bivariate analyses assessing continuous variables across three outcome categories (i.e., intact cognition, naMCI, and aMCI).

4.5.2 Multivariable Analysis

Logistic regression modelling with odds ratios (OR) and 95% confidence intervals (CIs) was used to address the two research questions. ORs represent the ratio of the odds of exposure (e.g., multilingualism) among cases (e.g., those with MCI) to the odds of exposure among controls (e.g., those who were cognitively intact). An OR=1 suggests there is no association

between the exposure and outcome, whereas an OR>1 and an OR<1 reflect risk factors and protective factors, respectively. Profile likelihood-based estimation for confidence intervals was used because it is the preferred method for relatively small samples and it allows for asymmetric CI estimates of nonlinear models (Evans et al., 1996).

Key covariates in models included age at baseline, *APOE*, country of birth, and education. When primary language spoken was included in the logistic regression models, it was not a significant predictor of overall MCI and did not substantially affect the point estimate, but it widened the confidence intervals (reduced the precision). Thus, primary language was not included in the logistic regression models presented. First-order interactions between each of the exposure variables and covariates were tested at $p<0.05$. There were no significant interactions in any of the models and thus the models were not stratified.

To consider the impact of other linguistic ability measures on the association between multilingualism and MCI, a sensitivity analysis was conducted on a linguistic ability subsample. These models included idea density and grammatical complexity as additional covariates.

Additional sensitivity analyses were conducted on a subsample of university-educated teachers (n=335) (see Appendix H). The vast majority of the Nun Study participants were teachers with a bachelor's degree or higher, limiting the ability to fully adjust for potential confounding by education and occupation using multivariable analysis. Thus, restriction rather than adjustment in multivariable analyses was used as a strategy to address confounding more stringently by education and occupation.

Binomial logistic regression was used for the two-category outcome in Research Question 1 (overall MCI vs. intact cognition). Multinomial logistic regression models were developed for the three-category outcome in Research Question 2 (intact cognition vs. naMCI vs.

aMCI) using the link=logit command under PROC LOGISTIC. Each series of models was repeated with a four-level exposure variable (2, 3, 4+ languages vs. 1 language), and two separate two-level exposure variables (2+ vs. 1 language, and 4+ vs. 1 to 3 languages); supplementary analyses summarized in Appendix J also assessed an exposure variable dichotomized as 4+ vs 1 language. See Appendix E for the detailed analysis plan.

Stepwise selection was the method used to determine the selection of variables in the final models. Stepwise selection involves adding or removing potential predictor variables and testing for statistical significance after each iteration. The significance level for variable selection was set to an alpha-level of 0.15 for entry into the model for interaction terms (SLENTRY command in SAS) and 0.05 for interaction terms to stay in the model once they passed the entry point (SLSTAY command in SAS), while the main effects were forced in each model tested.

The goal of variable selection techniques is to identify a set of predictors that balance inclusion of variables that significantly influence the outcome with developing the most parsimonious model. Forward selection begins with a model that contains no variables and then starts adding the most significant predictors one after the other in order of most to least significant, up to the specified level of significance. Forward selection is preferred when the number of variables under consideration is very large. Backward elimination begins with a model that contains all selected variables and then begins removing the least significant variables one after the other in order of least to most significant, up to the specified level of significance. Backward elimination is preferred when the sample size is very large. Stepwise selection combines both forward and backward selection techniques and was chosen for this study given the relatively limited sample size and number of variables under consideration.

4.5.2.1 Model Diagnostics

Lack of fit analyses, residual diagnostics, and multicollinearity tests were performed to assess how well the data fit the logistic regression models. The Hosmer-Lemeshow goodness-of-fit test (LACKFIT command in PROC LOGISTIC) is available in SAS for binomial logistic regression (intact cognition vs. overall MCI) and was used to assess the fit of these models. Models were rejected if the goodness-of-fit statistic p-values were less than 0.05. For multinomial logistic regression (intact cognition vs. aMCI vs. naMCI), these model fit tools were not available in SAS and model fit was assessed using the Mann-Whitney U statistic, investigating the area under the receiver operating characteristic curve (AUC (ROC)) (Mason & Graham, 2002) to determine adequate fit.

Residual diagnostics were used to identify influential outliers in the models. All binomial regression models were subjected to an investigation of residuals using the INFLUENCE and IPLOTS commands in PROC LOGISTIC. DFBETA, C, and CBAR plots were assessed to identify influential outliers with the critical value of ± 1.96 (corresponding to a 0.05 significance level) for binomial logistic regression. DFBETA values measure the changes in parameter estimates when an observation is deleted, while C and CBAR values identify how the observations influence parameter estimates. There was no evidence of influential outliers for binomial models. For multinomial logistic regression, a more limited set of tools was available in SAS, and influential outliers were assessed using Cook's distance. Cook's distance is used in regression analysis to find influential outliers in a set of predictor variables and shows the influence of each observation on the fitted response values. Influential outliers were identified based on values of Cook's distance greater than 1.0. There was no evidence of influential outliers for multinomial models.

Multicollinearity tests were conducted using the PROC REG command in SAS. Multicollinearity problems result from highly correlated predictor variables. Perfect multicollinearity makes estimation impossible while strong multicollinearity makes estimating imprecise. Multicollinearity was identified if two or more variables had large proportions of variance (greater than 0.50) with condition indices >30, or if the variance inflation factor (VIF) was greater than 10 or if tolerance values fall below 0.1 (Kleinbaum et al., 1988). There was no evidence of multicollinearity between the three different definitions of multilingualism (exposures) and other covariates.

4.5.2.2 Missing Data

This study used a complete-case approach to analyze missing data. Participants were excluded if they had missing data on the exposure, outcome, or key covariates. A complete-case analysis can introduce biases in the study results, based on missingness. Thus, it is important to examine the potential impact of missing data. To explore the nature of missing data and to assess the impact of removing participants with missing data, we conducted bivariate analyses to examine differences in frequencies among participants with complete vs. missing values. Specifically, Pearson chi-square tests or Fisher's exact tests for small counts were used for categorical variables, and t-tests or ANOVA tests for continuous variables. These tests were used to assess the statistical significance of the following comparisons: the main analytic sample with excluded participants from the total Nun Study sample (Table K1) and the linguistic ability subsample with excluded participants from the main analytic sample (Table K2). See Appendix K for the results of missing data analyses.

4.6 Ethics

The Nun Study received ethics approval by the institutional review boards from the University of Kentucky as well as from the University of Waterloo (current project: Office of Research Ethics number 20174). To protect the identity and maintain confidentiality of the Nun Study participants, they are identified by an assigned ID number. For further identity protection, neuropathologic assessments of deceased participants are assigned an additional ID number. Informed consent from the study participants was first obtained in 1990 as well as again in 2006. The data from the Nun Study are stored securely and only accessible to researchers who have read and signed confidentiality agreements regarding the ethical protocol. Access was restricted to the subset of data required for this project.

5.0 Results

The results section summarizes univariate, bivariate, and multivariable analyses for research questions one (binomial logistic regression) and two (multinomial logistic regression) for the main analytic sample and the linguistic ability subsample. A full summary of key findings is shown at the end of the results section (see Tables 24-26).

5.1 Univariate Analyses

Univariate statistics for categorical measures (frequencies and percentages) and continuous measures (means and standard deviations) describing the main analytic sample (n=384) and the linguistic ability subsample (n=122) are presented in Tables 2-3.

In both analytic samples, the majority of participants were bilinguals, followed by monolinguals and then those who spoke three languages. In the main analytic sample, half of the participants (50.8%) were bilingual and 29.2% were monolingual, whereas 40.2% of individuals were bilingual and 33.6% were monolingual in the linguistic ability subsample (Table 2). In the main analytic sample, 30% of participants were cognitively intact and the majority (70.1%) had MCI at baseline. Of the 70.1% of participants with MCI, 41.4% had non-amnestic MCI whereas 28.7% had amnestic MCI. In the linguistic ability subsample, 44.3% had normal cognition and 55.7% had MCI at baseline (35.3% non-amnestic vs. 2.50% amnestic type).

The mean age of the main analytic sample was 82.7 years (SD=5.1), whereas the mean age of the linguistic ability subsample was slightly lower (80 years; SD=2.9) (Table 3). For both the main and linguistic ability samples, the majority of participants (80.0% and 76.2%, respectively) did not possess an *APOE-ε4* allele (i.e., noncarrier). In the main analytic sample, 94.3% of individuals were born in the U.S., while those in the subsample were all born in the U.S. As well, this is a highly educated population, with more than 90% of participants in the

main analytic sample having a bachelor's degree or higher. The linguistic ability subsample was restricted to university-educated participants, where 40.2% had a bachelor's degree and 59.8 had a master's degree or higher. Idea density and grammatical complexity were measured using quartile ranking from low to high, thus each quartile has approximately 25% of participants.

Table 2. Number of Languages and Cognitive States at Baseline in the Main Analytic Sample and Linguistic Ability Subsample, The Nun Study

	Main Analytic Sample n=384		Linguistic Ability Subsample[1] n=122	
Characteristic	**n**	**%**	**n**	**%**
Number of languages				
1	112	29.17	41	33.61
2	195	50.78	49	40.16
3	59	15.36	26	21.31
4	10	2.61	3	2.46
5	8	2.08	3	2.46
Cognitive states at baseline				
Cognitively intact	115	29.95	54	44.26
Overall MCI	269	70.05	68	55.74
Non-amnestic MCI	159	41.41	43	35.25
Amnestic MCI	110	28.65	25	20.49

[1]Restricted to participants with a bachelor's degree or master's degree or higher who are born in the U.S.

Table 3. Baseline Covariates in the Main Analytic Sample and Linguistic Ability Subsample, The Nun Study

	Main Analytic Sample n=384		Linguistic Ability Subsample n=122	
Characteristic	**Mean**	**SD**	**Mean**	**SD**
Age at baseline (years)	82.65	5.12	80.01	2.88
Characteristic	**n**	**%**	**n**	**%**
Presence of APOE-ε4[1]				
No	307	79.95	93	76.23
Yes	77	20.05	29	23.77
Country of birth (Born in the US)				
No	22	5.73	-	-
Yes	362	94.27	122	100.00
Education				
Grade school	17	4.43	-	-
High school	16	4.17	-	-
Bachelor's degree	152	39.58	49	40.16
Master's degree+	199	51.82	73	59.84
Idea density quartile (%)[2]				
1 (low)	-	-	19	15.57
2	-	-	30	24.59
3	-	-	36	29.51
4 (high)	-	-	37	30.33
Grammatical complexity quartile (%)[3]				
1 (low)	-	-	23	18.85
2	-	-	32	26.23
3	-	-	34	27.87
4 (high)	-	-	33	27.05

[1]One or more *APOE*-ε4 alleles

[2]Measured using the average number of ideas expressed per ten words

[3]Measured based on degree of sentence development and scores ranged from zero (simple one clause-sentences) to seven (complex sentences using multiple clauses

5.2 Research Question One: Is multilingualism (speaking more than one language) associated with a reduced risk of overall MCI, after adjusting for key covariates (age, *APOE*, country of birth, education, idea density, and grammatical complexity)?

5.2.1 Bivariate Analyses of the Association Between Number of Languages Spoken and Overall MCI

Tables 4 and 5 summarize the bivariate analyses of the association between number of languages spoken and cognitive states (cognitively intact vs. overall MCI) in the main analytic sample (Table 4) and linguistic ability subsample (Table 5).

In the main analytic sample, there was no significant difference between multilingualism (four-level variable [2, 3, 4+ languages vs. 1 language] and the two separate two-level variables [2+ vs. 1 language], and [4+ vs. fewer]) and cognitive status (Table 4). Similarly, the association between the number of languages spoken (three multilingualism variables defined above) and cognitive states was not statistically significant in the linguistic ability subsample (Table 5).

Table 4. Number of Languages Spoken by Overall MCI Status (Two-level) at Baseline in the Main Analytic Sample, The Nun Study (n=384)

Multilingualism	**Cognitive States**		
	Cognitively Intact (n=115)	*Overall MCI* (n=269)	*Total* (n=384)
	%	%	%
Number of languages			
1	27.83	29.74	29.17
2	48.70	51.67	50.78
3	16.52	14.87	15.36
4	3.48	2.23	2.60
5	3.48	1.49	2.08
2+ languages	72.17	70.26	70.83
4+ languages	6.96	3.72	4.69

*p<0.05; **p<0.01; *** p<0.001

Table 5. Number of Languages Spoken by Overall MCI Status (Two-level) at Baseline in the Linguistic Ability Subsample, The Nun Study (n=122)

Multilingualism	**Cognitive States**		
	Cognitively Intact (n=54)	*Overall MCI* (n=68)	*Total* (n=122)
	%	%	%
Number of languages			
1	25.93	39.71	33.61
2	46.30	35.29	40.16
3	22.22	20.59	21.31
4	1.85	2.94	2.46
5	3.70	1.47	2.44
2+ languages	74.07	60.29	66.39
4+ languages	5.56	4.41	4.92

*p<0.05; **p<0.01, *** p<0.001

5.2.2 Bivariate Analyses of the Association Between Covariates and Overall MCI

Tables 6 and 7 summarize the bivariate analyses of the association between covariates and cognitive states (cognitively intact vs. overall MCI) at baseline in the main analytic sample and linguistic ability subsample.

In the main analytic sample, participants with overall MCI were significantly older than those who were cognitively intact (mean=83.7 vs 80.3 years; $p<0.001$) (Table 6). While the prevalence of carrying at least one *APOE*-e4 allele was higher in those with overall MCI compared to those who were cognitively intact, this difference did not reach statistical significance. A significantly greater proportion of participants born outside of the U.S. developed MCI than were cognitively intact (7.8% vs. 0.9%; $p=0.007$). The association between education and cognitive states was statistically significant ($p<0.001$), with lower levels of education (i.e., high school or less) more common in those with MCI compared to those who were cognitively intact (11.52% vs. 1.74%). As well, participants who had a master's degree or higher were more likely to have normal cognition than develop MCI (65.2% vs. 46.1%).

In the linguistic ability subsample, there were no significant differences by overall MCI status for age and presence of *APOE*-e4 (Table 7). Education was significantly associated with cognitive states ($p<0.05$): of those with a master's degree or higher, 70.4% were cognitively intact compared to 51.5% who had developed MCI. In addition, idea density was significantly associated with cognitive states ($p<0.05$), with those in the lowest quartile ranking — accounting for 16% of the subsample — over-represented as 22.1% of participants with MCI and only 7.4% of those who were cognitively intact. However, grammatical complexity was not significantly associated with cognitive status.

Table 6. Covariates by Overall MCI Status at Baseline in the Main Analytic Sample, The Nun Study (n=384)

Covariates	Cognitive States		
	Cognitively Intact (n=115)	*Overall MCI* (n=269)	*Total* (n=384)
Age at baseline (years)			
Mean (SD)	80.27 (3.24)***	83.66 (5.44)	82.65 (5.12)
Presence of APOE-ε4 (%)[1]			
Yes	17.39	21.19	20.05
No	82.61	78.81	79.95
Country of birth			
(Born in the US) (%)	99.13**	92.19	94.27
Yes	0.87	7.81	5.73
No			
Education (%)			
Grade school	0.87***	5.95	4.43
High school	0.87	5.58	4.17
Bachelor's degree	33.04	42.38	39.58
Master's degree+	65.22	46.10	51.82

*p<0.05; **p<0.01, *** p<0.001

[1]One or more *APOE-ε4* alleles

Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; SD= standard deviation; MCI= mild cognitive impairment

Table 7. Covariates by Overall MCI Status at Baseline in the Linguistic Ability Subsample, The Nun Study (n=122)

Covariates	Cognitive States		
	Cognitively Intact (n=54)	*Overall MCI* (n=68)	*Total* (n=122)
Age at baseline (years)			
Mean (SD)	79.51 (2.54)	80.42 (3.08)	80.01 (2.88)
Presence of APOE-ε4 (%)			
Yes	20.37	26.47	23.77
No	79.63	73.33	76.23
Education (%)			
Grade school	-	-	-
High school	-	-	-
Bachelor's degree	29.63*	48.53	40.16
Master's degree+	70.37	51.47	59.84
Idea density[1]			
1 (lowest quartile)	7.41*	22.06	15.57
2	22.22	26.47	24.59
3	40.74	20.59	29.51
4 (highest quartile)	29.63	30.88	30.33
Grammatical complexity[2]			
1 (lowest quartile)	11.11	25.00	18.85
2	22.22	29.41	26.23
3	33.33	23.53	27.87
4 (highest quartile)	33.33	22.06	27.05

*p<0.05; **p<0.01, *** p<0.001

[1]Measured using the average number of ideas or emotions expressed per ten words

[2]Measured based on degree of sentence development. Scores ranged from zero (simple one clause-sentences) to seven (complex sentences using multiple clauses)

Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; SD= standard deviation; MCI= mild cognitive impairment

Note: restricted to participants with a bachelor's degree or higher who were born in the U.S.

5.2.3 Binomial Logistic Regression Analyses for the Association Between Number of Languages Spoken and Overall MCI

Results from a series of binomial logistic regression analyses for the association between multilingualism and overall MCI are presented in Tables 8-13, using the main analytic sample and linguistic ability subsample. Tables 8-13 reflect the three different definitions of multilingualism: a four-level variable (2, 3, 4+ languages vs. 1 language) in Tables 8 and 9, and two separate two-level variables, 2+ vs. 1 language in Tables 10 and 11, and 4+ vs. ≤ 3 languages in Tables 12 and 13. Models A to E for the main analytic sample were sequentially adjusted for age, *APOE*-ε4 status, country of birth and education (three-level). Models A to F for the linguistic ability subsample were sequentially adjusted for age, *APOE*-ε4 status, and education (two-level), in addition to idea density and grammatical complexity. There was no significant effect modification between the different multilingualism exposures and covariates. Although *APOE*-ε4 was not a significant covariate in these models, it was retained in the final models to increase comparability with the models for MCI subtypes, where it was a significant covariate.

Table 8 summarizes the odds ratios and 95% CIs for the association between the four-level multilingualism variable and overall MCI in the main analytic sample. In the unadjusted models (Model A), number of languages was not significantly associated with overall MCI. Speaking four or more languages (but not two or three) was significantly associated with lower odds of overall MCI when adjusted for age, *APOE*, and country of birth (OR=0.32, 95% CI=0.11-0.96) compared to speaking one language. However, speaking four or more languages became non-significant (OR=0.40, 95% CI=0.13-1.21) after further adjustment for education. Overall, in the fully adjusted Model E, the association between the number of languages spoken and overall MCI was not significant. Table 9 summarizes the odds ratios and 95% CIs for the

association between the four-level multilingualism variable and overall MCI in the linguistic ability subsample. In this subsample, multilingualism (2, 3, 4+ vs. 1) was not significantly associated with overall MCI in any of the models (i.e., Model A to Model F).

Table 10 summarizes the ORs and 95% CIs for the association between speaking 2+ languages vs. one language and overall MCI in the main analytic sample. In the crude model and all adjusted models, speaking two or more languages was not significantly associated with overall MCI (final model: OR=0.77, 95% CI=0.45-1.31). Similarly in Table 11 from the linguistic ability subsample, speaking 2+ languages vs. one language was not significantly associated with overall MCI in Models A-F (final model: OR=0.62, 95% CI=0.26-1.44).

Tables 12 and 13 summarize the odds ratios and 95% CIs for the association between speaking four or more languages vs. fewer and overall MCI in the main analytic sample and linguistic ability subsample, respectively. In both analytic samples, speaking four or more languages was not significantly associated with overall MCI compared to three or fewer (final model for the main analytic sample: OR=0.47, 95% CI=0.17-1.32; final model for the linguistic ability subsample: OR=0.72, 95% CI=0.11-4.54).

Similar non-significant findings between the association of number of languages spoken and overall MCI were found in additional binomial logistic regression analyses using the university-educated teachers subsample (n=335) (see Appendix H). Additional analyses suggest that excluding *APOE*-ε2ε4 did not affect the association between multilingualism and overall MCI (n=379) (see Appendix I). In addition, the association between speaking 4+ languages vs. 1 language (excluding those participants who spoke two or three languages) and overall MCI was also not significant (n=129) (see Appendix J).

5.2.4 Binomial Logistic Regression Analyses for the Association Between Covariates and Overall MCI

Within the main analytic sample, age at baseline, country of birth, and education were significantly associated with overall MCI. Age was consistently positively associated with overall MCI in the main analytic sample in all final models in Tables 8, 10, and 12 (2, 3, 4+ vs. 1 language: OR=1.19, 95% CI=1.12-1.27; 2+ vs. 1 language: OR=1.18, 95% CI=1.11-1.26; 4+ vs. $\leq$ 3 languages: OR=1.19, 95% CI=1.17-1.32). Country of birth (being born in the U.S.) was significantly associated with a decreased odds of overall MCI in all final models in Tables 8, 10, and 12 (2, 3, 4+ vs. 1 language: OR=0.12, 95% CI=0.01-0.67; 2+ vs. 1 language: OR=0.12, 95% CI=0.03-0.76; 4+ vs. $\leq$ 3 languages: OR=0.13, 95% CI=0.01-0.71). Thus, being born in the U.S. was a protective factor against overall MCI. Overall, higher education was associated with decreased odds of overall MCI: those with a bachelor's degree (OR=0.20) or master's degree (OR=0.16) were at least five times less likely to have MCI than those with a high school education or less (Table 8). Presence of an *APOE*-ε4 allele was not significant covariate in any model with overall MCI.

Within the linguistic ability subsample, age at baseline, *APOE*-ε4, country of birth, and education as well as idea density and grammatical complexity were not significantly associated with overall MCI in all the final models (Tables 9, 11, 13).

Table 8. Association Between Number of Languages Spoken (2, 3, 4+ vs. 1) and Overall MCI at Baseline, Main Analytic Sample, The Nun Study (n=384)

	***Overall MCI*[1]**				
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)	**Model E** OR (95% CI)
Number of languages (Ref.: Monolingual)					
2	0.99 (0.59-1.65)	0.81 (0.47-1.39)	0.82 (0.47-1.40)	0.72 (0.41-1.24)	0.79 (0.44-1.39)
3	0.84 (0.43-1.68)	0.76 (0.37-1.58)	0.77 (0.38-1.59)	0.73 (0.35-1.52)	0.88 (0.42-1.87)
4+[2]	0.50 (0.18-1.42)	**0.31 (0.10-0.93)**	**0.32 (0.11-0.96)**	**0.32 (0.11-0.96)**	0.40 (0.13-1.21)
Age at baseline (years)		**1.20 (1.13-1.28)**	**1.20 (1.13-1.28)**	**1.20 (1.13-1.28)**	**1.19 (1.12-1.27)**
Presence of APOE-ε4 allele (Yes vs. No [Ref.])			1.22 (0.68-2.24)	1.28 (0.71-2.36)	1.40 (0.78-2.60)
Country of birth (%) (Born in the US) (Yes vs. No [Ref.])				**0.10 (0.01-0.49)**	**0.12 (0.01-0.67)**
Education (%) (Ref.: Grade and high school)					
Bachelor's degree					**0.20 (0.03-0.77)**
Master's degree+					**0.16 (0.02-0.59)**

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model includes the exposure
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + born in the US
Model E includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + born in the US + education
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table 9. Association Between Number of Languages Spoken (2, 3, 4+ vs. 1) and Overall MCI at Baseline, Linguistic Ability Subsample, The Nun Study (n=122)

	***Overall MCI*[1]**					
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)	**Model E** OR (95% CI)	**Model F** OR (95% CI)
Number of languages						
(Ref.: Monolingual)	0.50	0.54	0.53	0.64	0.60	0.58
2	(0.21-1.16)	(0.23-1.29)	(0.22-1.26)	(0.25-1.59)	(0.24-1.50)	(0.23-1.47)
	0.61	0.62	0.61	0.76	0.77	0.73
3	(0.22-1.66)	(0.22-1.71)	(0.22-1.69)	(0.26-2.22)	(0.26-2.27)	(0.24-2.19)
	0.52	0.36	0.37	0.46	0.45	0.55
4+[2]	(0.09-3.12)	(0.06-2.30)	(0.06-2.36)	(0.07-3.03)	(0.07-2.99)	(0.08-3.71)
Age at baseline (years)		1.13	1.12	1.11	1.09	1.07
		(0.98-1.30)	(0.98-1.29)	(0.96-1.28)	(0.95-1.27)	(0.92-1.24)
Presence of APOE-ε4 allele			1.38	1.52	1.31	1.34
(Yes vs. No [Ref.])			(0.58-3.40)	(0.63-3.82)	(0.52-3.38)	(0.53-3.47)
Education (%)						
(Ref.: Bachelor's degree)				0.51	0.56	0.57
Master's degree+				(0.22-1.14)	(0.24-1.27)	(0.25-1.31)
Idea density						
(Quartiles 2 + 3 + 4 vs.					0.34	0.35
quartile 1 [Ref])					(0.09-1.09)	(0.09-1.11)
Grammatical Complexity						
(Quartiles 2 + 3 + 4 vs.						0.44
quartile 1 [Ref.])						(0.14-1.25)

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model includes the exposure
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education
Model E includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education + idea density
Model F includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education + idea density + grammatical complexity
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table 10. Association Between Number of Languages Spoken (2+ vs. 1) and Overall MCI at Baseline, Main Analytic Sample, The Nun Study (n=384)

	***Overall MCI*[1]**				
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)	**Model E** OR (95% CI)
Number of languages (Ref.: Monolingual) 2+ languages	0.91 (0.56-1.47)	0.75 (0.45-1.24)	0.76 (0.45-1.26)	0.68 (0.40-1.14)	0.77 (0.45-1.31)
Age at baseline (years)		**1.19 (1.13-1.27)**	**1.19 (1.13-1.27)**	**1.19 (1.13-1.27)**	**1.18 (1.11-1.26)**
Presence of APOE-ε4 allele (Yes vs. No [Ref.])			1.25 (0.70-2.30)	1.31 (0.73-2.41)	1.43 (0.79-2.65)
Country of birth (%) (Born in the US) (Yes vs. No [Ref.])				**0.09 (0.01-0.46)**	**0.12 (0.01-0.64)**
Education (%) (Ref.: Grade and high school)					
Bachelor's degree					**0.20 (0.03-0.76)**
Master's degree+					**0.15 (0.02-0.57)**

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model includes the exposure
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + born in the US
Model E includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + born in the US + education
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table 11. Association Between Number of Languages Spoken (2+ vs. 1) and Overall MCI, Linguistic Ability Subsample, The Nun Study (n=122)

	***Overall MCI*[1]**					
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)	**Model E** OR (95% CI)	**Model F** OR (95% CI)
Number of languages						
(Ref.: Monolingual)	0.53	0.55	0.54	0.66	0.63	0.62
2+ languages	(0.24-1.15)	(0.25-1.19)	(0.24-1.18)	(0.28-1.50)	(0.27-1.48)	(0.26-1.44)
Age at baseline (years)		1.12	1.11	1.10	1.09	1.07
		(0.98-1.28)	(0.98-1.28)	(0.96-1.26)	(0.95-1.25)	(0.93-1.23)
Presence of APOE-ε4			1.40	1.52	1.30	1.33
allele (Yes vs. No [Ref.])			(0.59-3.43)	(0.63-3.81)	(0.52-3.36)	(0.53-3.42)
Education (%)						
(Ref.: Bachelor's degree)				0.51	0.57	0.58
Master's degree+				(0.23-1.14)	(0.25-1.29)	(0.25-1.32)
Idea density						
(Quartiles 2 + 3 + 4 vs.					0.35	0.35
quartile 1 [Ref.])					(0.09-1.10)	(0.09-1.13)
Grammatical Complexity						
(Quartiles 2 + 3 + 4 vs.						0.43
quartile 1 [Ref.])						(0.14-1.21)

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model includes the exposure
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education
Model E includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education + idea density
Model F includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education + idea density + grammatical complexity
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table 12. Association Between Number of Languages Spoken (4+ vs. ≤ 3) and Overall MCI at Baseline, Main Analytic Sample, The Nun Study (n=384)

	***Overall MCI*[1]**				
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)	**Model E** OR (95% CI)
Number of languages					
(Ref.: Three or fewer languages)	0.52	0.36	0.37	0.40	0.47
4+ languages	(0.20-1.39)	(0.13-1.03)	(0.13-1.05)	(0.14-1.14)	(0.17-1.32)
Age at baseline (years)		**1.20**	**1.20**	**1.20**	**1.19**
		(1.13-1.28)	**(1.13-1.27)**	**(1.13-1.28)**	**(1.12-1.27)**
Presence of APOE-ε4 allele			1.24	1.30	1.42
(Yes vs. No [Ref.])			(0.69-2.27)	(0.73-2.39)	(0.79-2.62)
Country of birth (%)					
(Born in the US)				**0.11**	**0.13**
(Yes vs. No [Ref.])				**(0.01-0.54)**	**(0.01-0.71)**
Education (%)					
(Ref.: Grade and high school)					**0.20**
Bachelor's degree					**(0.03-0.76)**
					0.15
Master's degree+					**(0.02-0.56)**

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model includes the exposure
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + born in the US
Model E includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + born in the US + education
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table 13. Association Between Number of Languages Spoken (4+ vs. ≤ 3) and Overall MCI at Baseline, Linguistic Ability Subsample, The Nun Study (n=122)

	***Overall MCI*[1]**					
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)	**Model E** OR (95% CI)	**Model F** OR (95% CI)
Number of languages (Ref.: Three or fewer languages)						
4+ languages	0.79 (0.14-4.39)	0.51 (0.08-3.03)	0.52 (0.09-3.13)	0.58 (0.10-3.56)	0.58 (0.09-3.58)	0.72 (0.11-4.54)
Age at baseline (years)		1.14 (1.00-1.31)	1.13 (0.99-1.31)	1.11 (0.97-1.29)	1.10 (0.96-1.28)	1.08 (0.93-1.25)
Presence of APOE-ε4 allele (Yes vs. No [Ref.])			1.33 (0.56-3.22)	1.50 (0.62-3.72)	1.29 (0.52-3.28)	1.32 (0.53-3.38)
Education (%) (Ref.: Bachelor's degree)						
Master's degree+				**0.46 (0.21-0.99)**	0.51 (0.23-1.11)	0.51 (0.23-1.12)
Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])					0.36 (0.09-1.13)	0.37 (0.10-1.16)
Grammatical Complexity (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])						0.45 (0.15-1.28)

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model includes the exposure
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education
Model E includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education + idea density
Model F includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education + idea density + grammatical complexity
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

5.2.5 Summary of Results for Research Question One

The results for research question one using both analytic samples found that the number of languages spoken was not associated with overall MCI after adjusting for key covariates (age, *APOE*, country of birth, education, idea density, and grammatical complexity). Although speaking 4+ languages (but not 2 or 3) was associated with a significantly lower risk of overall MCI compared to monolinguals in unadjusted models, this association weakened to non-significance after controlling for education. In conclusion, the study findings suggest that multilingualism was not a significant predictor of overall MCI.

5.3 Research Question Two: Does the association of multilingualism with MCI vary by subtype (amnestic MCI versus non-amnestic MCI), after adjusting for key covariates (age, *APOE*, country of birth, education, idea density, and grammatical complexity)?

5.3.1 Bivariate Analyses of the Association Between Number of Languages Spoken and Subtypes of MCI

Results addressing the second research question are presented in Section 5.3. Tables 14 and 15 summarize the bivariate analyses of the association between number of languages spoken and subtypes of MCI (cognitively intact vs. aMCI vs naMCI) in the main analytic sample and linguistic ability subsample, respectively.

In general, a similar pattern can be observed across the three levels of cognitive states in the main analytic sample and linguistic ability subsample. Across the three exposures of multilingualism, there was no significant difference by cognitive states.

Table 14. Number of Languages by Subtypes of MCI (Three-level) in the Main Analytic Sample, The Nun Study (n=384)

Multilingualism	**Cognitive States**			
	Cognitively Intact (n=115)	*Non-Amnestic MCI* (n=159)	*Amnestic MCI* (n=110)	*Total* (n=384)
	%	%	%	%
Number of languages				
1	27.83	30.82	28.18	29.24
2	48.70	49.69	54.55	50.78
3	16.52	15.09	14.55	15.36
4	3.48	2.52	1.82	2.60
5	3.48	1.89	0.91	2.08
2+ languages	72.17	69.18	71.82	70.83
4+ languages	6.96	4.40	2.73	4.69

*p<0.05; **p<0.01, *** p<0.001

Table 15. Number of Languages by Subtypes of MCI (Three-level) in the Linguistic Ability Subsample, The Nun Study (n=122)

Multilingualism	**Cognitive States**			
	Cognitively Intact (n=54)	*Non-Amnestic MCI* (n=43)	*Amnestic MCI* (n=25)	*Total* (n=122)
	%	%	%	%
Number of languages				
1	25.93	39.53	40.00	33.61
2	46.30	34.88	36.00	40.16
3	22.22	23.26	16.00	21.31
4	1.85	2.33	4.00	2.46
5	3.70	0.00	4.00	2.46
2+ languages	74.07	60.47	60.00	66.39
4+ languages	5.56	2.33	8.00	4.92

*p<0.05; **p<0.01, *** p<0.001

5.3.2 Bivariate Analyses for the Association Between Covariates and Subtypes of MCI

Tables 16 and 17 summarize the bivariate analyses of the association between covariates and the three-level cognitive states (cognitively intact vs. naMCI vs. aMCI) in the main analytic sample and linguistic ability subsample.

In the main analytic sample, participants with naMCI and aMCI were significantly older than those who were cognitively intact (mean = 83.1 years for naMCI; 84.5 years for aMCI; normal cognition=80.3 years; $p<0.001$) (Table 16). Those with aMCI (30.0%) were more likely to have an *APOE*-ε4 allele compared to those with naMCI (15.15%) and normal cognition (17.4%). Country of birth was a significant predictor of the three-level cognitive states, whereby those who had developed naMCI (7.6%) or aMCI (8.2%) were more likely to born outside of the U.S., compared to those who were cognitively intact (0.9%). In addition, those who were cognitively intact (1.7%) were significantly less likely to have low educational attainment (high school or less) compared to those with naMCI (13.2%) or aMCI (9.1%).

In the linguistic ability subsample, participants did not differ based on their age at first cognitive assessment, educational attainment, or grammatical complexity (Table 17). However, those with aMCI were significantly more likely to have an *APOE*-ε4 allele (48.0% in aMCI vs 14.0% in naMCI and 20.4% in cognitively intact), and lower idea density (36.5% in aMCI vs 14.0% in naMCI and 7.4% in cognitively intact).

Table 16. Covariates by Subtypes of MCI (Three-level) in the Main Analytic Sample, The Nun Study (n=384)

Covariates	Cognitive States			
	Cognitively Intact (n=115)	*Non-Amnestic MCI* (n=159)	*Amnestic MCI* (n=110)	*Total* (n=384)
Age at baseline (years)				
Mean (SD)	80.27 (3.24)[a***]	83.09 (5.27)[b]	84.49 (5.59)[b]	82.65 (4.86)
Presence of APOE-ε4 (%)				
Yes	17.39**	15.09	30.00	20.05
No	82.61	84.91	70.00	79.95
Country of birth (Born in the U.S.) (%)				
Yes	99.13*	92.45	91.82	94.27
No	0.87	7.55	8.18	5.73
Education (%)				
Grade and high school	1.74***	13.21	9.09	8.59
Bachelor's degree	33.04	39.62	46.36	39.58
Master's degree+	65.22	47.17	44.55	51.82

*p<0.05; **p<0.01, *** p<0.001

[a]Means are significantly different from 'b'

[b]Means are not significantly different from each other but are significantly different from 'a'

Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; SD= standard deviation; MCI= mild cognitive impairment

Table 17. Covariates by Subtypes of MCI (Three-level) in the Linguistic Ability Subsample, The Nun Study (n=122)

Covariates	Cognitive States			
	Cognitively Intact (n=54)	*Non-Amnestic MCI* (n=43)	*Amnestic MCI* (n=25)	*Total* (n=122)
Age at baseline (years) Mean (SD)	79.51 (2.54)[b]	80.40 (3.36)[b]	80.44 (2.58)[b]	80.01 (2.88)
Presence of APOE-ε4 (%)				
Yes	20.37**	13.95	48.00	23.77
No	79.63	86.05	52.00	76.23
Education (%)				
Grade and high school	-	-	-	-
Bachelor's degree	29.63	44.19	56.00	40.16
Master's degree+	70.37	55.81	44.00	59.84
Idea density				
1 (lowest quartile)	7.41*	13.95	36.00	15.57
2	22.22	27.91	24.00	24.59
3	40.74	20.93	20.00	29.51
4 (highest quartile)	29.63	37.21	20.00	30.33
Grammatical complexity				
1 (lowest quartile)	11.11	23.26	28.00	18.85
2	22.22	27.91	32.00	26.23
3	33.33	25.58	20.00	27.87
4 (highest quartile)	33.33	23.26	20.00	27.05

*p<0.05; **p<0.01, *** p<0.001
[a]Means are significantly different from 'b'
[b]Means are not significantly different from each other but are significantly different from 'a'
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; SD= standard deviation; MCI= mild cognitive impairment
Note: restricted to university-educated participants born in the U.S.

5.3.3 Multinomial Logistic Regression Analyses for the Association Between Number of Languages Spoken and Subtypes of MCI

To test the association between each of the multilingualism exposures and three-level cognitive status, multinomial logistic regression was used. There was no significant effect modification when testing each of the multilingual exposures with the covariates, and thus the models for the three-level cognitive states were not stratified. Final models were adjusted for key covariates of age, *APOE*, country of birth, education, idea density, and grammatical complexity, and these covariates were consistent with analyses for overall MCI. Subtypes of MCI (aMCI and naMCI) were compared against the reference group of participants who were cognitively intact at baseline.

Appendix G (Tables G1, G3, and G5) summarizes the association between number of languages spoken and subtypes of MCI from the main analytic sample. Throughout Models A to E, the number of languages spoken (2, 3, 4+ vs. 1 language, 2+ vs. 1 language, and 4+ vs. fewer languages) was not associated with naMCI or aMCI.

Appendix G (Tables G2, G4, and G6) summarizes the association between number of languages spoken and subtypes of MCI from the linguistic ability subsample. Similarly, throughout Models A to F, number of languages spoken (2, 3, 4+ vs. 1 language, 2+ vs. 1 language, and 4+ vs. fewer languages) was not associated with subtypes of MCI.

Similar multivariable results were generated from the university-educated teachers subsample (n=335), which stringently controlled for confounding by education and occupation (see Appendix H). Additional sensitivity analyses of 4+ languages vs. 1 language (n=129) (refer to Appendix J) and additional multivariable models excluding participants with *APOE*-ε2ε4 (refer to Appendix I) also failed to reach significance between multilingualism and subtypes of MCI.

5.3.4 Multinomial Logistic Regression Analyses for the Association Between Covariates and Subtypes of MCI

Within the fully adjusted models in the main analytic sample (Tables G1, G3, and G5), older age was consistently associated with higher odds of both naMCI and aMCI: naMCI (2, 3, 4+ vs. 1 language: OR=1.17, 95% CI=1.09-1.25; 2+ vs. 1 language: OR=1.16, 95% CI=1.09-1.24; 4+ vs. ≤ 3 languages: OR=1.16, 95% CI=1.09-1.24), and aMCI (2, 3, 4+ vs. 1 language: OR=1.23, 95% CI=1.15-1.32; 2+ vs. 1 language: OR=1.22, 95% CI=1.14-1.31; 4+ vs. ≤ 3 languages: OR=1.23, 95% CI=1.14-1.31). Presence of an *APOE-ε4* allele was significantly associated with aMCI, but not naMCI. There was a greater than two-fold increase in the odds of aMCI when individuals had at least one *APOE-ε4* allele compared to not possessing an *APOE-ε4* allele (2, 3, 4+ vs. 1 language: OR=2.35, 95% CI=1.19-4.65; 2+ vs. 1 language: OR=2.40, 95% CI=1.21-4.74; 4+ vs. ≤ 3 languages: OR=2.35, 95% CI=1.19-4.65). Being born in the U.S. was associated with a significantly lower odds ratios for aMCI. Compared to those with a high school degree or less, participants with a bachelor's or master's degree showed consistently lower odds of aMCI and naMCI across all models, but whether this associated reached statistical significance depended on the measure of multilingualism, level of education, and MCI subtype, with more consistent associations for naMCI.

Within the fully adjusted models for the linguistic ability subsample, age, *APOE-ε,* idea density, and grammatical complexity were not significantly associated with naMCI (Tables G2, G4, and G6); education was only significantly associated with aMCI for models of 4+ vs. ≤ 3 languages: OR=0.29, 95% CI=0.09-0.90 (Table G6). However, presence of an *APOE*-ε4 allele was a significant predictor of aMCI, and there was a four-fold increase in the odds of aMCI (2, 3, 4+ vs. 1 language: OR=4.14, 95% CI=1.26-13.58; 2+ vs. 1 language: OR=3.77, 95% CI=1.17-12.09; 4+ vs. ≤ 3 languages: OR=4.06, 95% CI=1.25-13.24). In addition, idea density was

significantly and negatively associated with aMCI. Consistently, participants who had high idea density had a reduced odds of aMCI compared to individuals with low idea density (2, 3, 4+ vs. 1: OR=0.21, 95% CI=0.05-0.87; 2+ vs. 1: OR=0.22, 95% CI=0.05-0.90; 4+ vs. ≤ 3: OR=0.22, 95% CI=0.05-0.90).

5.3.5 Summary of Results for Research Question Two

The results of research question two using both analytic samples found that the number of languages spoken was not associated with the odds of MCI subtypes, after adjusting for key covariates (age, *APOE,* country of birth, education, idea density, and grammatical complexity). Written linguistic ability (specifically high idea density) was significantly associated with a reduced odd of aMCI.

A full summary of key findings for both research questions is provided in the following Tables 18-20.

Table 18. Summary Table of Sequentially Adjusted Models of the Association Between Number of Languages Spoken and Overall MCI, Main Analytic Sample (n=384)

	Overall MCI				
Multilingualism	*Model A* Unadjusted model	*Model B* Age at baseline (years)	*Model C* Age at baseline (years) + presence of *APOE*-ε4	*Model D* Age at baseline (years) + presence of *APOE*-ε4 + country of birth	*Model E* Age at baseline (years) + presence of *APOE*-ε4 + country of birth + education
Number of languages (Ref.: Monolingual)					
2	×	×	×	×	×
3	×	×	×	×	×
4+	×	✓	✓	✓	×
Number of languages (Ref.: Monolingual)					
2+ languages	×	×	×	×	×
Number of languages (Ref.: Three or fewer languages)					
4+ languages	×	×	×	×	×

×= not significant

✓= significant

Table 19. Summary Table of Fully Adjusted Models of the Association of Multilingualism with Overall MCI, Amnestic MCI and Nonamnestic MCI; Main Analytic Sample (n=384)

	Outcome		
	Overall MC1 (n=269)	*Subtypes of MCI* naMCI (n=159)	aMCI (n=110)
Four-level variable:			
*2, 3, 4+5 languages (*Ref.: monolingual)	×	×	×
2	×	×	×
3	×	×	×
4+5	✓	✓	✓
Age at baseline (years)	×	×	✓
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	✓	×	✓
County of birth (Born in the U.S.) (%) (Yes vs. No [Ref.])			
Education (%) (Ref.: Grade and high school)			
Bachelor's degree	✓	✓	×
Master's degree+	✓	✓	×
Two-level variable:			
2+ languages (Ref.: monolingual)	×	×	×
Age at baseline (years)	✓	✓	✓
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	×	×	✓
County of birth (Born in the U.S.) (%) (Yes vs. No [Ref.])	✓	×	✓
Education (%) (Ref.: Grade and high school)			
Bachelor's degree	✓	✓	×
Master's degree+	✓	✓	✓
Two-level variable:			
4+ languages (Ref.: fewer)	×	×	×
Age at baseline (years)	✓	✓	✓
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	×	×	✓
County of birth (Born in the U.S.) (%) (Yes vs. No [Ref.])	✓	×	✓
Education (%) (Ref.: Grade and high school)			
Bachelor's degree	✓	✓	×
Master's degree+	✓	✓	✓

×= not significant

✓= significant

Note: results are from final models

Table 20. Summary Table of Fully Adjusted Models of the Association of Multilingualism with Overall MCI, Amnestic MCI and Nonamnestic MCI; Linguistic Ability Subsample (n=122)

	Outcome		
	Overall MCI (n=68)	*Subtypes of MCI* naMCI (n=43)	aMCI (n=25)
Four-level variable:			
*2, 3, 4+5 languages (*Ref.: monolingual)	×	×	×
2	×	×	×
3	×	×	×
4+5	×	×	×
Age at baseline (years)	×	×	✓
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	×	×	×
Education (%) (Ref.: Bachelor's degree) Master's degree+	×	×	✓
Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	×	×	×
Grammatical Complexity (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])			
Two-level variable:			
2+ languages (Ref.: monolingual)	×	×	×
Age at baseline (years)	×	×	×
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	×	×	✓
Education (%) (Ref.: Bachelor's degree) Master's degree+	×	×	×
Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	×	×	✓
Grammatical Complexity (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	×	×	×
Two-level variable:			
4+ languages (Ref.: fewer)	×	×	×
Age at baseline (years)	×	×	×
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	×	×	✓
Education (%) (Ref.: Bachelor's degree) Master's degree+	×	×	✓
Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	×	×	✓
Grammatical Complexity (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	×	×	×

×= not significant

✓= significant

Note: results are from final models and restricted to US-born university-educated participants

6.0 Discussion

6.1 Summary of Study Findings

This study investigated the association of multilingualism — the number of languages spoken — with MCI, an early stage of cognitive impairment in individuals who maintain the ability to independently perform most ADLs. This cognitive state can be indicative of further cognitive decline and lead to different types of dementias (e.g., AD or frontotemporal dementia). The homogeneity of the study participants controlled for a variety of complex confounders, such as SES and income. The influence of other known confounders, including age, country of birth, presence of an *APOE*-ε4 allele, educational attainment, and other linguistic abilities, was controlled in analyses.

Half of the participants were bilinguals, whereas one-third were monolinguals. The prevalence of overall MCI status at baseline was 70% in the main analytic sample and 55% in the linguistic ability subsample, a high prevalence of MCI at the first cognitive assessment. In both samples, the prevalence of non-amnestic MCI was slightly higher than amnestic MCI.

The number of languages spoken was not significantly associated with overall MCI or its subtypes, after adjusting for key confounders. In the main analytic sample, speaking more than four languages was significantly associated with a reduced risk of overall MCI when adjusted for age, presence of an *APOE*-ε4 allele, and country of birth. However, when further controlled for education, this association became non-significant. In the linguistic ability sample, although multilingualism did not significantly reduce the risk of overall MCI or its subtypes, written language ability (specifically idea density) was significantly associated with a reduced risk of amnestic MCI, even after controlling for education.

6.2 Discussion of the Study Results

6.2.1 Research Question One: Overall MCI Status

In research question one, we examined the association of multilingualism with risk of overall MCI status at baseline in a population-based sample adjusted for various key factors, such as age and genetics, education, country of birth, and additional measures of linguistic ability. Considerable inconsistency in the literature remains regarding the protective effect of multilingualism on cognitive states (i.e., MCI status or dementia). Differences between our results and the studies finding an association between the number of languages and overall MCI or dementia may be due to differences in populations (clinic-based vs. population-based samples), cognitive outcomes (MCI, dementia, AD, cognitive test scores or global cognitive function), measures of outcome (age at onset of MCI vs. risk of MCI), study designs (cross-sectional vs. longitudinal studies), and definitions of multilingualism (language use and proficiency, or lifelong bilingualism) as well as in addressing confounding by key covariates.

Differences in clinic and population-based samples may explain inconsistencies between our study's results and previous results investigating MCI status. A significant association between bilingualism and overall MCI status has been reported in most clinic-based samples (e.g., Ramakrishnan et al., 2017; Calabria et al., 2020; Bialystok et al., 2014; Berkes et al., 2020). For instance, studies have found that lifelong bilinguals had an onset of MCI symptoms 7.4 years (Ramakrishnan et al., 2017), 4.7 years (Bialystok et al., 2014), and 2 years (Berkes et al., 2020) later than monolinguals, even after controlling for occupation, educational level, immigration status, and sex. As well, another study even found that active bilinguals had a two-year delay in the age of onset of MCI compared to passive bilinguals (Calabria et al., 2020).

The above clinic-based studies reported a significant protective effect of speaking two languages on the age of onset for overall MCI, but they differed with respect to the length of delay in symptoms of MCI. Nonetheless, another clinic-based study from the U.S. (Li et al., 2021) found no significant difference between the age of onset of MCI in bilinguals and monolinguals within the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. The inconsistent results from clinic-based studies investigating the association between bilingualism and overall MCI may be due to different measures of bilingualism. The clinic-based studies that found a significant association used more stringent measures of bilingualism, such as regular use of both languages (Berkes et al., 2020), requiring bilinguals to have spent the majority of their lives, beginning at least in early adulthood, speaking two or more languages fluently and daily (Bialystok et al., 2014), constant use of more than one language (Ramakrishnan et al., 2017), or high proficiency in both languages with a balanced daily usage (Calabria et al., 2020). In contrast, Li et al. (2021) defined bilingualism as mastering a second language with minimal proficiency. Therefore, using stringent criteria to measure language proficiency (e.g., high frequency or lifelong language use) can influence the association between number of languages and cognition later in life. Bilinguals who actively use both languages daily will have greater brain stimulation and more practice with inhibition, which will lead to greater benefit to cognitive function and memory (Emmorey et al, 2008). The overall body of evidence from clinic-based samples suggests that lifelong and active bilingualism may be protecting individuals against overall MCI (Ramakrishnan et al., 2017; Calabria et al., 2020; Bialystok et al., 2014; Berkes et al., 2020). This increased daily active use of multiple languages may have been the key to their development of cognitive reserve via the mechanism of constant task-switching and inhibitory control between languages. The less stringent definition of multilingualism used in

this study could explain why we did not find a protective effect of number of languages with MCI or its subtypes.

Evidence regarding an association between bilingualism and MCI in population-based studies is very limited and to my knowledge is based on one previous study. In our study, multilingualism did not significantly lower the risk of MCI after adjustment for key covariates. These findings are inconsistent with those of another population-based study from the U.S. (Wilson et al., 2015). In the Wilson et al. (2015) study, second language instruction during youth (i.e., at least 5 years of instruction by age 18) was associated with a 30% lower risk of MCI compared to no instruction, after adjustment for age, sex, and education. Note that the Wilson et al. study did not control for the effects of *APOE*-ε4, which this thesis found to be a significant confounder of the association between multilingualism and aMCI. Overall, the evidence of a protective effect of multilingualism on delaying the age of onset of MCI or reducing the risk of MCI is limited, inconsistent, and unclear.

In contrast to the limited evidence for MCI, studies of the association between multilingualism and dementia/AD are more abundant; these studies also show differences in results based on their samples. Evidence of a protective effect of bilingualism on dementia/AD has primarily been based on clinic-based samples (Alladi et al., 2013; Bialystok et al., 2007; Craik et al., 2010; Bialystok et al., 2014; Woumans et al., 2015; Freedman et al., 2014), whereas population-based samples have not supported this association (Yeung et al., 2014; Crane et al, 2010; Zahodne et al., 2014, Ljungberg et al., 2016; Mukadam et al., 2018; Lawton et al., 2015; Sanders et al., 2012). Overall, there is on average a four to five-year delay in the age of onset of dementia among bilinguals compared to monolinguals in memory clinic-based samples (Alladi et al., 2014; Bialystok et al., 2007; Craik et al., 2010; Woumans et al., 2015; Freedman et

al., 2014; Schweizer et al., 2012). This protective effect persisted even after accounting for age, educational attainment, and occupation.

On the other hand, population-based studies typically have not found an association between bilingualism and dementia or AD. Studies across diverse population-based samples found similar non-significant results with bilingualism (Crane et al., 2010; Ljungberg et al., 2016; Zahodne et al., 2014). For example, population-based studies found that bilinguals did not have a lower risk of dementia than monolinguals from a Canadian cohort (Yeung et al., 2014) and non-native English speakers in the U.S. (Sanders et al., 2012). Similarly, bilingual status did not protect against cognitive decline among a Japanese-American cohort (Crane et al., 2010), a Swedish cohort (Ljungberg et al., 2016), and Hispanic-American immigrants (Zahodne et al., 2014). Furthermore, population-based samples are more generalizable to the general population than clinic-based samples. This is because samples from memory clinics are only recruiting participants who are affected by cognitive impairment and who seek treatment. Clinic-based samples may introduce selection bias. For example, clinic-based samples are individuals who have access to healthcare services and are willing to seek medical help (health-seeking behaviour). Population-based samples include individuals with cognitive impairments who are not seeking care at memory clinics or healthcare services. As well, in clinic-based samples, outcome data were collected retrospectively from memory clinics, and language exposure was obtained via interviews with participants or caregivers. These subjective reports (i.e., self-reported data) can be subject to recall bias.

Although in population-based studies an association between bilingualism and dementia/AD is generally not seen, some evidence of a significant impact of multilingualism has been reported when studying participants speaking more than two languages. Participants

speaking three or more languages (but not two) were significantly less likely to develop dementia and AD (Chertkow et al., 2010; Perquin et al., 2013; Kave et al., 2008). Some population-based studies have reported a protective effect (lower risk of dementia and/or better cognitive state) of speaking four or more languages on dementia, irrespective of educational level (Chertkow et al., 2010; Perquin et al., 2013).

In addition to differences in samples and cognitive outcomes, there are differences in the type of outcome measures (e.g., age at onset of MCI vs. risk of MCI). Clinic-based studies investigate age at onset of MCI or dementia/AD (i.e., participants all have cognitive impairment) whereas in population-based studies, the outcome is the risk of MCI or dementia/AD (i.e., participants include those with and without cognitive impairment). This may also explain why our findings of a lack of association between multilingualism and MCI was more consistent with other studies with a similar outcome measure of risk of cognitive impairment.

Moreover, several studies have found that the association between bilingualism and dementia/AD was significant only when the level of education was low (Kave et al. 2008; Gollan et al., 2011). Kave et al. (2008) found that speaking three or more languages was associated with cognitive state among participants with low education (Kave et al., 2008). Thus, multilingualism might have prevented cognitive impairment despite having low educational attainment. In addition, Gollan et al. (2011) found that in individuals with high educational attainment, education seemed to completely erase the protective effects of bilingualism on AD. Another study found that the association between speaking more than two languages and cognition was only significant in those with low education (Liu et al., 2017). Other studies support this idea, that multilingualism is associated with better cognition only in individuals with lower educational attainment (Litwin et al., 2017; Park et al., 2019). These findings are similar to our

study, where speaking four or more languages was significantly associated with reduced odds of MCI, after controlling for age, *APOE* and country of birth, but this association became non-significant after adjusting for the effect of education. It might be that speaking four or more languages does not give additional protection against MCI from high education. The Nun Study population is a highly educated cohort and thus our lack of a significant association between multilingualism and MCI is consistent with the lack of association seen among highly educated participants in other studies. Overall, these findings support the theory of a ceiling effect of cognitive reserve. This might be that for those who are highly educated, the effect of language on cognition does not provide additional beneficial effects: a maximum level of protection may have already been achieved through a high level of education, rendering any additional impact of the number of languages on MCI status non-significant. Previous studies, in addition to our current results, suggest that different cognitively stimulating factors help to build cognitive reserve against cognitive impairment and may compete with any protective effects of multilingualism. For example, findings from the Canadian Longitudinal Study of Aging (CLSA) support the ceiling effect of cognitively stimulating activities in a population-based study. Winch et al., (2021) found that when models were stratified by cognitive leisure activities, speaking four languages was significantly associated with lower odds of low executive function in those who participated in infrequent cognitive activities, but not in those who participated in frequent cognitive activities (daily or several times a month). This further supports that cognitively stimulating factors (i.e., multilingualism, education, and cognitive leisure activities) do not work independently but together contribute to a ceiling or maximum level of cognitive reserve against cognitive impairment.

Findings on the association between multilingualism and MCI or dementia/AD may also be influenced by the study design. Cross-sectional studies have found an association between multilingualism and the age of onset of cognitive impairment (Alladi et al., 2013; Craik et al., 2010; Woumans et al., 2015). In cross-sectional studies, there may be recall bias since participants are asked to self-report the onset of dementia symptoms (see review by Calvo et al., 2016). Moreover, since cross-sectional studies gather data on multilingualism and cognition at one point in time, temporality cannot be confirmed. While concerns of reverse causality typically exist with cross-sectional data, they are not a major concern in this study because data on multilingualism were collected before the baseline cognitive assessments, thus preserving temporality. On the other hand, no significant association between multilingualism and dementia/AD was observed in longitudinal studies (Mukadam et al., 2017; Ljungberg et al., 2016; Zahodne et al., 2014), consistent with results for MCI in this study. In longitudinal studies, participants start dementia-free at baseline, and the development of dementia/AD is recorded longitudinally during the study in follow-up assessments. This further helps to preserve temporality and recall bias of subjective self-reporting.

In addition, the diversity in the sample characteristics such as age and presence of *APOE* (powerful predictors of dementia), may contribute to differences in study findings. Despite the established influence of *APOE* on the risk of dementia, most previous studies mentioned from either clinic or population-based studies did not control for the effect of this known genetic factor when assessing the association of the number of languages and MCI or dementia/AD. Another factor that may influence the association between multilingualism and cognition is the country of birth, more broadly immigrant status. Our study found that those born outside the U.S had an increased risk of overall MCI. This may be due to the unhealthy immigrant effect since

the majority of the Nun Study immigrants (not born in the U.S.) were from Germany. They were fleeing from Germany after WWI and the Great Depression, which might have created early-life stressors before joining the Convent.

Linguistic ability more broadly may also have an influence on cognitive impairment beyond simply the number of languages. Additional sensitivity analyses in our study investigating the influence of other measures of linguistic ability on the impact of multilingualism on overall MCI showed no significant association between idea density and grammatical complexity and overall MCI. However, other linguistic abilities had a different effect when investigating the subtypes of MCI in research question two.

6.2.2 Research Question Two: Subtypes of MCI

In research question two, we examined the association of multilingualism with the risk of aMCI and naMCI at baseline in a population-based sample, controlling for the influence of age at baseline, genetics, level of education, country of birth, and written linguistic ability.

The association between multilingualism and MCI subtypes has rarely been investigated in previous studies. To the best of the author's knowledge, this is the first study examining the effect of speaking two or more languages on MCI subtypes. Previous limited studies have specifically investigated the effect of bilingualism on subtypes of MCI. One previous clinic-based study examined the potential influence of bilingualism on the age at onset of single and multiple domain aMCI (Ossher et al., 2013), and another clinic-based study examined the age of onset of aMCI and naMCI (Ramakrishnan et al., 2017). Furthermore, a population-based study examined the risk of developing aMCI and naMCI (Wilson et al, 2015). Our study shows that multilingualism was not significantly associated with aMCI or naMCI after controlling for key confounders. The study conducted by Ossher and colleagues (2013) found that bilinguals with

single-domain aMCI demonstrated a later age of diagnosis of four years (mean age = 79.4 years) than monolinguals (mean age = 74.9 years). This protective effect was not observed in multiple-domain aMCI, suggesting that the protective advantage of lifelong bilingualism may be specific to single-domain aMCI (Ossher et al, 2013). Previous reports have found that lifelong bilingualism is associated with a delay in the onset of AD rather than other dementias (Bialystok et al., 2007): this would be consistent with findings that lifelong bilingualism (measured as speaking two languages daily at least in early adulthood) leads to a delayed age of onset of single-domain aMCI (Ossher et al, 2013) since single-domain MCI is characterized only by memory impairment. The other clinic-based study found that bilinguals with aMCI had a later age at onset than monolinguals (mean = 63.6.vs. 55.3 years), while this was not seen for naMCI (Ramakrishnan et al., 2017). Thus, it may be that lifelong bilingualism plays a role in preserving memory and would be greater in aMCI compared to naMCI.

In contrast, however, Wilson and colleagues (2015) found that early-life language instruction was associated with a lower incidence of naMCI but not aMCI. However, these studies did not control for *APOE*, which was a significant predictor of aMCI in our study and previous studies have found that *APOE* is specifically linked to aMCI. Overall, evidence of an association between multilingualism and overall MCI and its subtypes is very limited and does not take into consideration key genetic factors. The *APOE* gene has been confirmed as the major genetic risk factor for aMCI and conversion from aMCI to AD (Chen et al., 2015; Zhu et al., 2018). *APOE*-e4 carriers have been demonstrated as experiencing an earlier onset of memory decline and greater disease progression than non-carriers (Ungar et al., 2014). Overall, evidence of a stronger protective multilingual effect for aMCI vs. naMCI is limited and inconclusive.

Writing is another cognitively stimulating activity that has many complexities and demands on cognitive resources. The benefit of written linguistic ability is best explained through the mechanism of increasing working memory capacity, and thus may build cognitive reserve (Olive, 2012; McCutchen, 2000). Our analyses included additional measures of linguistic ability (idea density and grammatical complexity), which have not been examined in previous studies of multilingualism and MCI. Our study found that written linguistic ability (specifically high idea density) was protective against aMCI. This is consistent with previous research on an early sample of the Nun Study reporting that low idea density and grammatical complexity were associated with low cognitive test scores, a higher degree of cerebral atrophy, and greater risk of AD (Snowdon et al., 1996).

In addition, a significant association between speaking four or more languages on the risk of dementia was observed, even after controlling for education (Hack et al., 2019), but this association was attenuated by written language ability characteristics, specifically idea density (Hack et al., 2019). This supports the proposed ceiling effect of cognitively stimulating activities, including multilingualism and written language ability, on risk of cognitive impairment. A study by Iraniparast and colleagues (2022) found that individuals with higher levels of written language abilities had a significantly greater likelihood of reversion from MCI to normal cognition than progression from MCI to dementia. Moreover, de Medeiros et al. (2007) examined if an autobiographic workshop influenced memory performance in community-dwelling older adults. Participants completed five memory assessments and submitted two writing samples at baseline and follow-up, which were evaluated for linguistic complexity (Medeiros et al., 2007). This study found a significant increase in verbal memory test scores at follow-up, indicating a possible positive influence of the writing workshop. These results in

addition to those of this study suggest that the influence of other linguistic measures on MCI warrants further investigation in studies of the association of multilingualism and MCI (Olive, 2012; McCutchen, 2000).

6.4 Strengths

There are several strengths of this research project. One of the major strengths of the Nun Study is the homogeneity of the study population. Our study controlled for confounders not previously studied. Research in the field of language and cognition has been criticized for its inability to control for SES as a confounder, because of the difficulty in adjusting for confounding influences from the country of birth (immigrant status) and SES. In this study, all participants had similar adult lifestyles since joining the convent, including SES (e.g., income), marital and reproductive histories, substance use, access to health services, and social activities and supports. The high level of homogeneity among participants greatly reduced or eliminated many potential confounders. In addition, our study also adjusted for the influence of *APOE* status, a known genetic factor for dementia that has not often been examined in studies of multilingualism and cognitive function. The strong control of confounding factors addresses limitations present in past literature.

In addition, the investigation of multilingualism as a predictor of MCI (earlier stage of cognitive impairment) instead of the more common outcome of dementia or AD is a strength, as MCI has not often been explored in previous studies. As well, this study explored the association between multilingualism and MCI subtypes, which have only rarely been investigated.

The assessment of MCI is also a strength. Previous research has often used one cognitive test (e.g., MMSE) to measure cognitive performance. The Nun Study's use of multiple CERAD neuropsychological tests for the definition of MCI offers a more robust and comprehensive

measure of outcome than a single cognitive test. In addition, this study uses performance-based measures of ADLs, which reduces biases compared to self-reported data.

The assessment of the exposure (multilingualism) in the sample population is also a strength. A large proportion of participants in the Nun Study are multilingual. In other studies, it may be difficult to find populations where a large percentage speak three, four or even five languages. Due to this difficulty in finding participants who speak three or more languages, previous studies have mostly examined the association of bilingualism and compared it with monolingualism. This study is the first to our knowledge to evaluate the relationship between a higher number of languages spoken (three or more) and overall MCI as well as subtypes of MCI.

Furthermore, a key strength of this project is the population-based prospective study design of the Nun Study since much of the literature investigating multilingualism and MCI is clinic-based and retrospective. Clinic-based studies are influenced by selection biases related to healthcare service use. In addition, clinic-based studies do not capture individuals who remain cognitively intact, since participants already have cognitive impairment. Our study was able to examine the risk of MCI and not the typical measure of age at onset of MCI. In addition, the availability of data on multilingualism before the measurement of MCI at the baseline cognitive assessments reduces concerns of reverse causality between our exposure and outcome. Hence, based on the timeline of the data collection, multilingualism preceded MCI.

A major strength of our study was the ability to investigate other measures of linguistic ability (written ability), which have rarely been examined in previous studies of multilingualism and cognition. Thus, studies may be more likely to find a significant association between multilingualism and cognition. This study is the first to our knowledge to evaluate the relationship between written linguistic ability and subtypes of MCI.

6.5 Limitations

The current project has many strengths, but it also does have limitations. Although the Nun Study population was homogeneous and was able to control for various confounders, this study population of religious sisters may raise issues for the generalizability of our findings.

Limitations of our study also include the self-reported measure of multilingualism. As well, multilingualism was defined as speaking two or more languages and data were not collected on other factors related to multilingualism, such as second language acquisition, language frequency and intensity, and lifelong bilingualism. In contrast, some studies of multilingualism and cognitive function have measured language proficiency by having participants actively use the language(s) they claimed to be fluent in. The equal use of multiple languages every day was also not a requirement in our study. Studies that have found an association between language and cognition have studied lifelong bilinguals (participants who speak two languages daily). Nonetheless, the questionnaire on multilingualism was intended for employment in teaching positions, and thus participants would likely have reported fluency in only the languages in which they were confident they could teach.

Small sample sizes were a limitation for the analyses of the linguistic ability subsample in this study since autobiographies were only available on a subset of participants, and thus these sensitivity analyses have limited statistical power with wider confidence intervals and less precise estimates. As well, the majority of Nun Study participants were highly educated (i.e., had attained at least a bachelor's degree), and very few had low educational attainment (i.e., high school or less). In addition, MCI is a heterogeneous cognitive state; because of small sample sizes, the current project was not able to take into consideration all the MCI subtypes, such as single and multiple-domain MCI.

Another limitation of this study is the heterogeneity of the MCI diagnosis and underlying pathology. Diagnostic criteria evolve over the years and in longitudinal studies, this is particularly an issue as data have already been collected. MCI diagnostic criteria have evolved since the Nun Study data collection began. Our definition of MCI did not assess the neuropathologic substrate (neurofibrillary tangles, neuritic plaques) of MCI nor pathologic changes (hippocampus or amygdala) of MCI, which would affect the clinical progression of MCI. For example, those showing severe neuropathology (neurofibrillary tangles and neuritic plaques) or hippocampal atrophy would be more likely to progress to dementia than revert to intact cognition (Abner et al., 2017). Our definition based solely on cognitive tests is more likely to reflect a transient MCI state compared to using additional assessments (e.g., biomarkers, brain imaging, or informant reports) for an MCI diagnosis.

6.6 Implications and Future Research Directions

The results of the current study add to the limited literature on the association of multilingualism with overall MCI and subtypes of MCI. This study provides novel information concerning the impact of other language measures on cognitive function, specifically written linguistic ability. This study's findings suggest that the number of languages spoken is not significantly associated with MCI or its subtypes. A significant protective effect of speaking four or more languages on MCI risk became non-significant when adjusting for the level of education. Importantly, this suggests the possible presence of a ceiling effect, where speaking four or more languages does not offer any additional cognitive protection in highly educated populations. Nonetheless, learning a new language may be beneficial in different populations, such as individuals with low levels of education.

This study also provides novel findings that may support engagement in writing as a strategy to decrease the risk of amnestic MCI, thus playing a significant role in preserving memory. Written ability was associated with aMCI even after being adjusted for education, bringing additional protection to highly educated populations. This is a key finding of the study because aMCI individuals are more likely to proceed to AD than to other dementias. Memory increases the quality of life and independence of older adults. It has a fundamental role in the lives of people, such as remembering names and previous experiences, remembering to take medications, learning new information and skills as well as holding knowledge about our lives and personal attributes and traits. This study contributes to our understanding that while multilingualism may not provide added cognitive benefits in highly educated populations, it may be valuable when considered in the context of other cognitively stimulating activities. Evidence generated by this study also suggests that early-life written linguistic skills may be one of many cognitively stimulating factors that maximize cognitive health throughout the lifespan. Importantly, there may be multiple strategies to maximize cognitive health through cognitively stimulating activities; for example, individuals who are not interested in learning multiple languages may benefit from mastering written skills in one language. Ultimately, these results support the need to engage in cognitively stimulating activities, and one way may be through language-based training to improve written skills. Public health and policy recommendations based on evidence of this study could include increasing access and support to cognitively stimulating activities more broadly.

Future studies could build on the current baseline results by investigating the association between multilingualism and MCI using longitudinal data and expand the focus on MCI across all of the subtypes of MCI (aMCI, naMCI, single and multiple-domain MCI). The study could

also be repeated in other populations to investigate the association between multilingualism and MCI across groups speaking a different language (e.g., where monolinguals are not those speaking English) and non-religious groups. With respect to other potential confounders or effect modifiers not mentioned, future studies could investigate comorbidities as well as sex and gender differences since very little is known about their influence on the association between multilingualism and cognitive status. Future studies could also consider the role of other linguistic abilities (e.g., reading ability) and other language characteristics, such as the age of language acquisition, the similarity of languages spoken, level of fluency, frequency and intensity of language use, and lifelong multilingualism. Additionally, future studies could look at differences in the acquisition of language, such as immigrants who speak a language from birth versus people who choose to learn a language later in life. Such knowledge could clarify the target audience and language-based interventions to promote multilingualism and writing skills as a strategy to reduce the risk of overall MCI. As well, an association between American Sign Language (ASL) with MCI or other cognitive outcomes could be another research area of interest in exploring the difference between spoken and sign language.

6.7 Conclusions

The high prevalence of age-related cognitive impairment combined with the continuing growth of the older population poses enormous challenges to the economy and society. It is vital to understand ways to protect against cognitive impairment in older adults and support independence in late life. Thus, the identification of modifiable protective factors is key to guiding dementia prevention strategies. Overall, delaying the onset or reducing the risk of MCI and dementia is a top priority for today's aging society. This study allowed us to explore the effect of cognitively stimulating activities (i.e., number of languages, written language) in a

highly educated population and contributes to evidence that there might be less of an impact of multilingualism in highly educated populations. By investigating the number of languages spoken, in addition to written linguistic ability, this study contributes to the understanding of how language skills and other cognitively stimulating activities (e.g., education) can act individually as well as in combination and how this may lead to a ceiling effect of the protective impact of cognitively stimulating activities on MCI and its subtypes. Ultimately, these findings may encourage individuals to engage in cognitively stimulating activities to potentially reduce the risk of MCI. In conclusion, supporting language-based and other cognitively stimulating activities is one important piece among other strategies, such as social and physical activities, that contribute to a multi-model framework to reduce the risk of cognitive impairment.

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Appendices

Appendix A: Literature Search Strategies
Table A1. Literature Search Strategy for PubMed

	Search terms:			
Database:	**Multilingualism**	**Mild Cognitive Impairment**	**Age**	**Time**
PubMed/Medline	Multilingual*[tiab] OR Multilingual*[MeSH] OR Multi-lingual*[tiab] OR Multi-lingual*[MeSH] OR Bilingual*[tiab] OR Dual Language*[tiab] OR Language Proficienc*[MeSH] OR Language*[MeSH:noexp] OR Multiple Language*[MeSH] OR Languages Spoken[MeSH] OR Type of Language*[MeSH] OR Individual Language*[MeSH] OR Similarity of language*[MeSH]	Mild Cognitive Impairment*[MeSH] OR Mild Cognitive Impairment*[tiab] OR Non-amnestic Mild Cognitive Impairment*[MeSH] OR Non-amnestic Mild Cognitive Impairment*[tiab] OR Amnestic Mild Cognitive Impairment*[MeSH] OR Amnestic Mild Cognitive Impairment*[tiab] OR Dementia[MeSH] OR Dementia[tiab] OR Alzheimer Disease[MeSH] OR Cognitive Function*[MeSH:noexp] OR Cognitive Impairment[MeSH:noexp] OR Cognitive Aging[MeSH:noexp]	Aged[Mesh] OR Older OR Elder*[tiab] OR Older Adult*[tiab]	Aging[MeSH] OR “Ageing” OR Follow-up stud* OR Prospective Stud* OR Prospective Cohort Stud* OR Longitudinal Cohort Stud* OR Longitudinal Stud*

Complete search strategy: #1 AND #2 AND #3 AND #4

#4 Aging[MeSH] OR “Ageing” OR Follow-up stud* OR Prospective Stud* OR Prospective Cohort Stud* OR Longitudinal Cohort Stud* OR Longitudinal Stud*

#3 Aged[Mesh] OR Older OR Elder*[tiab] OR Older Adult*[tiab]

#2 Mild Cognitive Impairment*[MeSH] OR Mild Cognitive Impairment*[tiab] OR Non-amnestic Mild Cognitive Impairment*[MeSH] OR Non-amnestic Mild Cognitive Impairment*[tiab] OR Amnestic Mild Cognitive Impairment*[MeSH] OR Amnestic Mild Cognitive Impairment*[tiab] OR Dementia[MeSH] OR Dementia[tiab] OR Alzheimer Disease[MeSH] OR Cognitive Function*[MeSH:noexp] OR Cognitive Impairment[MeSH:noexp] OR Cognitive Aging[MeSH:noexp]

#1 Multilingual*[tiab] OR Multilingual*[MeSH] OR Multi-lingual*[tiab] OR Multi-lingual*[MeSH] OR Bilingual*[tiab] OR Dual Language*[tiab] OR Language Proficienc*[MeSH] OR Language*[MeSH:noexp] OR Multiple Language*[MeSH] OR Languages Spoken[MeSH] OR Type of Language*[MeSH] OR Individual Language*[MeSH] OR Similarity of language*[MeSH]

Search performed on April 22, 2022, and retrieved 1069 records

Table A2. Literature Search Strategy for PsycINFO

	Search terms:			
Database:	**Multilingualism**	**Mild Cognitive Impairment**	**Age**	**Time**
PsycINFO	"Multilingual*" OR "Multi-lingual*" OR "Bilingual*" OR "Dual Language*" OR "Language Proficienc*" OR "Multiple Language" OR "Languages Spoken" OR "Mother Tongue" OR "Native Language" OR "Foreign Language" OR "Second Language" OR "Type of Language" OR "Individual Language" OR "Similarity of language"	"Mild Cognitive Impairment" OR "Non-amnestic Mild Cognitive Impairment" OR "Non-amnestic Mild Cognitive Impairment" OR "Amnestic Mild Cognitive Impairment" OR "Amnestic Mild Cognitive Impairment" OR "Dementia" OR "Alzheimer disease" OR "Cognitive Function" OR "Cognitive Abilit*" OR "Cognitive Disorders" OR "Cognitive Aging" OR "Cognitive Impairment"	Older OR Elder* OR "Older Adult*"	Aging OR Ageing OR "Follow-up stud*" OR "Prospective Stud*" OR "Prospective Cohort Stud*" OR "Longitudinal Cohort Stud*" OR "Longitudinal Stud*"

Complete search strategy: #1 AND #2 AND #3 AND #4 AND Peer-Reviewed Journals Only

#4 Aging OR Ageing OR "Follow-up stud*" OR "Prospective Stud*" OR "Prospective Cohort Stud*" OR "Longitudinal Cohort Stud*" OR "Longitudinal Stud*"

#3 Older OR Elder* OR "Older Adult*"

#2 "Mild Cognitive Impairment" OR "Non-amnestic Mild Cognitive Impairment" OR "Non-amnestic Mild Cognitive Impairment" OR "Amnestic Mild Cognitive Impairment" OR "Amnestic Mild Cognitive Impairment" OR "Dementia" OR "Alzheimer disease" OR "Cognitive Function" OR "Cognitive Abilit*" OR "Cognitive Disorders" OR "Cognitive Aging" OR "Cognitive Impairment"

#1 "Multilingual*" OR "Multi-lingual*" OR "Bilingual*" OR "Dual Language*" OR "Language Proficienc*" OR "Multiple Language" OR "Languages Spoken" OR "Mother Tongue" OR "Native Language" OR "Foreign Language" OR "Second Language" OR "Type of Language" OR "Individual Language" OR "Similarity of language"

Search performed on April 22, 2022, and retrieved 1662 records

Literature Search Strategy

April 2022

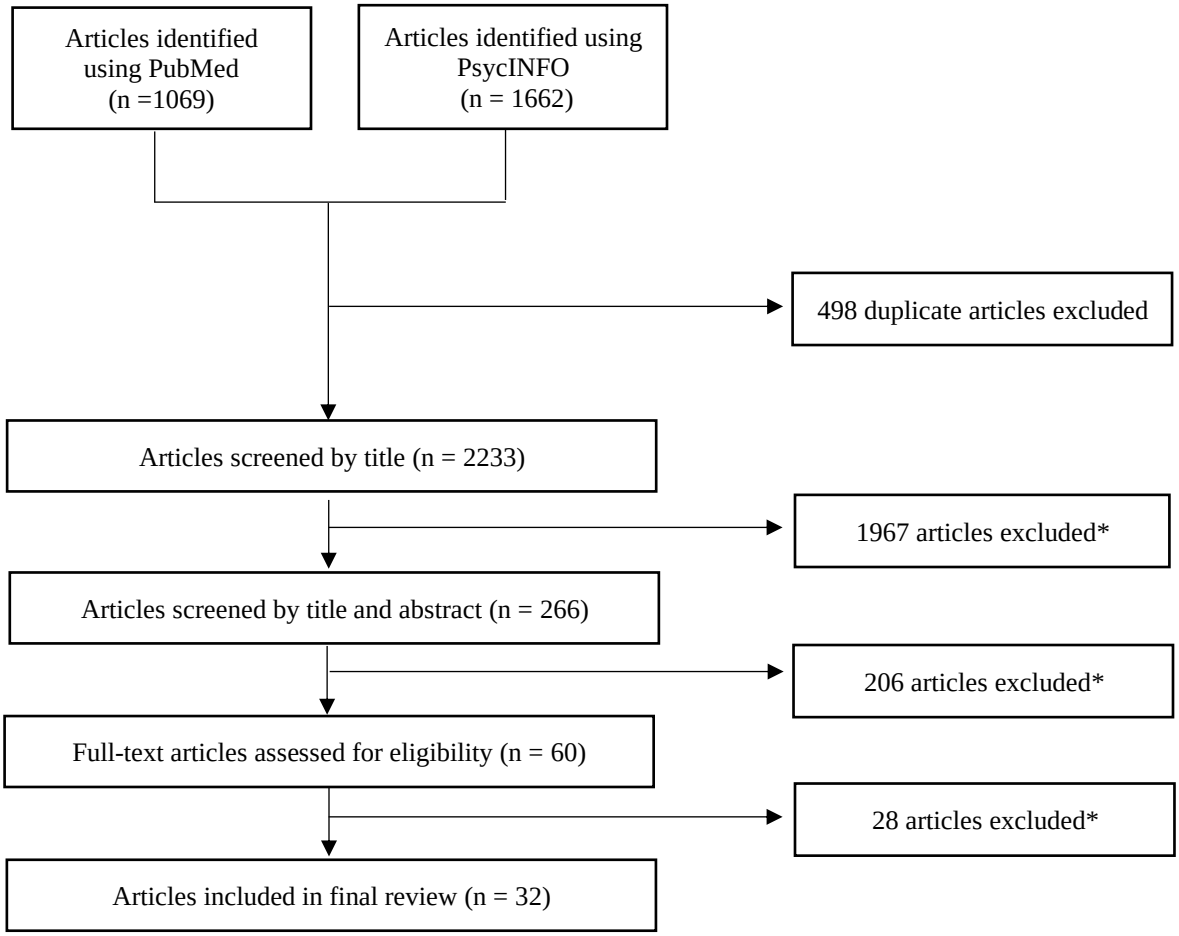


Figure A1. Flowchart of Systematic Literature Search Strategy

*Articles were excluded if:

1) The exposure was not multilingualism
2) The outcome was not mild cognitive impairment, non-amnestic mild cognitive impairment, amnestic mild cognitive impairment, dementia, or AD
3) The sample only included participants under the age of 65 years

Appendix B: Literature Search Summary Tables

Table B1. Summary Table of Research Literature on the Association Between Multilingualism and MCI/dementia

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Alladi, Bak, Duggirala, Surampudi, Shailaja, Shukla & Kaul (2013). Bilingualism delays age at onset of dementia, independent of education and immigration status.	-Study cohort consisted of 648 patients -mean age was 66.2 (ranging from 32-92 years) -Case records were reviewed of 648 patients with dementia from a specialist Memory Clinic in Hyderabad, India, between 2006-2012. -391 participants were bilinguals	- Bilingualism as the exposure - Controlled for: number of languages spoken, education, sex, rural/urban living, and occupation.	-Age of onset of dementia in AD dementia, frontotemporal dementia, vascular dementia, dementia with Lewy bodies, and mixed dementia.	- Independent samples t-test/one-way ANOVAs and Fisher exact and chi square tests for categorical variables (descriptive analysis) -Univariate general linear model (GLM)	-Bilinguals developed dementia 4.5 years later than the monolinguals. -significant difference in age of onset between AD dementia, frontotemporal dementia, and vascular dementia, and those patients that were illiterate. -No additional benefit of speaking more than 2 languages. -Even after controlling for confounding factors, the age of onset of dementia was protective in the bilingual group.
Bak, Nissan, Allerhand & Deary (2014).	- Wave 1: 1,091 participants of the Scottish Mental Survey (1947)	-Bilingualism: participants completed a questionnaire asking	-Cognitive tests: Matrix Reasoning, Letter Number Sequencing, Block	-Multiple linear regression controlling for covariates	- Bilinguals performed significantly better on reading, verbal

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Does bilingualism influence cognitive aging?	-Wave 2: 866 returned for assessment in 2008–2010 and 853 from the Lothian Birth Cohort that completed the bilingualism questionnaire	if they had learned any languages other than English. They were asked to specify the number of languages spoken and at what age as well as the frequency of use (conversation, reading, and media). -Covariates: models were adjusted for age, sex, and social class (subject's and their father's).	Design, Digit Symbol and Symbol Search from the Wechsler Adult Intelligence Scale-III, UK edition (WAIS-III), and Digit Span Backward from the Wechsler Memory Scale-III, UK edition (WMS-III) - Measure performance on general fluid-type intelligence, memory, speed of information processing, Moray House Test, Vocabulary and reading, and Verbal Fluency.		fluency and general intelligence. -Positive effect of bilingualism on later-life cognition, even those who learned a second language in adulthood -A significant interaction was found between CI and performance at age 73 years for the active bilingual group (greater frequency of language use).
Berkes, Bialystok, Craik, Troyer, & Freedman (2020). Conversion of mild cognitive impairment to Alzheimer Disease in monolingual and bilingual patients.	-75 Older bilinguals and 83 monolinguals -Memory clinic with MCI -longitudinal study	-Monolingualism vs. bilingualism	-Age of MCI and AD diagnosis and time of conversion across language groups	-2-way ANOVA	-Bilinguals were diagnosed with MCI at a later age than monolinguals (77.8 years and 75.5 years) -bilinguals converted faster from MCI to AD than

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
					monolinguals (1.8 and 2.8 years) -greater cognitive reserve by language status leads to faster conversion between MCI and AD
Bialystok, Craik, & Freedman (2007). Bilingualism as a protection against the onset of symptoms of dementia.	- Population consisted of 228 participants from the memory clinic at Baycrest Toronto, Canada (2002-2005) - Patients were diagnosed with AD at baseline. - Sample consisted of 184 participants (91=monolinguals and 93=bilinguals).	-Exposure: bilingualism (those who regularly speak at least two languages since earlier life) -Covariates: MMSE, occupation, and years of education.	-Age at onset of dementia symptoms	-ANOVA and regression analyses	-Bilinguals had a 4.1-year delay in the age at onset of dementia than monolinguals. -Bilinguals had a 4.3-year delay in the onset of AD symptoms and a 3.5-year delay in the onset of other dementias (vascular and Lewy Body) compared to monolinguals. -This delay was seen even after adjusting for immigrant status, education and occupation.
Bialystok, Craik, Binns, Ossher & Freedman (2014).	-Sample consisted of 149 participants from the Sam and Ida Ross	-Exposure: bilingualism via the Language and Social	-Onset of dementia symptoms via interview questionnaire	-ANOVA and logistic regression analyses	- Bilinguals delayed onset of MCI for 4.7 years and AD for 7.3

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Effects of bilingualism on the age of onset and progression of MCI and AD: Evidence from executive function tests.	memory clinic at Baycrest Toronto. -At baseline, individuals had AD (n=75) or MCI (n=74) -Individuals were excluded from the study if they had psychiatric conditions.	Background Questionnaire). -Bilingualism was classified as using both languages on a daily basis and early age of acquisition of second language. - Covariates: alcohol and smoking status, physical and social activities, and diet	(subjective reposting from participants or their proxy). - Based on Delis-Kaplan Executive Function tests.		years relative to monolinguals. - More years of delay than other studies (due to smaller sample size). -Immigrant status did not influence the association between bilingualism and the onset of dementia symptoms of AD/MCI.
Calabria, Hernández, Cattaneo, Suades, Serra, Juncadella,v& Costav (2020). Active bilingualism delays the onset of mild cognitive impairment.	**-T**hree groups of participants: 63 healthy individuals, 135 patients with MCI, 68 patients with AD.	-Different degrees of language experience and usage of Catalan and Spanish -Exposure: educational level and occupation	-Age at onset of cognitive symptoms, age at the first medical visit for cognitive impairments, and age at diagnosis in patients with MCI and patients with AD. - Comparison with healthy individuals are only for cognitive tests	-Stepwise multiple regression analyses	-Active bilingualism was a significant predictor of delay in the age at onset for all the clinical measures in MCI, but not AD patients. -active bilingualism was independent of occupation, educational level and job attainment. - This was only seen in MCI and AD patients
Chertkow, Whitehead, Phillips, Wolfson, Atherton & Bergman (2010).	-Sample consisted of 632 participants from the memory clinic of the Jewish General	-Multilingualism (speaking more than one language).	-Time of their initial diagnosis (AD or age at symptom onset)	- ANOVA and Linear regression analysis	- No significant benefits of bilingualism and age at diagnosis of AD

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Multilingualism (but not always bilingualism) delays the onset of Alzheimer disease: evidence from a bilingual community.	Hospital in Montreal, Canada. -Diagnosed with AD as baseline (253 multilinguals and 379 monolinguals). -Multilinguals: 135=immigrants -Monolinguals: 66=native French and 290=native English speakers.	-Definition did not take into account age of second language acquisition and age of immigration. Covariates: education, sex, occupation, SES, immigrant status.			or age at symptom onset. -Speaking more than two languages was slightly protective and associated. -Native French speakers who spoke more than two languages had delated onset of symptoms and AD. -A dose-response effect was seen in bilingual immigrants in delating the diagnosis of AD (bilinguals =5 years, trilinguals=6.4 years, more than three languages=9.5 years).
Crane, Gruhl, Erosheva, Gibbons, McCurry, Rhoads & White (2010). Use of spoken and written Japanese did not protect Japanese American men from	-Sample consisted of second-generation Japanese-American men born between 1900-1919. -No dementia at baseline. - 2520 participants and only 465 did not speak nor read	-Exposure consisted of spoken and written Japanese based on self-reports. Covariates: income, education, age, smoking status, APOE4 status and head circumference.	-Cognitive function via Cognitive Abilities Screening Instrument.	-Mixed effects modelling	- Spoken and written Japanese was not correlated with the rate of cognitive decline. -Self-report and missing data may have influenced the results of the study.

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
cognitive decline in late life.	Japanese, 1495 only speak Japanese and 560 can both speak and read.				
Csukly, Siralu, Fodor, Horvath, Salacz, Hidasi, Csibri, Rudas & Szabo (2016). The differentiation of amnestic type MCI from non-amnestic types by structural MRI.	-Participants included 62 aMCI, naMCI, and healthy controls based on the Petersen criteria.	-Covariates included age and gender.	-Outcome consisted of structural imaging methods and neuropsychological tests (all participants required routine brain MR examination and neuropsychological examination)	-General Linear Model Analysis	-Sizes of the hippocampus, the entorhinal cortex and the amygdala were decreased in aMCI compared to naMCI as well as controls -cortical thickness of the entorhinal cortex, the fusiform gyrus, the precuneus and the isthmus of the cingulate gyrus were significantly decreased in aMCI -Biggest differences= volume of the hippocampus (18% decrease in aMCI vs. controls) and the cortical thickness (20% decrease in aMCI vs. controls). -naMCI compared to controls (only the volume of the

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
					precuneus were decreased) Neuropsychological test: decreased anterograde, retrograde memory, and category fluency in aMCI compared to controls and naMCI.
DeLuca, Rothman, Bialystok, & Pliatsikas, (2019). Redefining bilingualism as a spectrum of experiences that differentially affects brain structure and function.	-65 healthy, right-handed bilingual adults (49 females, mean age: 31.7, SD: 7.24, range: 18–52) -Participants spoke a variety of first languages (L1), but all spoke English as their second language -Born in other countries and moved to the United Kingdom at varying ages (mean age: 26.41, SD: 7.73, range: 3.1–50.9)	-Exposure: Lifelong bilingualism (second language exposure and use) -Covariates: educational level and occupation	-Brain structure and function	-Generalized linear model (GLM)	-Differences in bilingual language experiences had different outcomes in terms of brain structure and function
Duncan, Nikelski, Pilon, Steffener,	-Data used from	-Exposure included multilingualism -Covariates:	-Outcome: MMSE	ANOVA .	-Speaking more than one language

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Chertkow & Phillips (2018). Structural brain differences between monolingual and multilingual patients with mild cognitive impairment and Alzheimer disease: Evidence for cognitive reserve.	Memory Clinic of the Jewish General Hospital in Montréal. -Sample had 34 monolingual MCI and 34 multilingual MCI -Patients had baseline MCI or AD. -MCI participants included amnestic MCI or amnestic plus (memory impairment and other domains).	years of education, age at time of scan, time from neuropsychological assessment to scan, MMSE, and episodic memory tests.			contributed to increased grey matter in the brain and delayed cognitive symptoms in MCI and AD patients. -Higher tissue density in multilingual MCIs versus monolingual MCIs. -Multilingualism may contribute to increased gray matter in LCC areas, thus delay cognitive symptoms of disease-related atrophy.
Gold, Kim, Johnson, Kryscio & Smith (2013). Lifelong bilingualism maintains neural efficiency for cognitive control in aging.	-The sample included 110 participants. -Total of 30 right-handed community dwelling participants (15 older adult monolinguals with a mean age of 63.3 years and 15 older adult bilinguals with a mean age of 64.1 years).	-Exposure: bilingualism -Covariates: sex, age, education level, SES	-Cognitive and demographic measures: the Peabody Picture Vocabulary Test, the Hollingshead Two-Factor Index of Social Position, The Cattell Culture Fair Intelligence Test, the Digits Span Subtests of the	-Hierarchical regression analyses	-Experiment 1: bilinguals had better perceptual switching scores than monolingual. -Experiment 2: Typical age-related performance decrease in perceptual task-switching and

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
	-Total of 80 right-handed community dwelling participants		Wechsler Memory Scale.		increase in fMRI activation. -Lifelong bilingualism prevents age-related declines.
Hack, Dubin, Fernandes, Costa, & Tyas (2019). Multilingualism and dementia risk: longitudinal analysis of the Nun Study.	-Nun Study, a longitudinal study of 678 religious sisters aged 75+ years at baseline -Analytic sample comprised of 345 participants -Participants did not have dementia at baseline	-Exposure: multilingualism was self-reported and collected in a 1983 survey. -The number of languages reported ranged from one to five. -Covariates: age, education, occupation and written linguistic ability (grammatical complexity and idea density)	-Dementia: annual cognitive assessments. -Cognitive function was measured by trained gerontologists using the CERAD neuropsychological battery test and MMSE for global function	-Bivariate analyses with Pearson chi-square tests -Yates continuity correction and Fisher's exact tests -Independent sample t-tests -Discrete-time survival analysis -Sensitivity analyses were assessed for fit based on Hosmer-Lemeshow goodness-of-fit test, as well as residual diagnostics, and tests of multicollinearity	-Multilingualism did not delay the onset of dementia. -Speaking four or more languages (but not two or three) was associated with a lower risk of developing dementia compared to monolinguals (OR= 0.13; 95% CI = 0.01-0.65) -This significant association weakened (OR= 0.53; 95% CI = 0.06, 4.91) when adding idea density in models.
Ihle, Oris, Fagot & Kliegel (2016). The relation of the number of languages spoken to performance	-Sample consisted of 2812 older adults -2073 performed a psychometric test on processing speed and	-Exposure is the number of languages -Covariates included different languages spoken on a regular basis, educational	-Psychometric tests on verbal abilities, basic processing speed, and cognitive flexibility.	-Bivariate and regression analyses.	-The number of languages spoken was linked to cognitive performance even after adjusting for

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
in different cognitive abilities in old age.	1692 on the based on cognitive flexibility. -Cross-sectional sample study randomly selected from Swiss administrations' records. -Data collected between 2011-2012, via the Vivre-Leben-Vivere (VLV) survey.	attainment, occupation, and activity engagement. -Stratified by age, sex and canton.			leisure activities, physical demand of job, but not above educational attainment and cognitive level of job. -Suggesting that speaking different languages on a regular basis may contribute to the build-up of cognitive reserve in older adults.
Jafari, Esmaili, Toufan, Aghamollaei (2015). Bilingual proficiency and cognitive reserve in Persian–English bilingual older adults.	-Sample consisted of 26 university educated teachers (8 females) with post-secondary education. -Persian and English participants with mean age of 67.52 years (range 60-75)	-Bilingualism: participants were bilingual in Persian and English early in life.	-Cognitive tests via lexical memory and Bergen dichotic listening tests	-Parametric statistical tests (independent t-test, paired t test and Pearson's correlation test)	-A significant correlation between the proficiency of bilingualism and dichotic listening scores ($p<0.045$), and lexical memory score ($p<0.043$). -Thus, showing the influence of bilingualism on cognitive reserve in bilingual older adults (linguistic experience-dependent neuroplasticity).

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Kavé, Eyal, Shorek & Cohen-Mansfield (2008). Multilingualism and cognitive state in the oldest old.	-Sample consisted of the oldest Israeli Jewish population (n=814, mean age= 83.0 years; SD=5.4) -Interviewed in 1989 and then assessed twice more within 12 years.	-Bilingualism, trilingual, and speaking more than three languages -Self-reported on the number of languages spoken -Covariates: age, birthplace, age at immigration, education, and gender.	-Cognitive performance via scores on Katzman cognitive screening test and Folstein mini mental state exam (MMSE).	-Regression analyses	-Cognitive performance differed among bilinguals, trilinguals, and multilinguals (number of languages spoken was linked cognitive scores beyond the influence of age, gender, birthplace, age at immigration, or education). -Those who reported being most fluent in a language other than their native language performed better compared to those whose mother tongue was their best language.
Kowoll, Degen, Gladis & Schröder (2015). Neuropsychological profiles and verbal abilities in lifelong bilinguals with mild cognitive impairment	-Between June 2012 and March 2014, 86 subjects were recruited from the Memory Clinic of the University of Heidelberg -41 subjects were lifelong bilinguals (mean age= 73.6; SD=	-Bilingualism defined as participants who spent the majority of their lives using at least two languages. -Covariates included age, gender, and years of education	-Cognitive test scores: Neuropsychological performance on CERAD-NP, clock-drawing test, and the logical memory subscale of the Wechsler Memory Scale	-ANOVA with post hoc Games-Howell tests	-Bilingual MCI patients scored lower on the verbal fluency and picture naming task in their dominant language -Bilingual AD participants showed a decreased performance in their

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
and Alzheimer's disease.	11.5) and 45 were monolinguals (mean age= 78.1; SD= 10.9). -17 subjects = cognitively healthy, 22 =MCI according to the aging-associated cognitive decline criteria (AACD), and 47 individuals were diagnosed with AD				nondominant language than bilingual MCI patients and bilingual controls
Kowoll, Degen, Gorenc, Küntzelmann, Fellhauer, Giesel & Schröder (2016). Bilingualism as a contributor to cognitive reserve? Evidence from cerebral glucose metabolism in mild cognitive impairment and Alzheimer's disease.	-30 patients diagnosed with MCI and early-stage AD, recruited between June 2012 and March 2014 -16 patients were lifelong bilinguals and 14 were classified as monolinguals -Participants spoke nine different first languages and seven different second languages -Clinic-based sample from the Memory Clinic of the University of Heidelberg.	-Bilingualism (exposure) was matched for age, sex and MMSE scores (covariates)	-Neuropsychological test battery (outcome): German version of the CERAD-NP neuropsychological assessment battery, MMSE, Trail Making Test, logical memory, Wechsler Memory Scale, clock-drawing test.	-Test scores from CERAD, WMS, and TMT were transformed into z-scores. -Significant level was set to $p<0.05$ with threshold $k>30$.	-Bilingual participants showed significantly greater impairment of glucose uptake in frontotemporal, parietal regions and left cerebellum compared to monolinguals. -Bilingualism is likely to contribute to cognitive reserve as they had more severe brain changes than monolinguals.

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Lawton, Gasquoine, & Weimer (2015). Age of dementia diagnosis in community dwelling bilingual and monolingual Hispanic Americans.	-Sample consisted of 81 bilingual and monolingual dementia cases between 1998 and 2008 from the Sacramento area Latino Study on Aging. - Community dwelling Hispanic Americans (immigrant and born in the US).	-Exposure was bilingualism -Covariates consisted of immigrant status or US born	-Age of clinically diagnosed AD and vascular dementia via neuropsychological tests and objective diagnostics	-ANOVA	-Mean age of dementia diagnosis was higher in the monolinguals (mean age = 81.10 years) compared to bilinguals (mean age= 79.31) -Bilinguals were significantly better educated than monolinguals; however, U.S. born bilinguals & monolinguals did not differ by education.
Li, Han Lam, Li, Matthews, Cheung, & Gozes (2021). Correlation between the bilingual status and the onset age of AD and MCI subjects: evidence from the ADNI dataset.	-580 Alzheimer's Disease subjects and 1264 Mild Cognitive Impairment subjects	-Exposure: bilingualism -Covariates: age, education, occupation	-Onset Age of AD and MCI across a clinical sample	-Simple least-square regression analysis	-Monolinguals did not statistically manifest earlier onset compared to the bilinguals. -Inconsistent with findings on bilingual advantage in clinic-based studies.
Ljungberg, Hansson, Adolfsson, Nilsson (2016). The effect of language skills on dementia in a	-Sample consisted of 736 monolinguals and 82 bilinguals over the age of 60 years. -Data source: Betula prospective cohort	-Exposure: bilingualism -Participants self-reported their second language proficiency based on a Likert	-Dementia diagnosis outcome as the dependent variable (yes/no) -The 112 Dementia cases included AD,	-Cox proportional hazard regression	-Participants did not have dementia at baseline, but after 10 years, 112 developed dementia (102 =

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Swedish longitudinal cohort.	study in Umea, Sweden -Participants were those whose native tongue was Swedish	scale. Those who had a score four or higher were categorized as bilinguals, whereas those who only spoke Swedish were categorized as monolinguals -Covariates: age, sex, and APOEε4 allele	Lewy body dementia, vascular dementia, frontotemporal dementia, Parkinson dementia and unspecified.		monolinguals and 10 bilingual). -No significant association between bilingualism on delaying the onset of all types of dementia compared to monolinguals (HR= 1.43, 95%, CI= 0.73-2.85, p =0.29). Nor does it have an association with AD alone (HR=1.52, 95% CI = 0.62-3.71, p = 0.36). This insignificant result may be due to the low frequency of language use among bilinguals in this study, since only 60% of the participants used their second language while traveling.
Mukadam, Jichi, Green & Livingston (2018).	-Data was collected from the Australian Longitudinal Study of Ageing for over 20	-Bilingualism (those who said they spoke another language at home other than English) was self-	-Cognitive function via the Mini- Mental State Examination (MMSE) and National Adult	-Linear mixed models were used to assess the effect of bilingualism on	-Bilinguals had lower baseline MMSE scores compared to monolinguals (mean

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
The relationship of bilingualism to cognitive decline: The Australian Longitudinal Study of Ageing.	years (population-based study) -2087 participants aged 65 years and older who lived in Adelaide, South Australia. -Bilinguals were younger, born outside of Australia and immigrants from Poland, Italy, Germany and other European countries	reported via administered questionnaire in English -Subjective reports correlated with objective measures of language proficiency -Covariates included demographics (age, sex, years of education, birthplace, and occupation), social networks (lived alone, marital status), physical health (smoking, alcohol use, diet, exercise), and mental health (history of mental illness).	Reading Test (NART), which consisted of executive function tests, Boston naming test and verbal fluency tests.	MMSE score over time -t-tests to compare numerical variables and chi-squared tests for categorical variables.	= −2.23 points; 95% CI= 1.56–2.90). However, this was due to education and NART scores. -Thus, bilingual and monolinguals did not differ in MMSE decline over time nor on executive function tests.
Olsen, Pangelinan, Bogulski, Chakravarty, Luk, Grady, & Bialystok (2015). The effect of lifelong bilingualism on	28 healthy older adults: -14 = monolinguals speaking English (7 males and 7 females, M age = 70.6 years, SD = 3 years)	Exposure: bilingualism Covariates: age and years of education	Outcome: Scores on MMSE, Stroop response, Trail-making response time, and Verbal fluency	Repeated measures ANOVAs were used to investigate potential differences in neocortical and hippocampal volumes as a function	-Iincreasing age was related to decreasing temporal cortical thickness in the monolinguals but not in bilinguals. -Bilingualism

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
regional grey and white matter volume	-14 = lifelong bilingual experience (6 males and 8 females; M age = 70.4 years, SD = 3.7 years).			of language experience.	preserves frontal and temporal lobe function in aging.
Ossher, Bialystok, Craik, Murphy & Troyer (2013). The effect of bilingualism on amnestic mild cognitive impairment.	-Sample consisted of 111 older adults from newspaper physician referrals	-Exposure of bilingualism -Covariates included age, duration of symptoms (MCI), education, MMSE, and sex	-Outcome: age of diagnosis for those with single or multiple domain aMCI	-Two-way ANOVA	-Bilinguals with single-domain aMCI demonstrated a later age of diagnosis (mean = 79.4 years) than monolinguals (mean = 74.9 years). -Suggesting that protective advantage of bilingualism may be specific to single-domain aMCI
Perani, Farsad, Ballarini, Lubian, Malpetti, Fracchetti, & Abutalebi (2017). The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia.	Eighty-five patients were selected from two centers: the San Raffaele Hospital in Milan (n = 40; 19 male and 21 female) and the Bozen Central Hospital (n = 45; 13 male and 32 female).	Exposure: bilingualism Covariates: age, gender, disease duration, education	Outcome: Global cognitive status (i.e., MMSE scores), and equivalent scores of neuropsychological tests assessing four cognitive domains (i.e., verbal memory, visuospatial memory, language and attention functions).	-Means of a two independent sample t tests.	-Bilingual individuals were on average 5 years older than their monolingual peers when diagnosed with AD. -Cerebral hypometabolism was more severe in the group of bilingual individuals with AD. -Supports the neuroprotective

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
					effect of bilingualism by showing an increased connectivity in executive function. -the degree of lifelong bilingualism (high moderate or low use_ was significantly predictive.
Perquin, Vaillant, Schuller, Pastore, Dartigues, Lair & MemoVie Group. (2013). Lifelong exposure to multilingualism: new evidence to support cognitive reserve hypothesis.	-Sample consisted of 232 non-demented participants aged 65 and older (44 CIND and 188 (no CIND) from the MemoVie Study (a Luxembourg population) -Study design: retrospective nested case-control	-Multilingualism: self-reported questionnaire asking the number of languages spoken, age of acquisition and duration of practice (years). -Participants spoke 2-7 languages -The reference group was bilingualism -Covariates: various sociodemographic characteristics (age, education) and lifestyle behaviours	Outcome: i) cognitive impairment without dementia (CIND) - risk of CIND	-Univariate analyses and mixed models	- Those who spoke more than two languages had lower risk of CIND, after adjusting for education and age (OR= 0.30, 95%CI =0.10–0.92) compared to bilinguals. -Speaking 3 languages instead of 2, was linked with a seven-fold protection against CIND (OR = 0.14, 95% CI= 0.04– 0.45, p= 0.0010). -A delay of one year in speaking three

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
					languages was linked to an increased risk of CIND by 1.02 (OR=1.2, 95% CI=1.01-1.04).
Prior & Gollan (2011). Good language-switchers are good task-switchers: Evidence from Spanish–English and Mandarin–English bilinguals.	-Study consisted of 547 monolingual English speakers, and 2 bilingual groups (541 Spanish–English bilingual, and 543 Mandarin–English bilinguals) -Participants were undergraduate students at the University of California San Diego.	-Exposure of bilingualism was measured as having to first been exposed to both languages before the age of 6, and had been frequently using both languages (self-report questionnaire) -objective measures of language proficiency	-Participants completed cognitive and linguistic tests (non-linguistic task-switching, language-switching, Shipley vocabulary test, Verbal fluency and Matrices subtest).	-Analyses were performed for the following tests: non-linguistic task-switching, language-switching, Shipley vocabulary test, Verbal fluency and Matrices subtest -Means and SD were computed using SPSS	-Spanish–English bilinguals (high language use for both) had smaller task-switching costs than monolinguals after controlling for covariates (speed and parent education level). -Mandarin–English bilinguals, who did not use both languages frequently, did not have a task-switching advantage compared to monolinguals.
Ramakrishnan, Mekala, Mamidipudi, Yareeda, Mridula, Bak, & Kaul (2017). Comparative effects of education and	-Sample consisted of 115 patients with MCI aged 45 years and older from a specialist memory clinic in a university hospital in Hyderabad between	-Age at onset of MCI was compared between bilinguals and monolinguals and across high and low levels of	-Outcome: MCI was diagnosed according to Petersen's criteria via clinical evaluation and brain imaging.	-Univariate general linear model	-Bilingual MCI patients were found to have a clinical onset of cognitive symptoms 7.4 years later than monolinguals (65.2

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
bilingualism on the onset of mild cognitive impairment.	June 2006 and December 2014	education, adjusting for covariates	- age of MCI diagnosis		vs. 58.1 years; p = 0.004) -Education was not associated with delayed onset of MCI (1–10 years of education, 59.1 years; 11–15 years of education, 62.6 years; >15 years of education, 62.2 years; p = 0.426). -Study found that bilingualism is protective against MCI.
Tyas, Salazar, Snowdon, Desrosiers, Riley, Mendiondo & Kryscio (2007). Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study.	-Nun Study, a longitudinal study of 678 participants -All members of the School Sisters of Notre Dame were born before 1917 -Analytic sample: 470 Nun Study sample aged 75+ years at baseline and living in the United States from 1991–2002	-Multilingualism from archival records (survey from 1983) -Risk factors of age, education, and the apolipoprotein E gene were adjusted for in the model	Cognitive states: mild cognitive impairment, global impairment, and dementia. -Intact = normal scores on four cognitive tests in the CERAD neuropsychologic battery, intact global cognitive ability (MMSE) and intact ADLs -Mild cognitive impairment= at least	-Polytomous logistic regression model (intact cognition, mild cognitive impairments, global impairment, dementia or death) -Analyses are based on seven annual follow-ups from 1991–2002 (Analyzed 1,905 transitions of 470 participants)	-Age, education, and the APOE were all significantly associated with mild cognitive impairments. -Whereas, only age was associated with progression to dementia. -Risk factors for dementia may predispose individuals to develop MCI, and subsequent

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
			one specific area of impaired cognitive function (memory or naming), intact MMSE and ADLs -Global impairment: impaired global cognitive ability, ADLs, or both; other impairments in a specific area of cognitive function could also have been present. Did not meet criteria for dementia as only one area of cognitive function was impaired or, if two areas of cognition were impaired, activities of daily living were intact. -Dementia: decline in function, impairments in memory and at least one other area of cognitive function based on CERAD, and impaired ADLs.		progression to dementia depends on time -APOE was a significant covariate of transitions from intact to dementia

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Wilson, Boyle, Yang, James, & Bennett (2015). Early life instruction in foreign language and music and incidence of mild cognitive impairment.	-Longitudinal cohort study -Participants are from the Rush Memory and Aging Project. -964 older persons without cognitive impairment. -64 with dementia and 394 with MCI.	-Exposure: Foreign language and music - Covariates: age, sex, education, higher levels of foreign language, and music	-Risk of aMCI and naMCI.	-Linear regression model -Mixed methods effect	-In a proportional hazard adjusted model, higher levels (4> years) of foreign language (HR = 0.687, 95% CI: 0.482, 0.961) and music (HR = 0.708, 95% CI: 0.539, 0.930) instruction by the age of 18 were each associated with reduced risk of MCI. -Association remained after adjusting for early life indicators and was stronger for naMCI than aMCI. -Higher levels of foreign language and music during childhood and adolescence are associated with lower risk of developing MCI
Woumans, Santens, Sieben, Versijpt, Stevens, Duych (2015).	-Participants consisted of a European sample of AD patients. -69 monolinguals and 65 bilinguals	-Exposure of bilingualism was assessed by participants and their caregivers via	-Time for clinical manifestation of AD and AD diagnosis	Linear regression models	-Bilinguals had a delay of 4.6 years in clinical manifestation and 4.8 in diagnosis.

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
Bilingualism delays clinical manifestation of Alzheimer's disease.	diagnosed with AD were compared for time of clinical AD and diagnosis. -Recruited from two university hospitals	interviews related to proficiency and frequency of use of second language. -Bilinguals consisted of same language combination (French Dutch) -Covariates: Age, education, gender, and MMSE			-No significant influence from education, gender, occupation was observed between the association of bilingualism and manifestation of symptoms and AD diagnosis. -Concluded that bilingualism contributes to cognitive reserve and postpones the symptoms of dementia.
Yeung, John, Menec & Tyas (2014). Is bilingualism associated with a lower risk of dementia in community-living older adults? Cross-sectional and prospective analyses.	-The population consisted of 1616 community-living older adults -Data source was from the Manitoba Study of Health and Aging (MSHA), a prospective cohort study -Wave 1: 1991/ 1992 (1751 participants) -Follow up of Wave 2: 1996/1997 (990	-Exposure: language was self-reported -Study consisted of 3 groups, i) English Monolingual: those participants who spoke only English; ii) English Bilingual: those participants who spoke English as a first language and who could speak a second language; and iii) English as a Second Language	-Dementia was diagnosed by clinical tests in those who scored below the MMSE threshold -Normal cognition on MMSE: <78 but cognitive impairment with no dementia - Dementia: MMSE<78 and a clinical examination consistent with dementia (using Diagnostic and	-Bivariate analyses using X2 tests for categorical variables and the t-tests (assuming unequal variance) for continuous variables. -Bivariate analyses were adjusted for potential confounding factors (logistic regression models) -Standard regression diagnostics	-No significant association between being bilingual (ESL and bilingual English vs. monolingual) and dementia at wave 1 (cross-sectional analysis) -At follow-up, bilingualism was not associated with dementia at wave 2 (prospective cohort analysis).

Study	Study Population, Sample Characteristics, & Study Design	Exposure & Covariates	Outcome	Analysis	Results
	survived to the second assessment)	(ESL): those who were bilingual but who listed their first language as any language other than English. -Covariates included age, sex, education, subjective memory loss (SML), modified MMSE (3MS)	Statistical Manual of Mental Disorders criteria for dementia)	(multicollinearity and influential outliers) were conducted. -Interactions were assessed by putting interaction terms into the regression model	

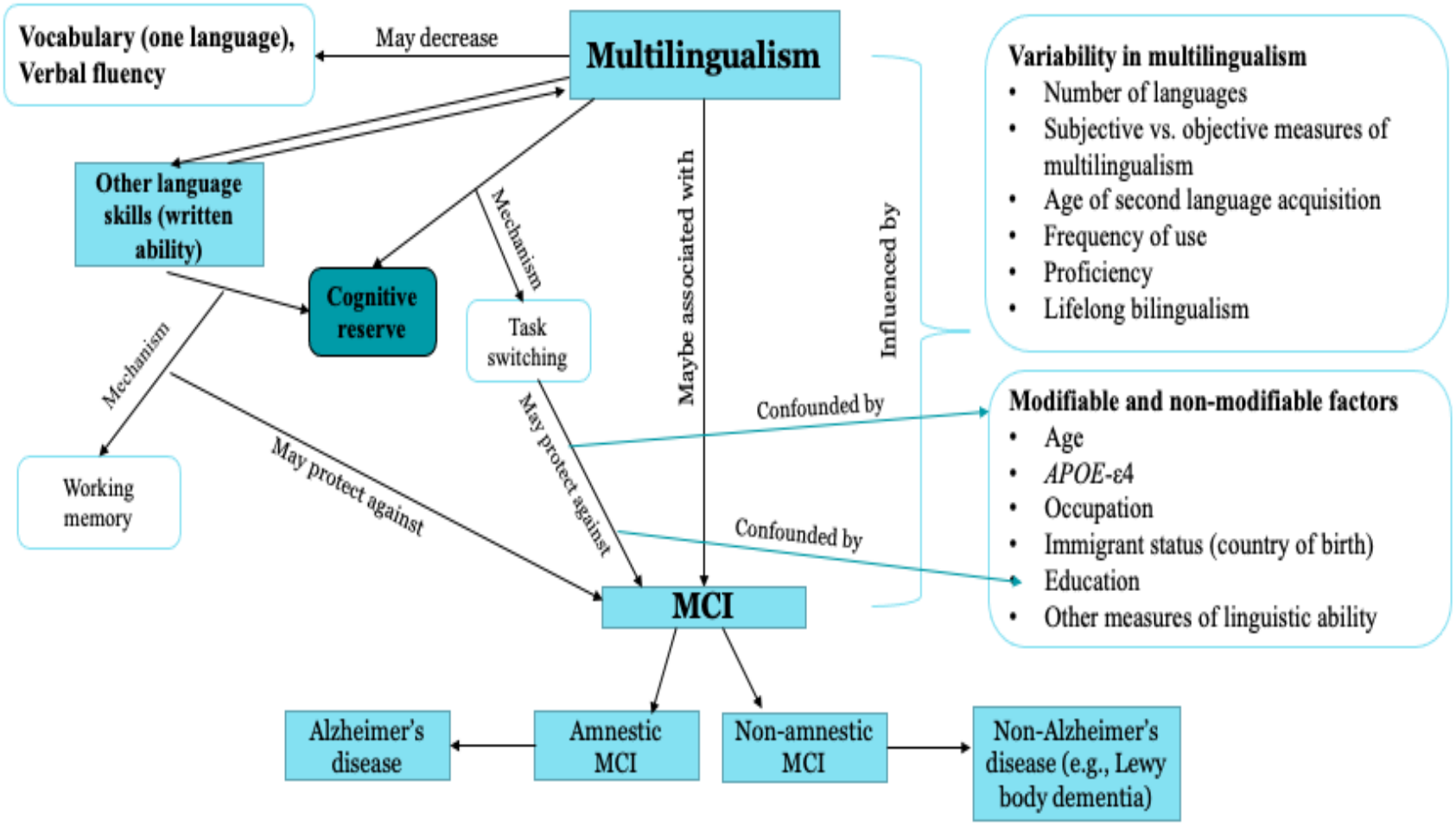
Appendix C: Description of the Cognitive Tests

Table C1. Description of the Cognitive Tests Used in CERAD

Test	**Test Description**
Delayed Word Recall	The test measures memory skills. Participants are presented with 10 words from a word list and after a period of rest, they are required to recall the 10 words. The participants have 90 seconds, and the maximum number of correct responses is 10.
Boston Naming	This test involves object naming from line drawings. This task asks subjects to name 15 objects presented as line drawings with a maximum of 10 seconds is allowed for each picture.
Verbal Fluency	Phonemic verbal fluency: This test involves listing the most words beginning with a certain letter (e.g., the letter F in English) as possible in one minute. The more words given in one minute the better the scores of the test. Repeated words and words unrelated to the category are excluded. Semantic verbal fluency: This test measures impairment in verbal production, language, and semantic memory. Involves listing the most words in a certain category (e.g., animal fluency) in one minute. They are scored based on the total number of different animals named within one minute. Unrelated words to the category or repeated words are excluded.
Constructional Praxis	This test requires participants to copy drawings of figures of increasing complexity (from a circle to a diamond, to a rectangle). They are allowed 2 minutes for each figure.
Global Cognition: MMSE	This is a general cognitive battery that measures immediate and delayed memory, orientation, concentration, praxis, and language. Mini-Mental State Exam (MMSE) is a scored form of cognitive mental status examination that includes eleven questions and requires about 5-19 minutes to administer.

Appendix D: Concept Map

Figure D1. Concept Map: Factors that May Influence the Association Between Multilingualism, Written Linguistic Ability, and MCI



Appendix E: Data Analysis Plan

Table E1. Analytic Plan for Assessing the Association of Multilingualism with Overall MCI (Main Analytic Sample)

Multilingualism: Unadjusted	Statistical method:	Binomial logistic regression[3]
	Outcome variable:	MCI (vs. intact cognition)
	Exposure variable:	Multilingualism (number of languages)[1]
Multilingualism: Confounding Variables and Interaction Terms	Statistical method:	Binomial logistic regression
	Outcome variable:	MCI (vs. intact cognition)
	Exposure variable:	Multilingualism (number of languages)
	Interaction terms:	Number of languages*(age at baseline, presence of *APOE*-ε4, country of birth, education)
	Potential Confounders:	Age at baseline, presence of *APOE*-ε4, country of birth, education
Multilingualism: Confounding Variables[2] *(assuming no interaction terms are significant)*	Statistical method:	Binomial logistic regression
	Outcome variable:	MCI (vs. cognitively intact)
	Exposure variable:	Multilingualism (number of languages)
	Potential Confounders:	Age at baseline, presence of *APOE*-ε4, country of birth, education
Multilingualism: Final	Statistical method:	Binomial logistic regression
	Outcome variable:	MCI (vs. cognitively intact)
	Exposure variable:	Multilingualism (number of languages)
	Confounding variables:	Significant covariates

[1]The set of models were repeated with three definitions of multilingualism as exposure variables: four-level variable (2, 3, 4+ languages vs. 1 language), and two separate two-level variables (2+ vs. 1 language, and 4+ vs. fewer).
[2]Interaction terms were not significant, thus models were not stratified
[3]These models were repeated using multinomial logistic regression for MCI subtypes (aMCI vs. naMCI vs. cognitively intact)
impairment, aMCI = amnestic cognitive impairment, *APOE*-ε4 = apolipoprotein E-ε4
Note: Sensitivity analyses included the linguistic ability subsample (n=122) with the inclusion of idea density and grammatical complexity (written language measures). Sensitivity analyses included an additional two-level variable (4+ vs. 1 language) (See Appendix J)
Abbreviations: MCI = mild cognitive impairment, naMCI = non-amnestic mild cognitive impairment, aMCI = amnestic cognitive impairment, *APOE*-ε4 = apolipoprotein E-ε4

Appendix F: Derivation of the University-educated Teachers Subsample

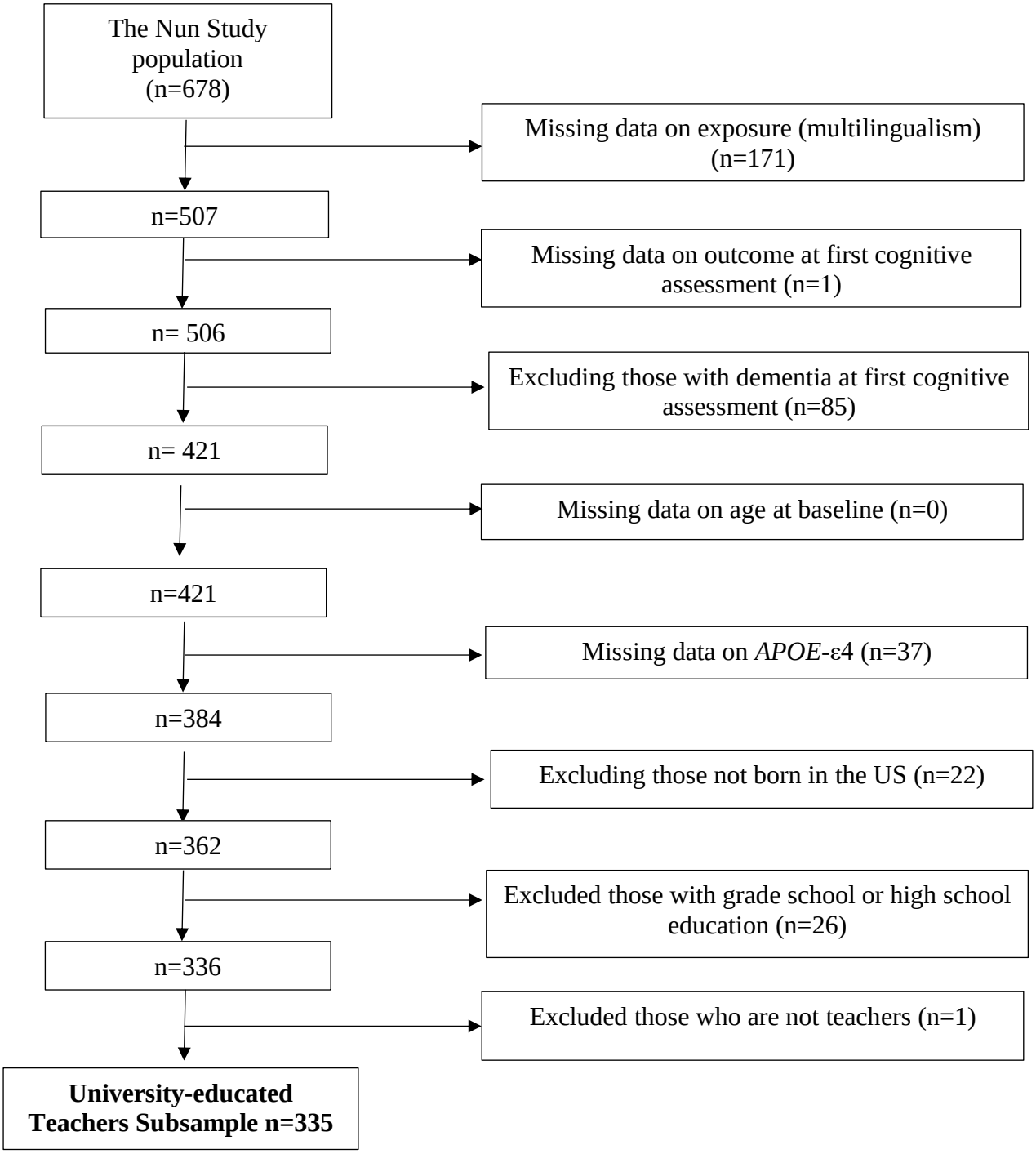


Figure F1. Derivation of the University-educated Teachers Subsample

Appendix G: Multinomial Logistic Regression Results for the Association Between Multilingualism and Subtypes of MCI

Table G1. Association Between Number of Languages Spoken (2, 3, 4+ vs. 1) and Subtypes of MCI, Main Analytic Sample, The Nun Study (n=384)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: Monolingual)		
	2	0.92 (0.53-1.62)	1.11 (0.60-2.04)
	3	0.83 (0.39-1.74)	0.87 (0.38-1.99)
	4+	0.57 (0.19-1.73)	0.39 (0.09-1.60)
Model B	*Number of languages* (Ref.: Monolingual)		
	2	0.78 (0.44-1.40)	0.86 (0.45-1.65)
	3	0.76 (0.35-1.65)	0.77 (0.32-1.84)
	4+	0.37 (0.12-1.18)	**0.22 (0.05-0.98)**
	Age at baseline (years)	**1.18 (1.10-1.25)**	**1.23 (1.15-1.32)**
Model C	*Number of languages* (Ref.: Monolingual)		
	2	0.77 (0.43-1.38)	0.92 (0.47-1.78)
	3	0.75 (0.34-1.62)	0.82 (0.34-1.97)
	4+	0.36 (0.12-1.18)	0.22 (0.05-1.04)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.24 (1.16-1.32)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.81 (0.42-1.58)	**2.08 (1.07-4.07)**
Model D	*Number of languages* (Ref.: Monolingual)		
	2	0.67 (0.37-1.22)	0.81 (0.41-1.57)
	3	0.71 (0.33-1.55)	0.78 (0.32-1.88)
	4+	0.37 (0.12-1.18)	0.22 (0.05-1.04)
	Age at baseline (years)	**1.18 (1.10-1.25)**	**1.24 (1.16-1.33)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.85 (0.43-1.66)	**2.18 (1.10-4.28)**

	Country of birth (%) (Born in the US) (Yes vs. No [Ref.])	**0.10 (0.01-0.78)**	**0.09 (0.01-0.78)**
Model E	*Number of languages* (Ref.: Monolingual)		
	2	0.74 (0.40-1.36)	0.88 (0.45-1.75)
	3	0.86 (0.38-1.91)	0.93 (0.37-2.30)
	4+	0.47 (0.14-1.50)	0.28 (0.06-1.32)
	Age at baseline (years)	**1.17 (1.09-1.25)**	**1.23 (1.15-1.32)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.94 (0.48-1.85)	**2.35 (1.19-4.65)**
	Country of birth (%) (Born in the US) (Yes vs. No [Ref.])	0.13 (0.02-1.09)	**0.11 (0.01-0.99)**
	Education (%) (Ref.: Grade and high school)		
	Bachelor's degree	**0.18 (0.04-0.83)**	0.28 (0.05-1.46)
	Master's degree+	**0.14 (0.03-0.67)**	0.20 (0.04-1.03)

Significant results are bolded
[1]reference category = cognitively intact
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Table G2. Association Between Number of Languages Spoken (2, 3, 4+ vs. 1) and Subtypes of MCI, Linguistic Ability Subsample, The Nun Study (n=122)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: Monolingual)		
	2	0.49 (0.19-1.28)	0.50 (0.17-1.53)
	3	0.69 (0.23-2.06)	0.47 (0.12-1.88)
	4+	0.28 (0.03-2.94)	0.93 (0.13-6.66)
Model B	*Number of languages* (Ref.: Monolingual)		
	2	0.54 (0.21-1.43)	0.55 (0.18-1.68)
	3	0.70 (0.23-2.13)	0.48 (0.12-1.93)
	4+	0.19 (0.02-2.14)	0.67 (0.09-5.19)
	Age at baseline (years)	1.13 (0.97-1.32)	0.12 (0.93-1.33)
Model C	*Number of languages* (Ref.: Monolingual)		
	2	0.56 (0.21-1.47)	0.49 (0.15-1.57)
	3	0.70 (0.23-2.12)	0.45 (0.11-1.92)
	4+	0.18 (0.02-2.05)	0.83 (0.10-6.82)
	Age at baseline (years)	1.13 (0.98-1.32)	1.09 (0.90-1.32)
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.61 (0.20-1.85)	**3.72 (1.29-10.74)**
Model D	*Number of languages* (Ref.: Monolingual)		
	2	0.62 (0.23-1.70)	0.70 (0.20-2.39)
	3	0.79 (0.25-2.52)	0.64 (0.14-2.93)
	4+	0.20 (0.02-2.39)	1.30 (0.15-11.43)
	Age at baseline (years)	1.12 (0.96-1.31)	1.06 (0.87-1.29)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.66 (0.21-2.02)	**4.76 (1.54-14.72)**
	Education (%)		

	(Ref.: Bachelor's degree) Master's degree+	0.67 (0.27-1.65)	**0.29 (0.09-0.88)**
Model E	*Number of languages* (Ref.: Monolingual)		
	2	0.59 (0.22-1.62)	0.66 (0.18-2.33)
	3	0.80 (0.25-2.55)	0.61 (0.12-3.06)
	4+	0.20 (0.02-2.38)	1.39 (0.15-12.62)
	Age at baseline (years)	1.11 (0.96-1.30)	1.03 (0.84-1.27)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.62 (0.20-1.94)	**3.99 (1.23-12.85)**
	Education (%) (Ref.: Bachelor's degree) Master's degree+	0.70 (0.28-1.74)	0.33 (0.10-1.05)
	Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	0.51 (0.13-2.05)	**0.20 (0.05-0.82)**
Model F	*Number of languages* (Ref.: Monolingual)		
	2	0.658(0.21-1.59)	0.61 (0.17-2.20)
	3	0.78 (0.24-2.49)	0.54 (0.11-2.83)
	4+	0.23 (0.02-2.84)	1.80 (0.19-16.70)
	Age at baseline (years)	1.09 (0.93-1.28)	1.01 (0.82-1.24)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.64 (0.21-2.01)	**4.14 (1.26-13.58)**
	Education (%) (Ref.: Bachelor's degree) Master's degree+	0.71 (0.28-1.78)	0.33 (0.10-1.07)
	Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	0.50 (0.12-2.01)	**0.21 (0.05-0.87)**
	Grammatical Complexity (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	0.51 (0.16-1.64)	0.34 (0.08-1.37)

Significant results are bolded

[1]reference category = cognitively intact

Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Table G3. Association Between Number of Languages Spoken (2+ vs. 1) and Subtypes of MCI, Main Analytic Sample, The Nun Study (n=384)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.87 (0.51-1.47)	0.98 (0.55-1.76)
Model B	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.74 (0.43-1.27)	0.77 (0.42-1.43)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.23 (1.15-1.31)**
Model C	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.73 (0.42-1.26)	0.82 (0.44-1.53)
	Age at baseline (years)	**1.17 (1.10-1.24)**	**1.23 (1.15-1.32)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.83 (0.43-1.62)	**2.12 (1.09-4.13)**
Model D	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.65 (0.38-1.14)	0.73 (0.39-1.39)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.23 (1.15-1.32)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.87 (0.45-1.71)	**2.21 (1.13-4.35)**
	Country of birth (%) (Born in the US) (Yes vs. No [Ref.])	**0.09 (0.01-1.74)**	**0.09 (0.01-1.72)**
Model E	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.74 (0.42-1.31)	0.84 (0.44-1.61)
	Age at baseline (years)	**1.16 (1.09-1.24)**	**1.22 (1.14-1.31)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.96 (0.49-1.89)	**2.40 (1.21-4.74)**
	Country of birth (%) (Born in the US) (Yes vs. No [Ref.])	0.13 (0.02-1.05)	**0.11 (0.01-0.94)**
	Education (%) (Ref.: Grade and high school)		

	Bachelor's degree	**0.18 (0.04-0.82)**	0.28 (0.05-1.43)
	Master's degree+	**0.14 (0.03-0.66)**	**0.19 (0.04-0.97)**

Significant results are bolded

[1]reference category = cognitively intact

Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Table G4. Association Between Number of Languages Spoken (2+ vs. 1) and Subtypes of MCI, Linguistic Ability Sample, The Nun Study (n=122)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.54 (0.23-1.27)	0.53 (0.19-1.44)
Model B	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.55 (0.23-1.32)	0.54 (0.20-1.49)
	Age at baseline (years)	1.11 (0.96-1.29)	1.12 (0.95-1.33)
Model C	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.56 (0.23-1.33)	0.51 (0.18-1.46)
	Age at baseline (years)	1.12 (0.97-1.29)	1.11 (0.93-1.32)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.63 (0.21-1.90)	**3.60 (1.26-10.27)**
Model D	*Number of languages* (Ref.: Monolingual)	0.63 (0.25-1.56)	0.73 (0.24-2.23)
	2+ languages		
	Age at baseline (years)	1.11 (0.96-1.28)	1.08 (0.90-1.30)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.68 (0.22-2.06)	**4.53 (1.49-13.79)**
	Education (%) (Ref.: Bachelor's degree)		
	Master's degree+	0.67 (0.28-1.64)	**0.29 (0.10-0.90)**
Model E	*Number of languages* (Ref.: Monolingual)		
	2+ languages	0.61 (0.25-1.52)	0.720(0.22-2.23)
	Age at baseline (years)	1.10 (0.95-1.27)	1.06 (0.88-1.29)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.64 (0.21-1.97)	**3.69 (1.16-11.71)**
	Education (%) (Ref.: Bachelor's degree)		
	Master's degree+	0.70 (0.29-1.73)	0.35 (0.11-1.11)
	Idea density (1 [Ref.] vs. 2 + 3 + 4)	0.54 (0.13-2.14)	**0.21 (0.05-0.85)**

Model F	*Number of languages* (Ref.: Monolingual) 2+ languages	0.60 (0.24-1.51)	0.67 (0.21-2.15)
	Age at baseline (years)	1.08 (0.93-1.25)	1.04 (0.86-1.27)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.65 (0.21-2.03)	**3.77 (1.17-12.09)**
	Education (%) (Ref.: Bachelor's degree) Master's degree+	0.72 (0.29-1.78)	0.35 (0.11-1.14)
	Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	0.53 (0.13-2.10)	**0.22 (0.05-0.90)**
	Grammatical Complexity (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	0.47 (0.15-1.49)	0.39 (0.10-1.51)

Significant results are bolded
[1]reference category = cognitively intact
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Table G5. Association Between Number of Languages Spoken (4+ vs. ≤ 3) and Subtypes of MCI, Main Analytic Sample, The Nun Study (n=384)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.62 (0.22-1.75)	0.38 (0.10-1.45)
Model B	*Number of languages* (Ref.: Monolingual)	0.44 (0.15-1.31)	0.25 (0.06-1.04)
	4+ languages		
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.23 (1.15-1.32)**
Model C	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.45 (0.15-1.33)	0.24 (0.06-1.05)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.24 (1.15-1.32)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.83 (0.43-1.61)	**2.09 (1.07-4.07)**
Model D	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.48 (0.17-1.44)	0.26 (0.06-1.14)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.23 (1.15-1.32)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.86 (0.44-1.69)	**2.20 (1.12-4.30)**
	Country of birth (%) (Born in the US) (Yes vs. No [Ref.])	**0.11 (0.01-0.87)**	**0.10 (0.01-0.84)**
Model E	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.57 (0.19-1.68)	0.30 (0.07-1.33)
	Age at baseline (years)	**1.16 (1.09-1.24)**	**1.23 (1.14-1.31)**
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.96 (0.49-1.88)	**2.35 (1.19-4.65)**
	Country of birth (%) (Born in the US) (Yes vs. No [Ref.])	0.15 (0.02-1.19)	0.12 (0.01-1.04)
	Education (%) (Ref.: Grade and high school)		

	Bachelor's degree	**0.18 (0.04-0.82)**	0.28 (0.05-1.45)
	Master's degree+	**0.14 (0.03-0.64)**	**0.19 (0.04-0.99)**

Significant results are bolded
[1]reference category = cognitively intact
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Table G6. Association Between Number of Languages Spoken (4+ vs. ≤ 3) and Subtypes of MCI, Linguistic Ability Sample, The Nun Study (n=122)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.41 (0.04-4.04)	1.48 (0.23-9.46)
Model B	*Number of languages* (Ref.: Monolingual)		
	4+ languages	0.26 (0.02-2.74)	0.99 (0.14-6.99)
	Age at baseline (years)	1.14 (0.99-1.33)	1.13 (0.94-1.34)
Model C	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.24 (0.02-2.59)	1.25 (0.17-9.46)
	Age at baseline (years)	1.15 (0.99-1.33)	1.11 (0.92-1.34)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.58 (0.19-1.74)	**3.51 (1.24-9.93)**
Model D	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.26 (0.02-2.79)	1.63 (0.21-12.78)
	Age at baseline (years)	1.13 (0.98-1.32)	1.07 (0.88-1.30)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.64 (0.21-1.96)	**4.68 (1.53-14.39)**
	Education (%) (Ref.: Bachelor's degree)		
	Master's degree+	0.61 (0.26-1.46)	**0.26 (0.09-0.76)**
Model E	*Number of languages* (Ref.: three or fewer)		
	4+ languages	0.26 (0.02-2.82)	1.80 (0.23-14.44)
	Age at baseline (years)	1.13 (0.97-1.31)	1.05 (0.86-1.28)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.61 (0.20-1.88)	**3.92 (1.22-12.57)**
	Education (%) (Ref.: Bachelor's degree)		
	Master's degree+	0.64 (0.27-1.53)	**0.29 (0.10-0.90)**
	Idea density (1 [Ref.] vs. 2 + 3 + 4)	0.54 (0.14-2.16)	**0.21 (0.05-0.85)**

Model F	*Number of languages* (Ref.: three or fewer) 4+ languages	0.30 (0.03-3.42)	2.40 (0.29-19.99)
	Age at baseline (years)	1.10 (0.95-1.29)	1.02 (0.83-1.25)
	Presence of APOE-ε4 allele (Yes vs. No [Ref.])	0.63 (0.20-1.95)	**4.06 (1.25-13.24)**
	Education (%) (Ref.: Bachelor's degree) Master's degree+	0.64 (0.27-1.55)	**0.29 (0.09-0.90)**
	Idea density (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	0.54 (0.14-2.13)	**0.22 (0.05-0.90)**
	Grammatical Complexity (Quartiles 2 + 3 + 4 vs. quartile 1 [Ref.])	0.52 (0.16-1.67)	0.36 (0.09-1.43)

Significant results are bolded
[1]reference category = cognitively intact
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Appendix H: Additional Multivariable Models Using the University-educated Teachers Subsample

Table H1. Association Between Number of Languages Spoken (2, 3, 4+ vs. 1) and Overall MCI at Baseline, University-educated Teachers Subsample, The Nun Study (n=335)

	***Overall MCI*[1]**			
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)
Number of languages (Ref.: Monolingual)				
2	0.88 (0.51-1.51)	0.69 (0.39-1.22)	0.70 (0.39-1.24)	0.74 (0.41-1.32)
3	0.81 (0.40-1.66)	0.77 (0.40-1.63)	0.78 (0.37-1.65)	0.84 (0.39-1.81)
4+5[2]	0.55 (0.20-1.57)	0.34 (0.11-1.01)	0.35 (0.12-1.06)	0.39 (0.13-1.18)
Age at baseline (years)		**1.20 (1.13-1.28)**	**1.20 (1.13-1.28)**	**1.19 (1.12-1.27)**
Presence of APOE-ε4 allele (No [Ref.] vs. Yes)			1.37 (0.76-2.54)	1.39 (0.76-2.2.58)
Education (%) (Ref.: Bachelor's degree) Master's degree+				0.75 (0.44-1.25)

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model, includes the exposure only
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table H2. Association Between Number of Languages Spoken (2+ vs. 1) and Overall MCI at Baseline, University-educated Teachers Subsample, The Nun Study (n= 335)

	***Overall MCI*[1]**			
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)
Number of languages (Ref.: Monolingual) 2+ languages	0.83 (0.50-1.38)	0.67 (0.39-1.14)	0.69 (0.40-1.17)	0.73 (0.42-1.26)
Age at baseline (years)		**1.19** **(1.12-1.27)**	**1.19** **(1.12-1.27)**	**1.18** **(1.11-1.26)**
Presence of APOE-ε4 allele (No [Ref.] vs. Yes)			1.40 (0.77-2.60)	1.42 (0.78-2.63)
Education (%) (Ref.: Bachelor's degree) Master's degree+				0.74 (0.44-1.23)

Bolded values indicate statistically significant results ($p<0.05$)

Model A, the crude model, includes the exposure only
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table H3. Association Between Number of Languages Spoken (4+ vs. ≤ 3) and Overall MCI at Baseline, University-educated Teachers Subsample, The Nun Study (n= 335)

	***Overall MCI*[1]**			
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)
Number of languages				
(Ref.: fewer)	0.61	0.42	0.44	0.47
4+ languages	(0.23-1.64)	(0.15-1.21)	(0.16-1.26)	(0.17-1.34)
Age at baseline (years)		**1.19**	**1.19**	**1.18**
		(1.12-1.28)	**(1.12-1.27)**	**(1.11-1.27)**
Presence of APOE-ε4 allele			1.49	1.41
(No [Ref.] vs. Yes)			(0.77-2.58)	(0.78-2.61)
Education (%)				
(Ref.: Bachelor's degree)				0.72
Master's degree+				(0.43-1.19)

Bolded values indicate statistically significant results ($p<0.05$)

Model A, the crude model, includes the exposure only
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
[2]Maximum number of languages spoken was five; participants speaking four or five languages were grouped together due to limited numbers
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group

Table H4. Association Between Number of Languages Spoken (2, 3, 4+ vs. 1) and Subtypes of MCI, University-educated Teachers Subsample, The Nun Study (n=335)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: Monolingual)		
	2	0.83 (0.46-1.51)	0.96 (0.50-1.82)
	3	0.87 (0.40-1.89)	0.73 (0.31-1.76)
	4+	0.66 (0.21-2.01)	0.40 (0.10-1.67)
Model B	*Number of languages* (Ref.: Monolingual)		
	2	0.67 (0.36-1.26)	0.72 (0.36-1.42)
	3	0.83 (0.37-1.84)	0.69 (0.28-1.72)
	4+5[2]	0.41 (0.13-1.33)	0.23 (0.05-1.02)
	Age at baseline (years)	**1.18 (1.10-1.26)**	**1.23 (1.14-1.32)**
Model C	*Number of languages* (Ref.: Monolingual)		
	2	0.67 (0.36-1.25)	0.76 (0.38-1.51)
	3	0.82 (0.37-1.83)	0.72 (0.29-1.81)
	4+	0.42 (0.13-1.36)	0.23 (0.05-1.09)
	Age at baseline (years)	**1.18 (1.10-1.26)**	**1.23 (1.14-1.32)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.94 (0.47-1.86)	**2.20 (1.11-4.39)**
Model D	*Number of languages* (Ref.: Monolingual)		
	2	0.69 (0.37-1.30)	0.83 (0.41-1.66)
	3	0.86 (0.38-1.94)	0.82 (0.32-2.10)
	4+	0.46 (0.14-1.45)	0.28 (0.06-1.32)
	Age at baseline (years)	**1.21 (1.13-1.31)**	**1.21 (1.13-1.31)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.94 (0.47-1.87)	**2.27 (1.14-4.55)**

	Education (%)	0.85 (0.48-1.49)	061 (0.33-1.14)
	(Ref.: Bachelor's degree)		
	Master's degree+		

Significant results are bolded

[1]reference category = cognitively intact

Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Table H5. Association Between Number of Languages Spoken (2+ vs. 1) and Subtypes of MCI, University-educated Teachers Subsample, The Nun Study (n=335)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: Monolingual) 2+ languages	0.82 (0.47-1.44)	0.85 (0.46-1.56)
Model B	*Number of languages* (Ref.: Monolingual) 2+ languages	0.68 (0.38-1.22)	0.66 (0.35-1.26)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.22 (1.14-1.31)**
Model C	*Number of languages* (Ref.: Monolingual) 2+ languages	0.68 (0.38-1.22)	0.70 (0.36-1.34)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.22 (1.14-1.31)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.96 (0.49-1.91)	**2.24 (1.13-4.46)**
Model D	*Number of languages* (Ref.: Monolingual) 2+ languages	0.71 (0.40-1.28)	0.78 (0.40-1.51)
	Age at baseline (years)	**1.17 (1.09-1.25)**	**1.21 (1.12-1.30)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.97 (0.49-1.92)	**2.32 (1.16-4.63)**
	Education (%) (Ref.: Bachelor's degree) Master's degree+	0.85 (0.48-1.49)	0.59 (0.32-1.10)

Significant results are bolded
[1]reference category = cognitively intact
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Table H6. Association Between Number of Languages Spoken (4+ vs. ≤ 3) and Subtypes of MCI, University-educated Teachers Subsample, The Nun Study (n=335)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**nMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: fewer) 4+ languages	0.74 (0.26-2.11)	0.43 (0.11-1.68)
Model B	*Number of languages* (Ref.: Monolingual) 4+ languages	0.53 (0.18-1.57)	0.29 (0.07-1.20)
	Age at baseline (years)	**1.17 (1.10-1.26)**	**1.22 (1.14-1.31)**
Model C	*Number of languages* (Ref.: Monolingual) 4+ languages	0.54 (0.18-1.61)	0.29 (0.07-1.24)
	Age at baseline (years)	**1.17 (1.10-1.25)**	**1.23 (1.14-1.32)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.96 (0.48-1.89)	**2.23 (1.12-4.44)**
Model D	*Number of languages* (Ref.: Monolingual) 4+ languages	0.56 (0.19-1.68)	0.32 (0.08-1.40)
	Age at baseline (years)	**1.17 (1.09-1.25)**	**1.21 (1.13-1.30)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	0.96 (0.48-1.90)	**2.29 (1.15-4.58)**
	Education (%) (Ref.: Bachelor's degree) Master's degree+	0.81 (0.47-1.41)	0.59 (0.32-1.09)

Significant results are bolded

[1]reference category = cognitively intact

Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Appendix I: Additional Multivariable Models Excluding Participants with APOE-ε2ε4

Table I1. Summary Table of Fully Adjusted Models of the Association of Multilingualism with Overall MCI, aMCI and naMCI, Excluding APOE-ε2ε4 Allele from the Main Analytic Sample (n=379)

	Outcome		
	Overall MC1	*Subtypes of MCI*	
		naMCI	aMCI
	(n=265)	(n=155)	(n=110)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Four-level variable: *Number of languages* (Ref.: Monolingual)			
2	0.76 (0.43-1.35)	0.72 (0.39-1.33)	0.85 (0.43-1.68)
3	0.86 (0.41-1.83)	0.86 (0.38-1.92)	0.87 (0.35-2.17)
4+	0.39 (0.13-1.19)	0.47 (0.15-1.52)	0.26 (0.05-1.23)
Age at baseline (years)	**1.19 (1.12-1.27)**	**1.16 (1.09-1.24)**	**1.23 (1.15-1.32)**
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	1.41 (0.77-2.66)	0.85 (0.42-1.73)	**2.58 (1.29-5.15)**
Country of birth (%) (Yes vs. No [Ref.])	**0.12 (0.01-0.66)**	0.13 (0.02-1.06)	0.12 (0.01-1.01**)**
Education (%) (Ref.: Grade and high school)			
Bachelor's degree	**0.21 (0.03-0.79)**	**0.19 (0.04-0.88)**	0.27 (0.05-1.40)
Master's degree+	**0.16 (0.03-0.61)**	**0.15 (0.03-0.70)**	0.20 (0.04-1.04)
Two-level variable: *Number of languages* (Ref.: Monolingual)			
2+ languages	0.75 (0.43-1.28)	0.73 (0.41-1.30)	0.80 (0.42-1.54)
Age at baseline (years)	**1.18 (1.11-1.26)**	**1.16 (1.08-1.24)**	**1.22 (1.14-1.31)**
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	1.45 (0.79-2.72)	0.88 (0.43-1.78)	**2.63 (1.32-5.24)**
Country of birth (%) (Yes vs. No [Ref.])	**0.12 (0.01-0.63)**	0.12 (0.02-1.03)	**0.11 (0.01-0.96)**
Education (%) (Ref.: Grade and high school)			
Bachelor's degree	**0.21 (0.03-0.78)**	**0.19 (0.04-0.88)**	0.26 (0.05-1.37**)**
Master's degree+	**0.16 (0.02-0.59)**	**0.15 (0.03-0.69)**	**0.19 (0.04-0.98)**
Two-level variable: *Number of languages* (Ref.: Three or fewer languages)			
4+ languages	0.46 (0.17-1.32)	0.58 (0.20-1.72)	0.29 (0.07-1.28)
Age at baseline (years)	**1.18 (1.11-1.27)**	**1.16 (1.08-1.24)**	**1.23 (1.14-1.32)**
Presence of APOE-ε4 allele (Yes vs. No [Ref.])	1.43 (0.78-2.68)	0.87 (0.43-1.76)	**2.59 (1.30-5.16)**
Country of birth (%) (Yes vs. No [Ref.])	**0.13 (0.01-0.71)**	0.14 (0.02-1.16)	0.13 (0.01-1.08)
Education (%) (Ref.: Grade and high school)			
Bachelor's degree	**0.21 (0.03-0.79)**	**0.19 (0.04-0.88)**	0.27 (0.05-1.39)
Master's degree+	**0.16 (0.02-0.58)**	**0.14 (0.03-0.66)**	**0.19 (0.04-0.99)**

Bolded values indicate statistically significant results ($p<0.05$)
Note: results are from final models (fully adjusted)

Appendix J: Additional Multivariable Models Between Participants Speaking 4+ Languages vs. Monolinguals

Table J1. Association Between Number of Languages Spoken (4+ vs. 1) and Overall MCI, The Nun Study, (n=129)

	***Overall MCI*[1]**			
	Model A OR (95% CI)	**Model B** OR (95% CI)	**Model C** OR (95% CI)	**Model D** OR (95% CI)
Number of languages (Ref.: Monolingual) 4+ languages	0.51 (0.18-1.44)	**0.32** **(0.10-0.98)**	0.35 (0.11-1.07)	0.45 (0.14-1.44)
Age at baseline (years)		**1.19** **(1.07-1.35)**	**1.18** **(1.06-1.34)**	**1.17** **(1.05-1.33)**
Presence of APOE-ε4 allele (No [Ref.] vs. Yes)			1.67 (0.62-5.00)	1.79 (0.66-5.47)
Education (%) (Ref.: Grade and high school) Bachelor's degree Master's degree+				0.64 (0.09-3.00) 0.33 (0.05-1.54)

Bolded values indicate statistically significant results ($p<0.05$)
Model A, the crude model, includes the exposure only
Model B includes the exposure + age at baseline (years)
Model C includes the exposure + age at baseline (years) + presence of *APOE*-ε4
Model D includes the exposure + age at baseline (years) + presence of *APOE*-ε4 + education
[1]The cut points for impaired cognitive test scores were set at 1.5 standard deviations below the age-appropriate mean
Abbreviations: *APOE*-ε4= Apolipoprotein E-ε4; MCI= mild cognitive impairment; OR= odds ratio; CI= confidence interval, Ref.= Reference group
Note: This is an additional measure of multilingualism. Participants who spoke two and three languages were excluded from this sample (n=129) as well as restricted to those born in the U.S.

Table J2. Association Between Number of Languages Spoken (4+ vs. 1) and Subtypes of MCI, The Nun Study (n=129)

		MCI[1]	
Model	**Variable**	**naMCI** OR (95% CI)	**aMCI** OR (95% CI)
Model A (Crude)	*Number of languages* (Ref.: Monolingual)		
	4+ languages	0.57 (0.19-1.73)	0.40 (0.10-1.65)
Model B	*Number of languages* (Ref.: Monolingual)		
	4+ languages	0.37 (0.11-1.23)	0.05 (0.05-1.09)
	Age at baseline (years)	**1.18 (1.04-1.33)**	**1.21 (1.06-1.38)**
Model C	*Number of languages* (Ref.: Monolingual)		
	4+ languages	0.39 (0.12-1.28)	0.26 (0.05-1.26)
	Age at baseline (years)	**1.17 (1.04-1.32)**	**1.20 (1.05-1.37)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	1.00 (0.32-3.13)	**3.32 (1.05-10.48)**
Model D	*Number of languages* (Ref.: Monolingual)		
	4+ languages	0.48 (0.14-1.64)	0.37 (0.07-1.91)
	Age at baseline (years)	**1.16 (1.03-1.31)**	**1.18 (1.03-1.35)**
	Presence of APOE-ε4 allele (No [Ref.] vs. Yes)	1.07 (0.34-3.40)	**3.74 (1.14-12.26)**
	Education (%) (Ref.: Grade and high school)		
	Bachelor's degree	0.45 (0.08-2.51)	1.55 (0.18-13.60)
	Master's degree+	0.31 (0.06-1.70)	0.48 (0.05-4.38)

Significant results in bold

[1]reference category = cognitively intact

Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4 carrier, aMCI = amnestic mild cognitive impairment, CI = confidence interval, OR = odds ratio

Note: Participants who spoke two and three languages were excluded from this sample (n=129), and models were restricted to those only born in the US

Appendix K: Assessment of Selection Bias in the Analytic Sample

To analyze the association between multilingualism and MCI, various exclusion criteria were required to generate the analytic sample. Tables K1 and K2 summarize the results assessing selection bias in the main analytic sample and linguistic ability subsample. Table K1 compares the excluded participants (n=294) from the total Nun Study population (n=678) with those who were included in the main analytic sample (n=384). Additionally, Table K2 compares the excluded participants (n=262) from the main analytic sample (n=384) with those who were included in the linguistic ability subsample (n=122). The linguistic ability sample (n=122) was restricted by level of education (university-educated) and country of birth (U.S. born) because the few participants with grade school or high school education meant sparse cells for these educational levels, which created modelling issues in multivariable analyses.

When the main analytic sample (n=384) was compared to those who were excluded from the total Nun Study population (n=294), there were significant differences in terms of the participants' cognitive status at baseline, age at first cognitive assessment, presence of an *APO*E-ε4 allele and level of education (Table K1). Individuals from the main analytic sample were significantly more likely to be cognitive intact than the excluded participants (29.95% vs. 18.49%, $p<0.0001$). Participants from the main analytic sample (n=384) were significantly younger at the first cognitive assessment (82.65 vs. 84.13 years, $p<0.0001$). When comparing the excluded participants from the main analytic sample, Table K1 shows that the presence of an *APO*E-ε4 allele was significantly more common in participants who were excluded from the total Nun Study sample compared to the main analytic sample (27.23% vs. 20.05%, $p=0.039$). This is not surprising as the main analytic sample was restricted to participants without dementia at baseline. These results likely reflect that dementia cases were excluded from the main analytic

sample. Additionally, level of education was significantly different between included and excluded participants, where those who were excluded had a higher percentage of participants with a lower educational attainment (i.e., high school degree or less) compared to the main analytic sample (24.49 vs. 8.60%). Again, these results would be expected as those who have dementia are more likely to have lower educational attainment.

A significant difference was also observed when comparing the linguistic ability subsample with those who were excluded from the main analytic sample (Table K2). There were significant differences in terms of number of languages spoken, participants' cognitive status at baseline, age at first cognitive assessment, immigrant status, level of education and idea density (Table K2). Specifically, participants who were excluded (n=262) were more likely to speak two languages compared to those in the linguistic ability subsample (n=122) (55.73% vs. 40.16%). However, of those in the linguistic ability subsample, 21.31% were trilingual speakers compared to 12.60% in the excluded participants, of those individuals who were cognitively intact, 44.26% participants were from the linguistic ability subsample; whereas, 23.28% were from the excluded participants of the main analytic sample. Likewise, participants from the linguistic ability subsample were less likely to have MCI compared to the excluded individuals (55.74% vs. 76.72%). These results were not surprising, as individuals in the linguistic ability subsample only included those who were university educated, and higher educational attainment were expected to contribute to better cognitive status. Specifically, participants in the linguistic ability subsample were more likely to have attained a master's degree or higher (59.84 vs. 48.09, $p<0.0001$). Additionally, participants from the linguistic ability subsample were significantly younger at the first cognitive assessment compared to the excluded participants (80.01 vs. 83.87, $p<0.0001$).

Overall, the excluded participants yielded significant differences between the main analytic sample and linguistic ability subsample. Thus, it is important to consider these selection bias analyses when interpreting the findings for the current project.

Table K1. Assessment of Selection Bias: Comparison of the Main Analytic Sample with Excluded Participants from the Total Nun Study Sample

	Total Nun Study Sample (n=678)	**Main Analytic Sample** (n=384)	**Excluded Participants from the Total Sample** (n=294)
Characteristic	*%*	*%*	*%*
Multilingualism			
1	29.59	29.17	30.89
2	50.49	50.78	49.59
3	15.58	15.36	16.26
4	2.37	2.60	1.63
5	1.97	2.08	1.63
Cognitive States			
Intact	25.00	29.95	18.49***
Overall MCI	56.07	70.05	37.67
Non-amnestic MCI	32.84	41.41	21.58
Amnestic MCI	23.23	28.65	16.10
Dementia	18.93	-	43.84
Age at baseline, Mean years (SD)	83.29 (5.47)	82.65 (5.12)	84.13 (5.78)***
Presence of APOE-ε4			
No	77.22	79.95	72.77*
Yes	22.78	20.05	27.23
Country of birth (U.S. born)			
No	6.05	5.73	6.46
Yes	93.95	94.27	93.54
Education			
High school or less	15.49	8.60	24.49***
Bachelor's degree	39.82	39.58	40.14
Master's degree+	44.69	51.82	35.37

*p<0.05, **p<0.01, ***p<0.001

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4 allele; SD = standard deviation

For the total Nun Study sample, complete data on the number of languages (n=507), cognitive states (n=676), presence of *APOE*-ε4 (n=619), country of birth (n=678), and educational level (n=678)

For the excluded participants sample, complete data on the number of languages (n=123), cognitive states (n=292), presence of *APOE*-ε4 (n=235), country of birth (n=294), and educational level (n=294)

Table K2. Assessment of Selection Bias: Comparison of the Linguistic Ability Subsample with Excluded Participants from the Main Analytic Sample

	Main Analytic Sample (n=384)	**Linguistic Ability Subsample** (n=122)	**Excluded Participants from Main Analytic Sample** (n=262)
Characteristic	*%*	*%*	*%*
Multilingualism			
1	29.17	33.61	27.10*
2	50.78	40.16	55.73
3	15.36	21.31	12.60
4	2.60	2.46	2.67
5	2.08	2.46	1.91
Cognitive States			
Intact	29.95	44.26	23.28***
Overall MCI	70.05	55.74	76.72
Non-amnestic MCI	41.41	35.25	44.27
Amnestic MCI	28.65	20.49	32.44
Dementia	-	-	-
Age at baseline, Mean years (SD)	82.65 (5.12)	80.01 (2.88)	83.87 (5.47)***
Presence of APOE-ε4			
No	79.95	76.23	81.68
Yes	20.05	23.77	18.32
Country of birth (U.S. born)			
No	5.73	-	8.40***
Yes	94.27	100.00	91.60
Education			
High school or less	8.60	-	12.60***
Bachelor's degree	39.58	40.16	39.31
Master's degree+	51.82	59.84	48.09
Idea density[5]			
1 (lowest quartile)	15.87	15.57	25.00
2	25.40	24.59	50.00
3	29.37	29.51	25.00
4 (highest quartile)	29.37	30.33	0.00
Grammatical complexity[6]			
1 (lowest quartile)	18.25	18.85	0.00
2	26.98	26.23	50.00
3	27.78	27.87	25.00
4 (highest quartile)	26.98	27.05	25.00

*p<0.05, **p<0.01, ***p<0.001

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4 allele; SD = standard deviation

For the linguistic ability subsample, complete data on the number of languages (n=122), cognitive states (n=122), presence of *APOE*-ε4 (n=122), country of birth (n=122), educational level (n=122), and idea density and grammatical complexity (n=122)

For the excluded participants sample, complete data on the number of languages (n=262), cognitive states (n=262), presence of *APOE*-ε4 (n=262), country of birth (n=262), educational level (n=262), and idea density and grammatical complexity (n=4)