Education and Mortality in Individuals with Alzheimer Neuropathology: A Test of the Cognitive Reserve Hypothesis

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. I understand that my thesis may be made electronically available to the public.

Abstract

Background: The cognitive reserve hypothesis describes a hypothetical mechanism to cope with brain damage: individuals with high reserve are thought to tolerate more Alzheimer neuropathology before symptom onset, show greater neuropathology at time of onset, and experience shorter survival post onset. This study assessed the association of educational attainment and academic performance, variables influencing reserve, with overall survival and examined whether Alzheimer neuropathology modified this association.

Methods: Analyses were based on the Nun Study, a longitudinal study of aging in 678 participants aged 75+ years at baseline. Data on highest level of educational attainment and first-year high school grades in English, Latin, Algebra, and Geometry, available from the convent archives, were used as measures of education and academic performance, respectively. Alzheimer neuropathology was assessed in postmortem autopsies according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and National Institute on Aging and Reagan Institute (NIA-RI) neuropathologic criteria. Cox proportional hazards regression models included cognitive status as a time-dependent covariate; age and apolipoprotein E (APOE), a genetic risk factor for Alzheimer's disease, as time-independent covariates; and Alzheimer neuropathology as an effect modifier.

Results: In unadjusted models, educational attainment (Bachelor's degree vs. high school or less: HR=0.88, 95% CI=0.49-1.56; Master's degree vs. high school or less: HR=0.81, 95% CI=0.45-1.44) and academic performance (Quartile 2 vs. Quartile 1: HR=0.79, 95% CI=0.55-1.14; Quartile 3 vs. Quartile 1: HR= 0.75, 95% CI=0.52-1.08; Quartile 4 vs.

Quartile 1: HR=0.83, 95% CI=0.58-1.21) were not significantly associated with overall survival. After adjusting for age, *APOE*-ε4 status, and cognitive status, the association of educational attainment (Bachelor's degree vs. high school or less: HR=0.96, 95% CI=0.54-1.71; Master's degree vs. high school or less: HR=1.03, 95% CI=0.57-1.86) and academic performance (Quartile 2 vs. Quartile 1: HR=0.73, 95% CI=0.50-1.06; Quartile 3 vs. Quartile 1: HR=0.76, 95% CI=0.53-1.10; Quartile 4 vs. Quartile 1: HR=0.89, 95% CI=0.61-1.29) with survival remained statistically non-significant. Results from models stratified by Alzheimer neuropathology, based on either the CERAD or the NIA-RI neuropathologic criteria, illustrated that the relationship of educational attainment and academic performance with survival was not modified by Alzheimer neuropathology.

Discussion: It was hypothesized that (1) educational attainment and academic performance would be positively associated with survival in the overall population and, (2) the above association(s) would be modified by the presence of Alzheimer neuropathology. In the absence of Alzheimer neuropathology, high educational factors were hypothesized to be associated with longer survival. Conversely, in the presence of Alzheimer neuropathology, high educational factors were expected to be associated with shorter survival; this hypothesis was based upon the cognitive reserve hypothesis. If educational attainment and academic performance contribute to levels of reserve, then those with higher levels of these educational factors should tolerate more Alzheimer neuropathology before they express symptoms of AD, have more severe neuropathology when they first express symptoms of AD, and consequently have a shorter survival. The results do not support the study hypotheses; however, there are several reasons that could explain the inconsistencies with previous research: (1) differences in research

methodology, (2) limited variation for the educational factors, (3) the relationship between education and survival is less established in older cohorts, such as the Nun Study population and, (4) educational factors are not significantly associated with survival in a population is homogeneous for many environmental and lifestyle factors throughout adult life. Overall, since the study results did not support our hypotheses, the research project did not find evidence to support the cognitive reserve hypothesis. Although we did not find evidence to support our hypotheses, this study contributed to our understanding of the mechanisms through which education influences survival. While not explored directly, our findings suggest that educational factors may influence survival through an alternate mechanism (i.e., other than cognitive reserve); high education may contribute to the accumulation of social and economic resources, and this in turn may influence survival. The above theory may explain why we did not find a statistical association between education and survival in a population that is homogeneous for factors such as income, housing, and access to healthcare. Furthermore, this study contributed to our understanding of the effect of educational factors on survival (since previous research presented conflicting results on this association of interest), and further allowed us to compare the differential effect of education on survival versus other health outcomes.

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To my family, my achievements are not mine alone, but they are our collective achievements because I would not be able to accomplish anything without your prayers, love, and support.

Dedication

To my parents: Their commitment, struggle, and sacrifice for my success has always motivated me to work harder to achieve my goals. Mama and Daddy, I hope that this achievement fulfills the dream you had for me. You were and will always be my source of inspiration. Thank you for your endless prayers, love, and support in all of my pursuits.

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List of Abbreviations

AD	Alzheimer's Disease
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
BRC	Brain Reserve Capacity
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence Interval
CIND	Cognitive Impairment No Dementia
DSM-IV	The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
HR	Hazard Ratio
MMSE	Mini-Mental State Examination
NIA-RI	National Institute on Aging-Reagan Institute
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NP	Neuritic Plaque
NFT	Neurofibrillary Tangle
OR	Odds Ratio

PSEN1	Presenilin 1
PSEN2	Presenilin 2
RR	Relative Risk

1. Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder associated with a loss in cognitive ability and difficulty in maintaining an independent lifestyle (Prince et al., 2013). This disorder is of growing concern because its main risk factor is age, and the world's population aged 65 and older is growing at an unprecedented rate. The prevalence of AD is expected to rise to 81.1 million by the year 2040 (Prince et al., 2013). This increase in prevalence will be paralleled with an increase in health care costs (Alzheimer Society of Canada, 2010; Prince et al., 2013). It is thus important to invest in AD research now, to find a way to either prevent or delay the onset of the disorder.

Cognitive reserve is implicated in the delayed onset of dementia symptoms in that it refers to a hypothetical mechanism that allows individuals to cope with brain damage: those with a higher level of reserve can tolerate a greater amount of damage before showing signs of cognitive impairment (Stern, 2002). However, these individuals with greater reserve are thus at a more advanced stage of AD when they do exhibit symptoms and are therefore expected to experience a more rapid rate of cognitive decline. Consequently, they have a shorter survival time after the onset of dementia symptoms (Tucker & Stern, 2011).

The cognitive reserve hypothesis has stimulated considerable amounts of research, but since reserve cannot be directly measured, the research has focused on factors that contribute to its levels. One example of a factor that influences reserve is education. A higher level of education is typically seen as a protective factor for mortality (Feldman, Makuc, Kleinman, & Cornoni-Huntley, 1989; Kunst & Mackenbach, 1994; Lleras-Muney, 2005; Marmot, Friel, Bell, Houweling, & Taylor, 2008; Pappas, Queen,

Hadden, & Fisher, 1993). In individuals with Alzheimer neuropathology, however, there is disagreement on the relationship between educational attainment and survival. Some studies suggest that a higher level of education is linked with a shorter survival after the onset of dementia symptoms (Freels, Nyenhuis, & Gorelick, 2002; Stern, Tang, Denaro, & Mayeux, 1995; Wilson et al., 2006). This finding can potentially be explained by the cognitive reserve hypothesis, because individuals with more reserve would be expected to be at a more advanced stage of the disease when they first exhibit symptoms and should therefore experience a shorter survival. Other studies suggest that there is no statistical association between educational attainment and survival after the clinical expression of dementia symptoms (Bowen et al., 1996; Brehaut, Raina, & Lindsay, 2004; Fritsch et al., 2001; Geerlings, Deeg, Schmand, Lindeboom, & Jonker, 1997; Helmer, Joly, Letenneur, Commenges, & Dartigues, 2001; Hier, Warach, Gorelick, & Thomas, 1989; Larson et al., 2004; Qiu, Backman, Winblad, Aguero-Torres, & Fratiglioni, 2001; Wolfson et al., 2001). Further, while the literature focuses on educational attainment as a factor that influences reserve, it pays little attention to other elements of formal education (i.e., academic performance).

This research project used secondary data from the Nun Study, a longitudinal study of aging and AD in 678 participants aged 75+ years from the School Sisters of Notre Dame religious congregation in the United States (Snowdon et al., 1996). The purpose of the project was to test the cognitive reserve hypothesis by assessing (1) whether there was a relationship of educational attainment and academic performance with survival in the overall population and, (2) whether the above relationships differed in subgroups defined by the presence or absence of Alzheimer neuropathology.

The study participants' highest degree and first-year high school grades in Geometry, Algebra, Latin and English courses were used to measure levels of educational attainment and academic performance, respectively. Neuropathologic evaluations for deceased participants were used to assess level of Alzheimer neuropathology. Note that previous studies on reserve used brain glucose metabolism and blood flow as a secondary measure of neuropathology (Garibotto et al., 2008; Stern, Alexander, Prohovnik, & Mayeux, 1992) since the Nun Study has direct measures of neuropathology, this project could directly assess whether Alzheimer neuropathology modified the association between educational factors and survival. The Nun Study was ideal for assessing the relationship between educational factors and survival because, in addition to having data on educational attainment, academic performance and direct measures of neuropathology, the Nun Study participants were relatively homogeneous in midlife to late life with regard to environment and lifestyle (Tyas et al., 2007), thus minimizing the influence of confounding variables on the relationship of interest.

2. Literature Review

2.1. Dementia

Dementia is an umbrella term that refers to a broad class of symptoms, characterized by a loss in cognitive ability and difficulty in maintaining an independent lifestyle (Alzheimer Society of Canada, 2010; Prince et al., 2013). There are two forms of dementia: reversible and irreversible. As the name suggests, reversible dementias are curable, and are caused by disorders such as thyroid and kidney disease, vitamin deficiency, and depression. Irreversible dementias, however, are incurable; major subtypes include Alzheimer's disease (AD), vascular dementia, frontotemporal dementia, Lewy body dementia, and Creutzfeldt-Jakob disease (Alzheimer Society of Canada, 2010).

The global prevalence of dementia was about 35.6 million people in 2010; this number is expected to rise to 115.4 million by the year 2050 (Prince et al., 2013). While two-thirds of individuals with dementia reside in developing countries, a significant number of Canadians also suffer from the disorder. A report by the Alzheimer Society of Canada (2010) shows that an estimated 480,600 Canadians suffered from dementia in 2008 and this number is expected to increase to 1,125,200 in 2038. This increase in prevalence will be paralleled with a rise in healthcare costs: the total economic burden of dementia, as measured by direct healthcare costs, opportunity costs of informal caregivers, and indirect costs (e.g., reduced labour productivity for patients and informal caregivers), is expected to grow from $15 billion in 2008 to around $153 billion in 2038 (Alzheimer Society of Canada, 2010).

2.2. Alzheimer's Disease

AD is the most common form of dementia and it makes up about 60% of total dementia cases (Alzheimer Society of Canada, 2010). This disorder was first described in 1906 by the German neurologist, Dr. Alois Alzheimer (Carrillo, Thies, & Bain, 2012). Dr. Alzheimer conducted a brain autopsy on a patient who suffered from memory loss and language impairment; he observed severe atrophy, amyloid plaques, and neurofibrillary tangles (Carillo, Thies, & Bain, 2012). Amyloid plaques are toxic aggregates of the beta-amyloid protein. They occur outside neurons and disrupt communication between them (Herrup, 2012; Hyman et al., 2012). Neurofibrillary tangles, on the other hand, are caused by the hyper-phosphorylation of the tau protein; they occur inside the neuron and interfere with the transport of nutrients and other key molecules (Herrup, 2012; Hyman et al., 2012). A combination of the above two deposits contributes to neuronal death and atrophy (Herrup, 2012; Hyman et al., 2012). Amyloid plaques and neurofibrillary tangles are still considered the basis for AD diagnosis (Carrillo et al., 2012; Hyman et al., 2012; McKhann et al., 1984).

2.2.1. Diagnosis of Alzheimer's Disease

The diagnosis of AD is based upon two sets of criteria: clinical and neuropathologic. The clinical evaluations are conducted during an individual's life while neuropathologic evaluations are conducted after death. Common examples of clinical criteria are the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), Consortium to Establish a Registry for Alzheimer's Disease (CERAD), and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth

Edition (DSM-IV) criteria. Common examples of neuropathologic criteria are the CERAD and the National Institute on Aging-Reagan Institute (NIA-RI) criteria.

2.2.1.1. Clinical Criteria for Alzheimer's Disease

The NINCDS-ADRDA criterion classifies individuals into three categories: "probable AD", "possible AD, and "definite AD". A diagnosis of probable AD entails a typical onset of dementia and a further exclusion of disorders that could contribute to symptoms of memory and cognitive impairment (McKhann et al., 1984). A diagnosis of possible AD, on the other hand, describes individuals with an atypical onset of dementia; individuals with possible AD can have co-morbid disorders, but AD should be the most likely cause for the symptoms (McKhann et al., 1984). Further, a diagnosis of definite AD is made when the diagnosis of probable AD is confirmed with the results of neuropathologic evaluations (McKhann et al., 1984). The NINCDS-ADRDA criterion was originally published in 1984 and revised in 2011. A major revision that was made to the above criterion was the inclusion of five biomarkers (i.e., fluid and imaging techniques) for AD (Jack et al., 2011). These biomarkers measure levels of amyloid-beta and neuronal injury, which are associated with AD-type neuropathology, and were incorporated into the NINCDS-ADRDA criterion to improve the diagnosis of AD (Jack et al., 2011).

The DSM-IV criterion entails a memory deficit in addition to one of the following cognitive deficits: aphasia (speech disturbance), apraxia (disturbance in motor activities), agnosia (disturbance in recognizing objects), and a disturbance in executive functioning (American Psychiatric Association, 2000). The above deficits are progressive and result in the inability to perform daily activities. Similar to the NINCDS-ADRDA criterion, the

DSM-IV criterion requires the exclusion of other brain disorders that contribute to dementia symptoms (American Psychiatric Association, 2000). The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, published in May 2013, is the revised diagnostic criterion for mental disorders. The above criterion refers to 'dementia' as 'neurocognitive disorder', and the latter term is further classified as major or mild neurocognitive disorder. The revised term places less emphasis on memory impairment and instead focuses on overall cognitive decline. The purpose of the above amendment was to classify conditions that begin with a decline in other cognitive domains such as language (American Psychiatric Association, 2013).

Lastly, the CERAD clinical criterion includes a standardized battery of evaluations for the clinical diagnosis of AD. The standardized evaluations gather demographic, clinical, neurological, and neuropsychological information (Fillenbaum et al., 2008). Overall, the CERAD battery is designed to measure cognitive impairments in the following areas: language, memory, praxis, and general intellectual status (Morris et al., 1989).

2.2.1.2. Neuropathologic Criteria for Alzheimer's Disease

Neuropathologic criteria for AD, used for the neuropathologic evaluations for deceased individuals, are based on neuritic plaque (NP) and neurofibrillary tangle (NFT) count and distribution (Hyman et al., 2012). The CERAD and NIA-RI neuropathologic criteria were used in the research project.

The CERAD criterion uses the frequency of NPs as a basis of AD diagnosis: NPs are a form of amyloid plaque that are linked with neuronal injury (Hyman et al., 2012). This method uses a three-step process for the neuropathologic diagnosis of the disease.

For step one, neuropathologists are asked to determine the frequency of NPs in severely affected areas of the neocortex; this information is integrated with the patient's age at death to derive an age-related plaque score in step two. In the final step, the age-related plaque score is combined with clinical information about dementia to create the following levels of diagnostic certainty: "definite AD", "probable AD", and "possible AD" (Mirra et al., 1991).

The NIA-RI criterion considers both NPs and NFTs for the neuropathologic diagnosis of AD. This criterion uses a modified version of the CERAD neuropathologic criterion to measure the frequency of NPs; the NP score is categorized into the following categories: "no neuritic plaques", "CERAD score sparse", "CERAD score moderate", and "CERAD score frequent" (Hyman et al., 2012). Similarly, the NFT distribution is categorized into the following: "no neurofibrillary tangles"; "Braak stage I or II", in which the tangles are primarily located in the entorhinal cortex and surrounding areas; "Braak stage III or IV", in which the tangles are present in the hippocampus and amygdala; and finally "Braak stage V or VI", in which the tangles are present throughout the neocortex (Hyman et al., 2012). The NP score and NFT distribution are ultimately combined to create four levels of AD neuropathologic certainty: "not [likely]", "low [likelihood]", "intermediate [likelihood]" or "high [likelihood]" (Hyman et al., 2012).

Each of the neuropathologic criteria discussed above has their strengths and weaknesses. As mentioned before, Alzheimer neuropathology consists of both amyloid plaques and NFTs (Hyman et al., 2012). The CERAD neuropathologic criterion only considers plaques and thus, it alone is not an accurate assessment of Alzheimer-type changes in the brain. The NIA-RI criterion might seem ideal because it measures both the

NP score and NFT distribution, but it cannot accurately categorize all cases. For instance, cases with a high NFT distribution but a moderate NP score are "technically unclassifiable" according to this particular criterion (Nelson, Kukull, & Frosch, 2010).

2.2.2. Risk Factors for Alzheimer's Disease

There are two categories of risk factors for AD: non-modifiable and theoretically modifiable. Examples of non-modifiable risk factors include age, gender, familial history, and genetics. In contrast, theoretically modifiable risk factors include cardiovascular factors, physical inactivity, tobacco use, and low levels of education (Barnes & Yaffe, 2011; Stern et al., 1994; Tyas et al., 2003; Tyas & Gutmanis, 2015). Note that only risk factors that relate to the project will be discussed in the sections below.

2.2.2.1. Non-modifiable Risk Factors

Age is the most well known risk factor for AD. The risk of developing dementia doubles every five years between 65 and 90 years of age (Carillo, Thies, & Bain, 2012). For individuals over age 100, the risk is as high as 41 percent (Carillo, Thies, & Bain, 2012). The above statistics are a cause for concern because individuals aged 60+ will make up 22% of the world's population by the year 2050 (Prince et al., 2013). While the statistics suggest an increased life expectancy of individuals around the world, they foreshadow a greater risk for non-communicable, age-related disorders such as AD (Carillo, Thies, & Bain, 2012).

Female sex is also a potential risk factor for AD. Some studies suggest that AD is more prevalent in women, after adjusting for age (Gao, Hendrie, Hall, & Hui, 1998; Henderson, 1988; Janicki & Schupf, 2010). Janicki & Schupf (2010) state that women could be more susceptible to AD due to a drop in estrogen levels and other hormonal

changes that occur post-menopause. In contrast to the studies cited above, reviews and meta-analyses of incidence studies found that female sex was not associated with an increased risk of AD (Swanwick & Lawlor, 1999; Ziegler-Graham, Brookmeyer, Johnson, & Arrighi, 2008). In light of the conflicting evidence, further research is required to clarify the role of female sex as a risk factor for AD.

AD is categorized as either familial or sporadic AD. The literature on familial AD shows that first-degree relatives of AD patients have a higher risk of dementia (Henderson, 1988). Research on the heritability of AD illustrates that the offspring of familial AD cases have a 50 percent chance of developing the disease themselves, because AD follows an autosomal dominant pattern of inheritance (Henderson, 1988; Janssen et al., 2003; Schu, Sherva, Farrer, & Green, 2012). In some cases these offspring develop presenile dementia at as early as 30 years of age; mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes are associated with the development of early symptoms (Janssen et al., 2003; Schu et al., 2012). Mutations in the above three genes are also linked with the formation of a particular isoform of the beta-amyloid protein, which is further associated with the development of beta-amyloid plaques (Schu et al., 2012).

In contrast to APP, PSEN 1, and PSEN 2 mutations, which are linked to familial AD, the apolipoprotein E (*APOE*) gene is associated with sporadic AD. The *APOE* protein has three allelic variants: ε2, ε3, and ε4. Each of these alleles has a varied effect on the charge and three-dimensional structure of the resultant protein (Roses, 1996; Schu et al., 2012). The ε4 allele is associated with an increased risk of developing AD (Roses, 1996; Schu et al., 2012). Individuals who inherit two ε4 alleles have a greater risk of

developing AD than individuals with one ε4 allele (Roses, 1996). Evidence suggests that the ε4 allele stimulates AD pathology because ε4 carriers experience an increase of beta-amyloid aggregates outside neurons, abnormal phosphorylation of the tau protein, neural toxicity, and tangle formation. Simultaneously, they experience a decrease in synaptic repair, synaptic plasticity, neurite growth, and anti-inflammatory action (Schu et al., 2012). Further, the *APOE* protein plays a role in cholesterol production and transport. The ε4 allele is implicated in the malfunction of cholesterol transport: individuals who inherit the ε4 allele have reduced cholesterol levels in the blood and brain tissues (Hamanaka et al., 2000; Poirier, 2005). The maintenance of brain cholesterol homeostasis is important because cholesterol is implicated in the development of the central nervous system, neural plasticity, and in neurotransmitter release (de Chaves & Narayanaswami, 2008).

2.2.2.2. Theoretically Modifiable Risk Factors

In contrast to the non-modifiable risk factors discussed above, theoretically modifiable lifestyle factors such as cardiovascular factors (e.g., Type 2 diabetes, mid-life hypertension, mid-life obesity), physical inactivity, tobacco use and low levels of education, can also increase the risk of AD (Barnes & Yaffe, 2011; Henderson, 1988). While studies suggest that the cardiovascular factors and physical inactivity influence the development of AD through vascular mechanisms, the mechanism through which tobacco use influences the risk of AD is unclear (Barnes & Yaffe, 2011; Cataldo, Prochaska, & Glantz, 2010; Henderson, 1988; Tyas et al., 2003). Research by Tyas et al. (2003) demonstrated a dose-response relationship between tobacco use and AD, where medium or heavy levels of smoking were associated with an increased risk of AD. The

absence of an association between very heavy levels of smoking and AD could be due to survival bias. Plausible explanations for the association between medium and heavy levels of smoking with increased risk of AD are that tobacco use is associated with a greater number of amyloid plaques (Tyas et al., 2003), it is associated with oxidative stress and inflammation, and it increases the risk for cardiovascular diseases (Barnes & Yaffe, 2011). Further, several studies demonstrate that education, a social determinant of health (see Section 2.4.1), is inversely associated with the risk of developing AD (Evans et al., 1997; Fratiglioni et al., 1997; Letenneur et al., 1999; Ott et al., 1999). Similar to tobacco use, the explanation of how educational attainment influences the development of AD is unclear. While some researchers propose an association between educational attainment and anatomical features of the brain, such as brain weight, others suggest that high levels of education delay the onset of AD because education contributes to cerebral reserve (Bezerra et al., 2012). The relationship between educational factors and cerebral reserve will be discussed in more detail in the following section.

2.3. Reserve

Cognitive reserve refers to a mechanism that allows individuals to cope with brain damage (Stern, 2002). To exemplify, some individuals appear cognitively intact despite having advanced AD neuropathology at the time of death (Katzman et al., 1989). Since the individuals do not show symptoms of AD despite having the disease-specific pathology, there appears to be a factor that is preventing or delaying the clinical manifestation of the disease. Reserve is the suggested factor (Stern, 2002).

2.3.1. Brain Reserve Versus Cognitive Reserve

Two forms of reserve have been identified: brain reserve and cognitive reserve (Stern, 2002). The first, brain reserve, is passive and includes measures such as brain size, neuronal count and synaptic density (Stern, 2012). The brain reserve model suggests that individuals differ with respect to their brain reserve capacity (BRC), and this difference, in turn, influences their response to brain damage. Consider the following illustration. Person 2 has a lower level of BRC in comparison to Person 1; a lesion depletes Person 2's BRC past the critical threshold point, leading to functional impairment. Since a lesion of the same size has no impact on Person 1, the individual with a higher BRC, brain reserve is a potential protective factor against the clinical expression of brain damage (Stern, 2002).

In contrast to the brain reserve model, cognitive reserve is an active form of reserve. This model suggests that all individuals have the same level of BRC, but they vary in their capability to process a given task, and therefore have a differential response to brain damage (Stern, 2002). Levels of cognitive reserve are influenced via two neural mechanisms: neural reserve and neural compensation. Neural reserve refers to the ability to use more efficient brain areas to complete a task: AD patients with increased levels of neural reserve can maintain function despite neuropathology because they use the remaining brain areas in a more efficient manner (Stern, 2002). Individuals with neural compensation capabilities, however, are resilient against brain damage because they have the ability to recruit additional networks to complete a particular task (Stern, 2002). Consider the following example involving a mathematician: "a trained mathematician might be able to solve a mathematics problem in many different ways, while a less

experienced individual might have only one possible solution available" (Stern, 2002, p. 452).

Although the models of brain and cognitive reserve are distinct, they are not mutually exclusive. Evidence shows that measures of cognitive reserve such as socioeconomic status, income, educational attainment, and occupational attainment influence BRC (Stern, 2006). Animal studies demonstrate that enriching environments have a direct impact on AD neuropathology (Tucker & Stern, 2011). Enriching environments are associated with neurogenesis in the dentate gyrus of the hippocampus (Tucker & Stern, 2011). Since this evidence suggests an interaction between the brain and cognitive reserve models, this paper encompasses both with the term cerebral reserve, which will now be used exclusively.

2.3.2. The Influence of Educational Attainment on Reserve

The topic of cerebral reserve has stimulated considerable amounts of research; however, since reserve cannot be directly measured, research focuses on factors that influence its levels. A higher level of education is one example of a factor that contributes to reserve. The four studies detailed below firmly support the theory of cerebral reserve; this support is particularly striking in view of the different methodologies used.

Stern et al. (1992) assessed the association between educational attainment and neuropathology, using blood flow as a proxy measure of brain damage. After controlling for cognitive function, individuals with higher levels of education experienced a reduction in blood flow to the parietotemporal cortex (Stern et al., 1992). Note that this brain region is highly associated with cognitive deficits specific to AD (Snowdon et al., 1996). Garibotto et al. (2008) conducted a similar study, but used glucose metabolism as

an indicator of brain damage. Similar to decreases in blood flow, a decrease in glucose metabolism signifies a higher severity of neuropathology. There was an inverse relationship between educational attainment and glucose metabolism in the posterior parietotemporal cortex of individuals with probable AD, after adjusting for cognitive function (Garibotto et al., 2008). The studies by Stern et al. and Garibotto et al. support the cerebral reserve hypothesis because they demonstrate that individuals with higher educational attainment preserve good cognitive function, in comparison to those with a lower level of education, despite having a greater degree of brain damage (as indicated by blood flow and glucose metabolism in the parietotemporal cortex).

Roe, Xiong, Miller, & Morris (2007) also assessed the cerebral reserve hypothesis by examining the association between educational attainment and dementia status in individuals who met the neuropathologic criteria for AD. The rationale for the study arose from the observation that some individuals fail to exhibit clinical symptoms of AD even close to the time of death, despite the presence of abundant NFTs and senile plaques. The researchers recruited participants who met the Khachaturian, NIA-RI, or CERAD criteria for AD and further compared their degree of neuropathology with their dementia status at a final cognitive assessment (Roe et al., 2007). Participants with more years of education were less likely to demonstrate signs of functional impairment, irrespective of the neuropathologic criteria used. The above research supports the cerebral reserve hypothesis because it illustrates that high educational attainment allows individuals to better cope with brain damage (Roe, Xiong, Miller, & Morris, 2007).

Hall et al. (2007) also evaluated the cerebral reserve hypothesis, but they used the rate of cognitive decline as an outcome measure, rather than the degree of brain damage.

Each additional year of education was associated with a delay in the clinical expression of dementia by 0.21 years on the Buschke Selective Reminding Test; however, once dementia symptoms became apparent, the rate of memory decline increased by 0.10 years for each additional year of education (Hall et al., 2007). Although the above finding seems paradoxical at first, it supports the cerebral reserve hypothesis because this hypothesis predicts that individuals with higher levels of reserve accumulate severe neuropathology before showing signs of functional impairment. However, since the individuals are at a more advanced stage of the disorder once they do exhibit clinical symptoms, they are expected to experience an accelerated rate of cognitive decline (Tucker & Stern, 2011).

2.3.3. The Influence of Academic Performance on Reserve

While several studies have examined if educational attainment influences levels of reserve, there is limited research on whether academic performance contributes to its levels. Only two studies (Bezerra et al., 2012; Mehta et al., 2009) were found that examined academic performance and the risk of developing dementia. Since the research by Bezerra et al. (2012) and Mehta et al. (2009) (detailed below) suggests that early-life academic performance influences the risk of developing dementia in late life, there is potential in testing whether academic performance influences levels of cerebral reserve.

Bezerra et al. (2012) evaluated whether poor academic performance, as measured by grades in Portuguese, mathematics, and geography, influenced the risk of developing dementia in late life. High academic performance was measured by a cut-off score of seven out of ten. After controlling for gender, age, years of education, socioeconomic status, and health status, each additional half-point above the cut-off score significantly

reduced the likelihood of dementia for participants who studied mathematics (odds ratio (OR)=0.21, 95% confidence interval (CI)=0.08-0.58) and Portuguese (OR=0.72, 95% CI=0.69-0.91) (Bezerra et al., 2012). High academic performance in geography, on the other hand, had no effect on the risk of dementia.

Mehta et al. (2009) conducted a study to assess whether poor school performance, as measured by self-assessed school performance, was associated with AD. A greater proportion of individuals with lower school performance developed AD: 26% of participants with "below average" performance, 12% of participants with "average" performance, and 11% of participants with "above average" performance developed AD ($p< 0.001$) (Mehta et al., 2009). The above results are comparable to those of the Bezerra et al. study because they suggest that academic performance influences the risk of developing AD. They differ from the results of the Bezzera et al. study, however, because they suggest that "above average" self-assessed school performance has no significant effect on the development of the disorder of interest.

2.3.4. Other Factors That Potentially Influence Reserve

Occupation is also a widely studied factor that may contribute to cerebral reserve. A higher level of occupational attainment is associated with a reduction in the risk of developing dementia (Bickel & Cooper, 1994; Qiu et al., 2003; Stern et al., 1994).
A study by Stern et al. (1995) provides evidence for the notion that specific characteristics of an occupation contribute to cerebral reserve by illustrating an inverse relationship of higher interpersonal skills and physical demand factor scores with cerebral blood flow even after controlling for age, cognition and education. Occupational

characteristics thus influence reserve, but they have an effect independent from education (Stern, 2006).

Apart from educational and occupational factors, participation in leisure and cognitive activities may also contribute to levels of reserve. Activities such as travelling, knitting, and gardening are associated with a decrease in the risk of developing dementia (Fabrigoule et al., 1995). Further, after controlling for factors such as baseline cognitive status, age, sex, education and general health, cognitive activities such as reading, writing, playing board games and playing a musical instrument also decrease the risk of dementia (Scarmeas & Stern, 2003; Verghese et al., 2003; Wilson, Barnes, & Bennett, 2003). Participation in leisure activities could contribute to cerebral reserve because it is associated with higher levels of neural reserve and compensation (Scarmeas & Stern, 2003). In contrast, the association between the activities of interest and dementia could be a subclinical effect of the disorder, in that individuals with severe dementia symptoms have a low participation in leisure activities (Friedland et al., 2001).

Research based on the Nun Study illustrates that language skills may also potentially contribute to levels of cerebral reserve. The Nun Study includes handwritten autobiographies that are part of the convent archives. These autobiographies include a brief description of birthplace, ancestry, and important events of each participant's life (Snowdon et al., 1996). The autobiographies were coded for two markers of language skills: idea density and grammatical complexity. Idea density refers to "the average number of ideas expressed per ten words" (Snowdon et al., 1996, p. 529). Grammatical complexity refers to sentence structure and forms of embedding/subordination (Snowdon et al., 1996). Preliminary work by Tyas, Snowdon, Desrosiers, Riley & Markesbery

(2009) suggests that individuals with high idea density and high grammatical complexity were more likely to appear cognitively intact despite having Alzheimer neuropathology, in comparison to individuals with lower levels of the two variables. The above findings persisted after controlling for age at death, education, and *APOE*-ε4 status (Tyas et al., 2009). Other studies found that low early-life idea density, but not grammatical complexity, is associated with late-life cognitive decline (Riley, Snowdon, Desrosiers, & Markesbery, 2005; Snowdon et al., 1996). Low idea density is also associated with low brain weight, a high degree of cerebral atrophy, and a high degree of Alzheimer neuropathology (Riley et al., 2005).

Multilingualism is suspected to contribute to reserve because it is associated with enhanced cognitive function. According to research by Hack et al. (2012), individuals who could speak four or more languages were 86% less likely to develop dementia, in comparison to individuals who were monolingual; these findings were based on data from the Nun Study. However, the above association was weaker in analyses that accounted for the influence of idea density. Further research is required on the relationship between multilingualism and reserve, and on the role of idea density in the above relationship (Hack, Tyas, Dubin, Fernandes, & Riley, 2012).

2.4. The Influence of Education on Survival

2.4.1. The Association Between Education and Survival in the General Population

Education is a social determinant of health. Low levels of education are associated with poor overall health, low self-confidence, high stress, and high mortality. Conversely, early-life educational opportunities are positively associated with a child's development, chances of survival, and overall health and wellbeing (Chappell, Ota,

Berryman, Elo, & Preston, 1996; Kunst & Mackenbach, 1994; Lleras-Muney, 2005; Mackenbach et al., 2015; Marmot, Friel, Bell, Houweling, & Taylor, 2008; Smith et al., 1998; Sorlie, Backlund, & Keller, 1995; World Health Organization, 2014a; World Health Organization, 2014b). The strength of the association between education and mortality differs across countries and age/employment subgroups. Kunst and Mackenbach (1994) found small inequalities in mortality by educational level in countries such as the Netherlands, Sweden, Denmark, and Norway, but large inequalities in the United States, France, and Italy; similarly, Mackenbach (2015) found small inequalities in mortality by education in Southern Europe but large inequalities in Eastern Europe. Further, the inverse association between high educational attainment and mortality is stronger for working individuals aged less than 65 years, in comparison to the older individuals that are not in the work force (Chappell et al., 1996; Sorlie et al., 1995).

2.4.2. The Association Between Education and Survival in Individuals With Alzheimer's Disease

Appendix A provides a summary table for all studies that examined the association between education and survival in individuals with AD. While education is protective of mortality in the general population, as detailed in Section 2.4.1, two studies (Freels et al., 2002; Stern et al., 1995) suggest that higher educational attainment is associated with decreased survival after diagnosis of AD. Stern et al. (1995) found that individuals with AD and more than eight years of education had a greater risk of mortality (hazard ratio (HR)=1.76, 95% CI=1.11-2.77) than individuals with eight or less years of education, after controlling for age, gender, and cognitive function. Freels et al. (2002) conducted a similar study and concluded that higher educational attainment in

individuals with AD was associated with a shorter survival, after adjusting for age, sex, and cognitive function (HR=1.10, p= 0.01). The above findings can be explained by the cerebral reserve hypothesis. Recall that the cerebral reserve hypothesis predicts that individuals with higher levels of reserve experience a more rapid rate of cognitive decline closer to the diagnosis of dementia than those with lower levels of reserve, reflecting their greater degree of Alzheimer neuropathology (Stern, 2002; Tucker & Stern, 2011). Further, a rapid rate of cognitive decline is associated with a shorter survival (Hui et al., 2003; Wilson et al., 2006). A study by Wilson et al. (2006) found that after controlling for age, sex, race, education, baseline cognitive function, and global cognitive decline, individuals with a slower rate of cognitive decline had a reduced risk of death (relative risk (RR)= 0.31, 95% CI= 0.19-0.49) in comparison to individuals with accelerated cognitive decline. A similar study by Hui et al. (2003) reported that the participants with rapid cognitive decline had an eight times (RR= 8.88, 95% CI= 4.11-19.96) higher risk of mortality than those with the lowest rate of cognitive decline.

In contrast, some studies suggest that there is no association between educational attainment and survival after diagnosis of AD (Bowen et al., 1996; Brehaut et al., 2004; Fritsch et al., 2001; Geerlings et al., 1997; Helmer et al., 2001; Hier et al., 1989; Larson et al., 2004; Paradise, Cooper, & Livingston, 2009; Qiu et al., 2001; Wolfson et al., 2001). However, these studies have limitations. Six studies did not adjust for cognitive function (Fritsch et al., 2001; Geerlings et al., 1997; Helmer et al., 2001; Hier et al., 1989; Larson et al., 2004; Wolfson et al., 2001). Cognitive function is an important factor to consider when assessing the relationship between education and survival because it may be an intervening factor on the causal pathway between education and survival. Note that

while research suggests that high childhood IQ (i.e., a factor that promotes cognitive function) may contribute to increased educational success, in turn influencing survival (Whalley & Deary, 2001), our study assumed that cognitive function was an intervening factor between education and survival because this notion is consistent with the theory of cerebral reserve. Individuals with a higher level of education (i.e., greater cerebral reserve) are able to maintain cognitive function despite having Alzheimer-type neuropathology. However, once these individuals with more education express dementia symptoms, they experience a faster rate of cognitive decline, and consequently, a shorter survival.

The study by Geerlings et al. (1997) is a replication of the study by Stern et al. (1995). While the latter study found an inverse association between education and survival, Geerlings et al. (1997) did not. Possible reasons for the difference in results are that the participants of the Geerlings et al. study were about five years younger on average and at an earlier stage of AD; this may have impacted the results because younger participants may have had a reduced severity of AD neuropathology. Also, deceased participants in the Stern et al. study were more educated in comparison to the living participants, whereas in the Geerlings et al. study, both living and deceased participants had the same level of education. If high education is indeed associated with shorter survival, than the association of interest may have been driven by the more educated participants in the Stern et al. study.

Further, all of the studies described above only included participants who were diagnosed with AD. This is a limitation because these studies potentially excluded a group of major interest, individuals that suppress the clinical expression of AD due to

high levels of reserve. Note that the above limitation was based on the assumption that high reserve contributes to the suppression of AD symptoms; genetic or other factors, such as those that prevent development of AD neuropathology [see Section 6.2.]) may also influence the clinical expression of AD symptoms. The studies by Geerlings et al. (1999) and Brehaut et al. (2004) included participants with various categories of cognitive function. Geerlings et al. reported a positive relationship between education and mortality, but only in participants with low cognitive function (as measured by a Mini-Mental State Examination (MMSE) score of less than 20). The researchers found that a high level of educational attainment was associated with a higher risk of mortality (RR=1.17, 95% CI=1.02-1.34) in only those individuals who expressed severe dementia symptoms (Geerlings et al., 1999). Brehaut et al. found that education was protective of survival in individuals without dementia; however, there was no association between education and survival in individuals with dementia or those with cognitive impairment but no dementia (CIND). Brehaut et al. (2004) explained that the study had some limitations that could affect the results. First, the screening tool used to assess dementia status was not entirely accurate; at least 19% of the participants categorized as 'no dementia' were later found to have signs of cognitive impairment. Further, a large proportion of patients who were cognitively impaired had a low level of educational attainment. If a high level of education is in fact associated with a shorter survival, then the large proportion of cognitively impaired individuals with lower educational attainment could explain the lack of an association between education and survival (Brehaut, Raina, & Lindsay, 2004). Further, the researchers found a positive association between educational attainment and the rate of progression of AD in individuals

diagnosed with dementia or CIND, after controlling for cognitive function. This result supports the theory of cerebral reserve.

2.5. Summary

The theory of cerebral reserve explains why some individuals appear cognitively intact despite having Alzheimer neuropathology at death. An example of a factor that contributes to reserve is education. A higher level of education is typically seen as a protective factor for mortality. In individuals with AD, however, there is no clear consensus on the association between education and survival. Some studies suggest that a higher education is associated with a shorter survival after diagnosis of AD; this finding can be explained by the cerebral reserve hypothesis, which suggests that individuals with more reserve are at a more advanced stage of AD when they exhibit symptoms and are therefore expected to experience a rapid rate of cognitive decline, and consequently, a shorter survival. In contrast, some studies report no statistical association between education and survival in individuals with AD. Studies assessing the relationship between education and survival have limitations; they often do not adjust for cognitive function (see Section 2.4.2), AD neuropathology, and genetic risk factors for AD (i.e., *APOE*-ε4), or they only include participants who were diagnosed with AD. This research project examined the association between education and survival in individuals with and without AD neuropathology. The study further assessed whether an association existed between academic performance and survival, and whether Alzheimer neuropathology modified the above association.

3. Study Rationale and Research Questions

3.1. Study Rationale

The overall aim of the project was to assess the theory of cerebral reserve by evaluating (1) whether there was a positive relationship of educational attainment and academic performance with survival in the overall population and, (2) whether the above relationships differed in subgroups defined by the presence or absence of AD neuropathology.

The project used secondary data from the Nun Study, a longitudinal study of aging and AD, in 678 participants aged 75+ from the School Sisters of Notre Dame religious congregation (Snowdon et al., 1996). Educational attainment and academic performance were measured by highest level of education and high school grades, respectively. Neuropathologic evaluations of deceased participants provided measures of AD neuropathology.

The Nun Study data can clarify reported inconsistencies in the association between educational factors and survival because they include direct measures of neuropathology whereas existing research on the topic used proxy measures of brain damage (i.e., blood flow and glucose metabolism) (Garibotto et al., 2008; Stern et al., 1992). The research project can also contribute a novel perspective to literature on the cerebral reserve hypothesis because it evaluates whether AD neuropathology acts as an effect modifier for the relationship between educational factors and survival; researchers studying this topic typically match all participants on clinical status and are therefore unable to assess the effects of different levels of neuropathology on the relationship

between educational attainment and survival. In addition, the project will assess a novel association between academic performance and survival.

3.2. Research Questions and General Hypotheses

3.2.1. Research Questions

Question 1a: Is educational attainment associated with survival?

1b: Does this association persist after controlling for age and *APOE*-ε4 status?

1c: Does Alzheimer neuropathology modify this association?

Question 2a: Is academic performance associated with survival?

2b: Does this association persist after controlling for age and *APOE*-ε4 status?

2c: Does Alzheimer neuropathology modify this association?

3.2.2. General Hypotheses

It is hypothesized that there is a positive association of educational attainment and academic performance with survival, in the overall population, and that this association persists after controlling for age and *APOE*-ε4 status. It is also hypothesized that Alzheimer neuropathology modifies the association of educational attainment and academic performance with survival. Participants with low educational attainment and low academic performance have a shorter survival in comparison to participants with high educational attainment and high academic performance. The theory of cerebral reserve explains that individuals with a higher level of reserve (i.e. higher educational attainment and academic performance) have a delayed onset of dementia symptoms. However, when these individuals with high reserve do express symptoms, they are at a more advanced stage of AD and should thus experience a shorter survival.

4. Methods

4.1. Literature Search

A literature search on the relationship between educational factors and survival was conducted in October 2015 using the Medline database (1950 to present). The literature search included three sub-searches, one for each of the three main concepts: educational factors, mortality rate, and AD. MeSH terms, author keywords, and title/abstract (tiab) terms were identified for each of the above three concepts. The sub-search for the concept of educational factors was as follows: Grade* OR educational status[mesh] OR "academic achievement" OR "educational attainment" OR education[tiab]. The second sub-search for the concept of mortality rate included the following terms: mortality rate[tiab] OR survival analysis[mesh] OR Alzheimer disease/mortality[mesh] or survival[tiab]. The last sub-search included the search term Alzheimer disease[all fields] OR dementia[all fields]. The above three sub-searches were combined and yielded a total of 440 results. Four hundred and six out of 420 of these articles had irrelevant exposures or outcomes (e.g., examined risk factors for AD other than education) and were therefore excluded; the remaining 14 articles were saved for review.

A second literature search on the relationship between educational factors and survival was conducted in the PsycINFO database (1840 to present) in October 2015. Subject headings and index terms were identified for the three main search concepts: educational factors, mortality rate, and AD. The search included the following index terms and keywords ("educational degrees" or "student records" or "educational standards" or "grade" or "academic achievement" or "education" or "educational

attainment level") AND ("mortality rate" or "death rate") AND ("Alzheimer's disease" or "dementia"), and yielded a total of 43 results. Thirty-three articles were excluded on the basis of irrelevant exposures or outcomes (e.g., examined frailty and risk of death in older individuals in general, rather than in individuals with AD) and ten articles were excluded because they overlapped with the results of the Medline search.

A separate literature search was conducted using the Medline database (1950 to present) on the topic of reserve. Note that the aim of this section was to provide background information on reserve, and factors that influence it; thus, the literature search on the topic was not intended to be comprehensive. The search included the following terms (educational status[mesh] or education[tiab] or "academic achievement" or "school attainment") AND (cognitive reserve[tiab] or cognitive reserve/physiology*) AND (Alzheimer disease/diagnosis[mesh] or dementia/etiology[mesh]), and it generated a total of 60 results. Forty-nine of the above articles were excluded because they had irrelevant exposures or outcomes (e.g., examined the role of cognitive reserve in disorders other than AD or dementia). The remaining 11 articles were selected for review.

Furthermore, the reference lists of the retrieved articles on cerebral reserve and on the relationship between education and survival were also searched manually to extract additional literature. Two additional articles were retrieved using this manual search.

4.2. Data Source: The Nun Study

4.2.1. Study Population

The Nun Study is a longitudinal study of aging and AD (Snowdon et al., 1996). Between the years of 1991 and 1993, members of the School Sisters of Notre Dame

religious congregation aged 75+ were asked to participate in the study. Six hundred and seventy-eight sisters, out of an eligible 1,027, agreed to join the Nun Study (Snowdon et al., 1996). Each participant provided consent for annual cognitive and physical assessments, access to convent archives and brain donation at death (Snowdon et al., 1996; Tyas et al., 2007). Participants and nonparticipants did not significantly vary by birthplace, age, race, or annual mortality rate (Snowdon et al., 1996; Tyas et al., 2007).

The Nun Study was ideal for this project because its participants are relatively homogeneous in midlife to late life with regard to environment and lifestyle (Tyas et al., 2007), thus minimizing the influence of confounding variables on the relationship between the education-related variables and mortality rate.

4.2.2. Data Collection

The Nun Study includes assessments of cognitive and physical function using seven standard CERAD tests (Riley, Snowdon, & Markesbery, 2002) and standard Activities of Daily Living (ADL) measures (Riley et al., 2002). The CERAD battery of neuropsychological tests (i.e., Delayed Word Recall, Word Recognition, World List Memory, Verbal Fluency, Construction Praxis, Boston Naming, and the Mini-Mental State Exam) assesses a variety of cognitive abilities including memory, concentration, language, visuospatial ability, and orientation to time and place (Riley et al., 2002; Snowdon et al., 1996). The ADL measures include basic activities (i.e., dressing, walking, standing, feeding, and toileting) and instrumental activities (i.e., reading, telling time, taking medication, and handling money). All of the above activities, except toileting, are performance-based and the participants' ability to perform these activities is

used to evaluate physical function (Riley et al., 2002; Tyas, Snowdon, Desrosiers, Riley, & Markesbery, 2007).

Further, the Nun Study includes neuropathologic evaluations for deceased participants. These evaluations include the number of senile plaques and NFTs in specific brain areas such as the CA1 and subiculum of the hippocampus, the inferior parietal lobule (Brodmann areas 39 and 40), the middle temporal gyrus (Brodmann area 21), and the middle frontal gyrus (Brodmann area 9) (Snowdon et al., 1996). The above brain areas are cut into sections that are 8 microns thick; microscopic examinations using the modified Bielchowsky stain are used to quantify the plaques and tangles. The neuropathologist who conducted these evaluations was blinded to the participants' cognitive test scores (Riley et al., 2002). *APOE* genotyping was conducted on deceased participants using frozen brain tissue. *APOE* genotyping was performed on living participants using buccal cells (Saunders et al., 1996).

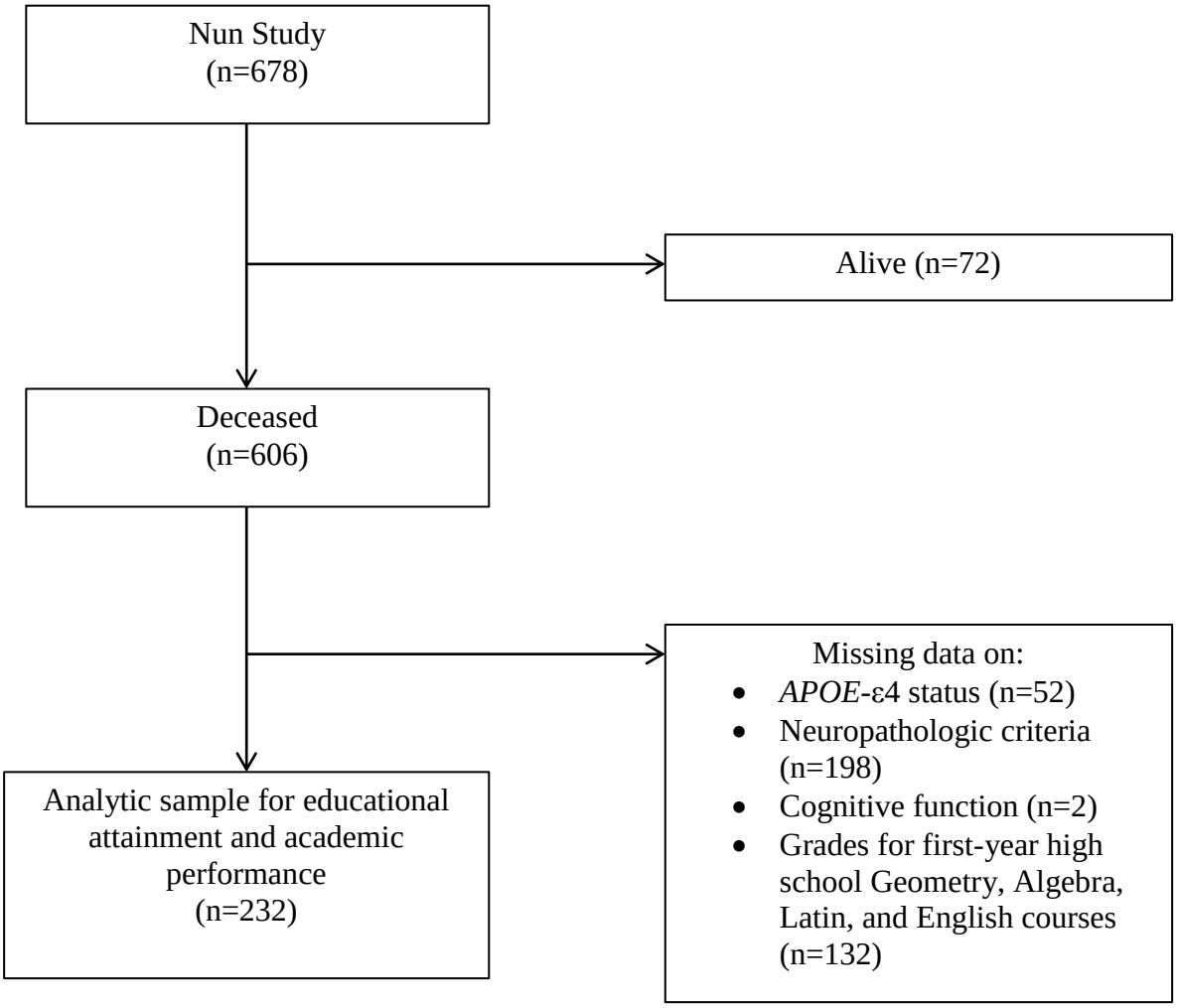
Apart from cognitive/physical assessments and neuropathologic evaluations, the Nun Study has access to archival records that include birth certificates, high school transcripts, handwritten autobiographies, and results from a survey that was administered in 1983 by the School Sisters of Notre Dame religious congregation (Patzwald & Wildt, 2004). The birth certificates and high school transcripts were used to determine the participants' age and academic performance, respectively. The 1983 survey included information about socio-demographics and family background and can be used to determine the participants' level of education (Patzwald & Wildt, 2004).

4.3. Analytic Sample

4.3.1. Main Analytic Sample

Figure 1 illustrates how the analytic sample was derived. The analytic sample consisted of only deceased Nun Study participants, since the research project assessed whether neuropathology was an effect modifier for the relationship between educational factors and survival, and neuropathologic evaluations are only available for deceased participants. Participants were excluded if they had missing data on *APOE*-ε4 status, CERAD neuropathologic criteria, NIA-RI neuropathologic criteria, cognitive status (at baseline and at last assessment), and grades for first-year high school Geometry, Algebra, Latin, and English courses. The remaining participants (n=232) constituted the analytic sample for educational attainment and academic performance.

Figure 1: Derivation of analytic sample



4.3.2. Sensitivity Analyses

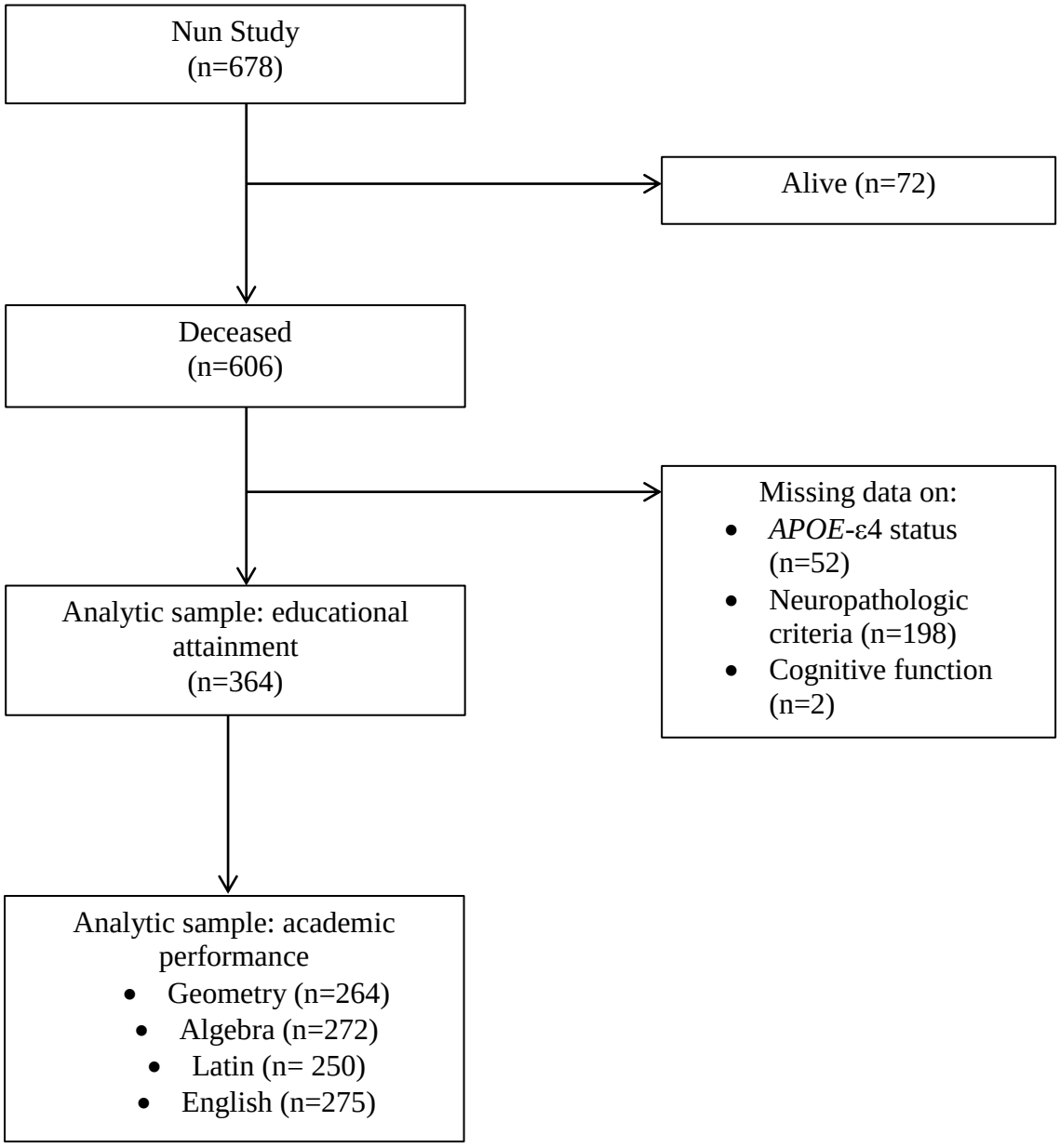
4.3.2.1. Sensitivity Analyses Using Alternate Samples for Educational Factors

Sensitivity analyses were conducted using (1) a larger sample restricted only by education and, (2) separate samples for each first-year high school Geometry, Algebra, Latin, and English course (as opposed to the main analytic sample where there was only one analytic sample for the mean academic performance across the four first-year high school courses). Figure 2 illustrates how the above samples were derived. Similar to the main analytic sample, the above samples only consisted of deceased Nun Study participants, because the project tested for whether Alzheimer neuropathology modified the association between educational factors and survival in the above samples, and neuropathologic evaluations are only available for deceased participants. Participants were excluded if they had missing data on *APOE*-ε4 status, CERAD neuropathologic criteria, NIA-RI neuropathologic criteria, and cognitive status (at baseline and at the last assessment). The remaining participants constituted the analytic sample that was restricted only by education (n=364). The samples for academic performance in first-year high school Geometry (n=264), Algebra (n=272), Latin (n=250), and English (n=275) courses were a subset of the educational attainment sample.

4.3.2.2. Sensitivity Analyses Using Alternate Categorizations for Academic Performance

Sensitivity analyses were also conducted by categorizing academic performance into (1) high (i.e., participants achieved at least 90 percent in each first-year high school Geometry, Algebra, Latin and English course) versus lower academic performance (less than 90%) and, (2) tertiles (as opposed to quartiles in the main analyses). Note that the analytic sample used for these analyses was consistent with that of the main analyses.

Figure 2: Derivation of analytic samples for sensitivity analyses



4.3.2.2. Assessment of Non-response Bias

Sensitivity analyses included an assessment of non-response bias. For this purpose, the analytic sample (n=232) was compared to the following samples of excluded participants: participants who were alive and were excluded because neuropathologic assessments are only available for deceased Nun Study participants (n=72), deceased participants who were excluded because they had missing data on the covariates (n=374), and the combined group of all excluded participants (n=446). The results showed that living participants were significantly younger ($p<0.0001$), were significantly less likely to be *APOE*-ε4 carriers ($p=0.01$), and had a significantly different cognitive status at baseline ($p<0.0001$) and at the last assessment ($p<0.0001$) in comparison to the analytic sample (see Appendix B, Table 1 for detailed results). Deceased participants who were excluded because they had missing data on covariates had a significantly different level of educational attainment ($p<0.0001$), were significantly older ($p=0.01$), and had a significantly different cognitive status at baseline ($p=0.0007$) in comparison to the analytic sample (see Appendix B, Table 2 for detailed results). Furthermore, the combined group of all excluded participants differed significantly on level of educational attainment ($p<0.0001$) and cognitive status at the last assessment ($p=0.01$) in comparison to the analytic sample (see Appendix B, Table 3 for detailed results).

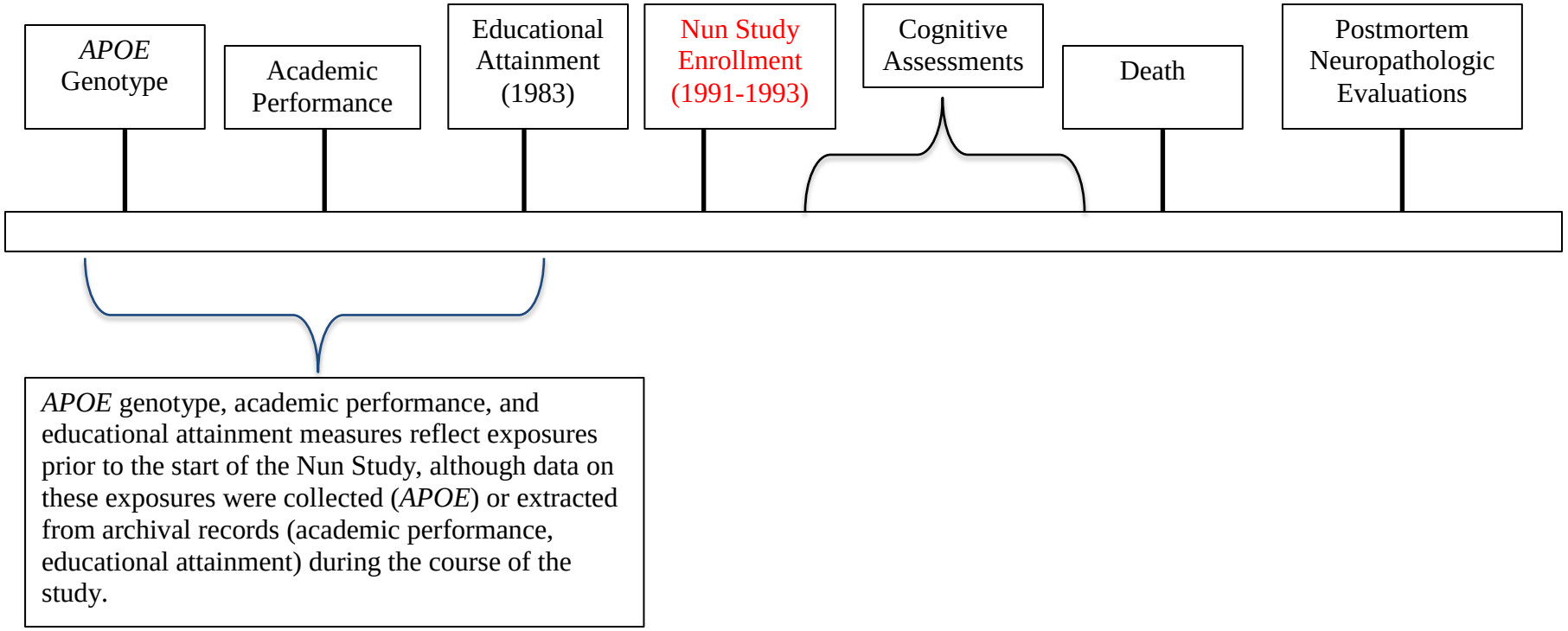
4.3.2.3. Additional Bivariate Analyses

While routine bivariate analyses were conducted to test the relationships of each covariate with the outcome, survival (see Section 4.6.1.), additional bivariate analyses were conducted to assess the relationships of (1) educational factors with age and, (2) neuropathologic criteria with all study covariates.

4.4. Measures

Figure 3 below illustrates a timeline of key components of the research project.

Figure 3: Timeline of study measures



4.4.1. Exposures and Outcome

The research project had two education-related exposures: level of educational attainment and academic performance. Level of educational attainment was categorized in the Nun Study as completion of grade school, high school, Bachelor's degree, and Masters degree or higher. Information about the level of education was obtained from a survey conducted in 1983 by the School Sisters of Notre Dame religious congregation. Information about academic performance was obtained from high school transcripts, which are part of the archival records of the School Sisters of Notre Dame and accessible to the Nun Study. The transcripts provided a listing of courses and the associated final course grades (as percentages) achieved by the individual participants. Academic performance was defined as quartiles of the final course grade combined across first-year high school Geometry, Algebra, Latin and English courses. First-year high school Geometry, Algebra, Latin, and English courses were used to assess academic performance because (1) language and math courses have been associated with a decreased risk of developing dementia (Bezerra et al., 2012), (2) the Nun Study participants most frequently took the above courses and thus the sample size is largest for these courses, (3) upper-year high school transcripts were not available for all of the four desired courses and, (4) university transcripts were not available in the Nun Study.

The outcome for the research project was survival, in other words, the time from entry into the study until death. The date of death is recorded for each deceased Nun Study participant.

4.4.2. Covariates

The covariates of interest for the research project included age, cognitive function, and *APOE*-ε4 status. Age was treated as a continuous variable. The statistical models adjusted for the participant's baseline age; thus, age mimicked a time-varying covariate in the research project (i.e., for every unit increase in age, the study period increased by the same amount). Age is an important covariate because it may confound the association between educational factors and survival, given that age is associated with educational attainment, where older cohorts were less educated than more recent cohorts (Sorlie et al., 1995), age is a risk factor for AD, and age is not an intervening variable in the pathway between education and survival.

Cognitive function was treated as a time-dependent covariate in the project: statistical models adjusted for participants' cognitive status at each of the up to 12 annual assessments. The categories for cognitive status included intact cognition, mild cognitive impairments, global impairment and dementia. Intact cognition was defined by scores within age-standardized norms on the CERAD neuropathological battery, and by intact ADLs and global cognitive ability (as assessed by the Mini-Mental State Examination) (Folstein, Folstein, & McHugh, 1975). Individuals with mild cognitive impairments were impaired in one cognitive domain but had intact global cognitive ability and preserved performance in ADLs. Individuals with global cognitive impairment were impaired in global cognitive ability and/or ADLs. Dementia was defined by a decline in global cognitive ability, and impairments in at least two cognitive domains (one of which was memory) as well as ADLs (Tyas et al., 2007). While cognitive function may also contribute to educational success, our project included cognitive function as a covariate

because this variable may be an intervening factor in the causal pathway between educational factors and survival. The theory of cerebral reserve suggests that individuals with high reserve (i.e., high educational factors) can delay the clinical expression of AD because they can maintain cognitive function despite the presence of AD neuropathology.

APOE-ε4 status was treated as a time-independent, dichotomous variable. The categories for *APOE*-ε4 status included the absence of any ε4 alleles or the presence of one or more ε4 alleles. *APOE*-ε4 status is a potential effect modifier for the association between educational factors and survival because research suggests that the presence of at least one ε4 allele is associated with a faster rate of cognitive decline in individuals who have eight or more years of education in comparison to individuals with a lower level of educational attainment (Seeman et al., 2005).

AD neuropathology (i.e., senile plaques and NFTs) was tested as an effect modifier in the project. The number and distribution of senile plaques and NFTs was assessed using the CERAD and NIA-RI neuropathologic criteria. As discussed in Section 2.2.1.2, the CERAD criterion only considers NPs for the diagnosis of AD and has three levels of diagnostic certainty while the NIA-RI criterion measures both the NP score and NFT distribution and categorizes them into four levels of AD neuropathologic certainty (Hyman et al., 2012). Both the CERAD and NIA-RI neuropathologic criteria were used in the research project to better assess whether Alzheimer neuropathology modified the relationship of interest.

4.5. Ethics

Ethics clearance for the Nun Study was originally obtained from the University of Kentucky in 1990. The Nun Study later shifted its location to the University of Minnesota. The study data are entered into the database in a manner that maximizes confidentiality. Study participants are identified by number, rather than by name. Deceased participants are given an additional code to protect records of neuropathologic evaluations. Identification numbers are randomly generated and thus unique to each Nun Study co-investigator. At the University of Waterloo, the Nun Study data are stored in locked cabinets and password-protected computers in areas that have restricted access. Furthermore, project members sign a confidentiality statement explaining the ethical considerations for the research before accessing the Nun Study data. The Office of Research Ethics at the University of Waterloo has granted ethics approval for the project (ORE# 16551).

4.6. Analytic Plan

A description of the general methods of analysis is provided below. The analyses were performed using SAS 9.4 statistical software (SAS Institute Inc., Cary, North Carolina).

4.6.1. Descriptive Analyses

Univariate and bivariate analyses were used to summarize and describe characteristics of the analytic sample. Univariate analyses were first performed to evaluate the central tendency, dispersion and frequency distributions of individual variables in the project. Bivariate analyses, which included the t-test, chi-square test and Analysis of Variance (ANOVA) test, were performed to evaluate the relationship between pairs of variables in the project. The t-test assessed the relationship between continuous and dichotomous variables. While the t-test can be performed using either the pooled method (assumes equal variances) or the Satterthwaite approximation (assumes unequal variances), the project always used the Satterthwaite approximation method. The ANOVA test assessed the relationship between continuous and multi-level categorical variables (i.e., variables that had more than two categories); post-hoc analyses were conducted using the Scheffé method. Note that the t-test and ANOVA test were used instead of the log-rank test; the log-rank test was not required because our analytic sample only included deceased participants and thus the data did not have any right-censored observations (see Section 4.6.2.) (Minikel, 2012; Rao & Schoenfeld, 2007). Further, the chi-square test assessed the relationship between sets of categorical variables; the Fisher's exact test was used as required. Lastly, Pearson correlation tests were used to assess the relationship between pairs of continuous variables.

4.6.2. Multivariate Modeling

Cox proportional hazards models were performed to evaluate the associations between (1) level of educational attainment and survival and (2) academic performance and survival. Unadjusted models, models adjusted for age and *APOE*-ε4 status, and models adjusted for age, *APOE*-ε4 status, and cognitive status were used to assess the association of educational attainment and academic performance with survival in the overall population. Models stratified for the presence and absence of AD neuropathology were used to assess whether Alzheimer neuropathology (as defined by the CERAD or NIA-RI neuropathologic criteria) modified the relationship of educational factors with survival.

Cox proportional hazards models were chosen for multivariate survival analysis because the outcome of interest was survival (i.e., time to death). This statistical technique was used to assess the effect of educational factors on survival, after controlling for age, *APOE*-ε4 status, cognitive function, and AD neuropathology. The Cox proportional hazards model provide an instantaneous hazard, or risk that the participant will die in the given time interval (see Section 4.4.1) (Fox, 2002; Walters, 2009). A common weakness of survival data is that it includes censored observations. An example of a censored observation is when a participant does not experience the outcome of interest (e.g., time to death) because he/she lived beyond the follow-up period of the study. A strength of our data was that it did not have right-censored observations because only deceased participants were included in the project and thus all of these participants experienced the outcome (i.e., time to death). One of the covariates for the project was

AD neuropathology, and neuropathologic evaluations are only available for deceased participants (see Section 4.3 for more details).

A key assumption of the Cox proportional hazards model is the proportional hazards assumption: the ratio of the hazard functions for two individuals is fixed and remains constant over time. The proportional hazards assumption was tested in the project in two ways: (1) by graphing the Schoenfeld residuals of each covariate against survival and (2) by using a Pearson correlation test for the Schoenfeld residuals of each covariate against survival (Singer & Willett, 2003). Results from the above two tests did not show statistically significant violations of the proportional hazards assumption (Singer & Willett, 2003).

5. Results

5.1. Univariate and Bivariate Results

Table 1 presents the descriptive characteristics for the analytic sample (n=232) by the outcome, survival. The mean age (at baseline) for the analytic sample was 83 years. A majority of the participants (75.9%) did not have any *APOE*-ε4 alleles. The cognitive status at baseline, in the order of most to least common, was mild cognitive impairments (50.4%), intact cognition (27.2%), dementia (14.2%), and global impairment (8.2%). The pattern of the most to least common cognitive status at the last assessment varied from that of the baseline cognitive assessment: 49.1% of the participants had dementia, 21.6% had global impairment, 17.7% had mild cognitive impairment, and 11.6% had intact cognition. While almost half of the participants had dementia at the last cognitive assessment, when dementia status was combined with neuropathologic assessment, 32.3% had definite AD and 25.9% had a high likelihood of AD according to the CERAD and NIA-RI neuropathologic criteria, respectively.

The analytic sample was a highly educated group of individuals. To demonstrate, 47.8% of the participants had a Bachelor's degree, 46.6% had a Master's degree or higher, while only 5.6% had a high school diploma or less. The analytic sample also achieved high academic success. To illustrate, the lowest quartile for the mean grade in first-year high school Geometry, Algebra, Latin, and English courses ranged from 65% up to 83%.

Bivariate analyses were conducted between each covariate and the outcome, survival. A significant, inverse relationship existed between baseline age and survival ($r=-.34$, $p<0.0001$). Cognitive status at baseline was also significantly associated with

survival ($p<0.0001$) using ANOVA. Results from Scheffé post-hoc tests indicated a significant difference in survival between categories of cognitive status: participants with global impairment had 2.85 years shorter survival than those with intact cognition, participants with dementia had 3.58 years shorter survival than those with intact cognition, and participants with mild cognitive impairments had 2.5 years shorter survival than those with dementia. Furthermore, AD neuropathology, as defined by the NIA-RI neuropathologic criteria, was also significantly associated with survival ($p=0.01$) using ANOVA. Results from Scheffé post-hoc tests indicated a significant difference in survival between individuals without AD and individuals with an intermediate likelihood of AD: individuals without AD had 1.95 years shorter survival in comparison to individuals with an intermediate likelihood of AD. Educational attainment, academic performance, cognitive function at the last assessment, *APOE*-ε4 status, and the CERAD neuropathologic criteria were not significantly associated with survival.

Table 1: Descriptive characteristics of the analytic sample (n=232)

Exposure	**%**			**Time to death Mean years (SD)**
Educational attainment				
Grade school	0.43			7.78 (0)
High school	5.17			7.95 (2.83)
Bachelor's degree	47.84			7.94 (3.14)
Master's degree or higher	46.55			7.95 (3.28)
Academic performance[1]				
Quartile 1 (65% - ≤83%)	24.57			7.29 (3.41)
Quartile 2 (>83% - ≤88%)	25			8.29 (2.95)
Quartile 3 (>88% - ≤92.25%)	26.29			8.32 (3.19)
Quartile 4 (>92.25%)	24.14			7.86 (3.10)
Covariates	**%**	**Mean (SD)**	**Median**	**Time to death Mean years (SD)**
Age** (years)	100	83.02 (4.89)	82.28	7.95 (3.17)
APOE-ε4 alleles				
0	75.86			8.02 (3.08)
1+	24.14			7.71 (2.83)
Cognitive status at baseline**				
Intact cognition[a2]	27.16			9.23 (2.78)
Mild cognitive impairments[ab]	50.43			8.16 (3.13)
Global impairment[bc]	8.19			6.39 (3.12)
Dementia[bc]	14.22			5.66 (2.52)
Cognitive status at last assessment				
Intact cognition	11.64			8.99 (2.61)
Mild cognitive impairments	17.67			7.58 (3.40)
Global impairment	21.55			8.16 (3.37)
Dementia	49.14			7.74 (3.10)
CERAD criteria				
No NPs	21.55			7.09 (3.16)
Possible AD	8.62			7.88 (2.97)
Probable AD	37.50			8.33 (3.26)
Definite AD	32.33			7.09 (3.09)
NIA-RI criteria*				
Not [likely][a]	19.83			7.01 (2.83)
Low [likelihood][ab]	30.60			7.61 (3.07)
Intermediate [likelihood][b]	23.71			8.96 (3.24)
High [likelihood][ab]	25.86			8.14 (3.27)

*p<0.05 **p<0.01

[1] Academic performance is the final grade combined across first-year high school Geometry, Algebra, Latin, and English

[2] a, b and c reflect significant differences in time to death across cognitive status at baseline and NIA-RI criteria groups

Abbreviations AD = Alzheimer's disease; *APOE*-ε4 = Apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; HR = hazard ratio; NIA-RI = National Institute of Aging-Reagan Institute; NP = neuritic plaques

5.2. Multivariate Results for Educational Attainment

Tables 2 and 3 present the results of the Cox regression analyses for the association between level of educational attainment and survival. In unadjusted models, education was not significantly associated with survival (Bachelor's degree vs. high school or less: HR=0.88, 95% CI=0.49-1.56; Master's degree vs. high school or less: HR=0.81, 95% CI=0.45-1.44).

After adjusting for age, *APOE*-ε4 status, and cognitive status, the association between education and survival remained statistically non-significant (Bachelor's degree vs. high school or less: HR=0.96, 95% CI=0.54-1.71; Master's degree vs. high school or less: HR=1.03, 95% CI=0.57-1.86). In this model, older age (HR=1.07, 95% CI=1.04-1.10) and more impaired cognitive status (HR=1.25, 95% CI=1.10-1.43) were significantly associated with shorter survival.

In models stratified by Alzheimer neuropathology based on the CERAD neuropathologic criteria, education was not significantly associated with survival in either the presence (HR=0.76, 95% CI=0.38-1.52) or absence (HR=2.86, 95% CI=0.92-8.84) of Alzheimer neuropathology. In the group of participants with Alzheimer neuropathology, both older age (HR=1.08, 95% CI=1.05-1.12) and more impaired cognitive status (HR=1.25, 95% CI=1.07-1.46) were significantly associated with shorter survival, while in the group of participants without Alzheimer neuropathology, only more impaired cognitive status (HR=1.84, 95% CI=1.34-2.51) was significantly associated with shorter survival. Models stratified by Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced similar results (see Table 3 for full results). Furthermore, in the subgroup of individuals without Alzheimer neuropathology, there

was no variation for *APOE*-ε4 status since no individuals in this group were *APOE*-ε4 carriers.

Table 2: The association between level of education and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer Neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=232)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=232)**	**Adjusted for Age, *APOE*-ε4, and Cognitive Status HR (95% CI) (n=232)**	**Yes HR (95% CI) (n=182)**	**No HR (95% CI) (n=50)**
Education (vs. ≤High school)					
Bachelor's degree	0.88 (0.49, 1.56)	0.92 (0.52, 1.63)	0.96 (0.54, 1.71)	0.76 (0.38, 1.52)	2.86 (0.92, 8.84)
Master's degree or higher	0.81 (0.45, 1.44)	0.93 (0.52, 1.68)	1.03 (0.57, 1.86)	0.80 (0.40, 1.60)	2.84 (0.90, 8.94)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.07 (1.04, 1.10)**	**1.08 (1.05, 1.12)**	1.04 (0.97, 1.13)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.32 (0.97, 1.79)	1.15 (0.84, 1.58)	1.35 (0.97, 1.89)	--[2]
Cognition			**1.25 (1.10, 1.43)**	**1.25 (1.07, 1.46)**	**1.84 (1.34, 2.51)**

[1] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 3: The association between level of education and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=232)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=232)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=232)**	**Yes HR (95% CI) (n=186)**	**No HR (95% CI) (n=46)**
Education (vs. ≤High school)					
Bachelor's degree	0.88 (0.49, 1.56)	0.92 (0.52, 1.63)	0.96 (0.54, 1.71)	0.84 (0.41, 1.74)	2.06 (0.73, 5.79)
Master's degree or higher	0.81 (0.45, 1.44)	0.93 (0.52, 1.68)	1.03 (0.57, 1.86)	0.89 (0.43, 1.85)	2.26 (0.72, 7.03)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.07 (1.04, 1.10)**	**1.08 (1.04, 1.11)**	1.05 (0.99, 1.11)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.32 (0.98, 1.80)	1.15 (0.84, 1.58)	1.32 (0.95, 1.84)	--[2]
Cognition			**1.25 (1.10, 1.43)**	**1.23 (1.06, 1.44)**	**1.65 (1.18, 2.32)**

[1] National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.3. Multivariate Results for Overall Academic Performance

Tables 4 and 5 present the results of the Cox regression analyses for the association between academic performance and survival. In unadjusted models, academic performance was not statistically associated with survival (Quartile 2 vs. Quartile 1: HR=0.79, 95% CI=0.55-1.14; Quartile 3 vs. Quartile 1: HR= 0.75, 95% CI=0.52-1.08; Quartile 4 vs. Quartile 1: HR=0.83, 95% CI=0.58-1.21).

After controlling for age, *APOE*-ε4 status, and cognitive status, the association between academic performance and survival remained statistically non-significant (Quartile 2 vs. Quartile 1: HR=0.73, 95% CI=0.50-1.06; Quartile 3 vs. Quartile 1: HR=0.76, 95% CI=0.53-1.10; Quartile 4 vs. Quartile 1: HR=0.89, 95% CI=0.61-1.29). In this model, older age (HR=1.08, 95% CI=1.05-1.11) and more impaired cognitive status (HR=1.23, 95% CI=1.08-1.41) were significantly associated with shorter survival.

In models stratified for Alzheimer neuropathology based on the CERAD neuropathologic criteria, academic performance was not statistically associated with survival in either the presence (Quartile 2 vs. Quartile 1: HR=0.75, 95% CI=0.49-1.14; Quartile 3 vs. Quartile 1: HR=0.78, 95% CI=0.52-1.19; Quartile 4 vs. Quartile 1: HR=0.92, 95% CI=0.59-1.42) or absence (Quartile 2 vs. Quartile 1: HR=1.04, 95% CI=0.43-2.51; Quartile 3 vs. Quartile 1: HR=1.10, 95% CI=0.45-2.73, Quartile 4 vs. Quartile 1: HR=0.86, 95% CI=0.39-1.89) of Alzheimer neuropathology. Both older age (HR=1.09, 95% CI=1.05-1.12) and more impaired cognitive status (HR=1.25, 95% CI=1.07-1.46) were associated with shorter survival in individuals with Alzheimer neuropathology, but only more impaired cognitive status (HR=1.72, 95% CI=1.25-2.36) was associated with shorter survival in individuals without Alzheimer neuropathology.

Models stratified by Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced similar results (see Table 5 for full results). Furthermore, in individuals without Alzheimer neuropathology, there was no estimate of the association between academic performance and *APOE*-ε4 status since no individuals in this group were *APOE*-ε4 carriers.

Table 4: The association between overall academic performance and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

Variables	Unadjusted HR (95% CI) (n=232)	Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=232)	Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=232)	Alzheimer neuropathology[1] Yes HR (95% CI) (n=182)	Alzheimer neuropathology[1] No HR (95% CI) (n=50)
Academic Performance[2] (vs. Quartile 1)					
Quartile 2	0.79 (0.55, 1.14)	0.69 (0.48, 1.002)	0.73 (0.50, 1.06)	0.75 (0.49, 1.14)	1.04 (0.43, 2.51)
Quartile 3	0.75 (0.52, 1.08)	0.71 (0.50, 1.03)	0.76 (0.53, 1.10)	0.78 (0.52, 1.19)	1.10 (0.45, 2.73)
Quartile 4	0.83 (0.58, 1.21)	0.83 (0.60, 1.20)	0.89 (0.61, 1.29)	0.92 (0.59, 1.42)	0.86 (0.39, 1.89)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.09 (1.05, 1.12)**	1.03 (0.96, 1.10)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.33 (0.98, 1.81)	1.19 (0.87, 1.62)	1.37 (0.99, 1.91)	--[3]
Cognition			**1.23 (1.08, 1.41)**	**1.25 (1.07, 1.46)**	**1.72 (1.25, 2.36)**

[1] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
[2] Academic performance is the final grade combined across first-year high school Geometry, Algebra, Latin, and English courses
[3] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 5: The association between overall academic performance and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=232)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=232)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=232)**	**Yes HR (95% CI) (n=186)**	**No HR (95% CI) (n=46)**
Academic Performance[2] (vs. Quartile 1)					
Quartile 2	0.79 (0.55, 1.14)	0.69 (0.48, 1.002)	0.73 (0.50, 1.06)	0.72 (0.47, 1.09)	1.38 (0.58, 3.28)
Quartile 3	0.75 (0.52, 1.08)	0.71 (0.50, 1.03)	0.76 (0.53, 1.10)	0.77 (0.51, 1.16)	2.28 (0.71, 7.34)
Quartile 4	0.83 (0.58-1.21)	0.83 (0.60-1.20)	0.89 (0.61-1.29)	0.91 (0.60, 1.40)	1.02 (0.42, 2.50)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.08 (1.04, 1.12)**	1.02 (0.96, 1.08)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.33 (0.98, 1.81)	1.19 (0.87, 1.62)	1.34 (0.96, 1.85)	--[3]
Cognition			**1.23 (1.08, 1.41)**	**1.23 (1.06, 1.43)**	**1.77 (1.22, 2.55)**

[1] National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] Academic performance is the final grade combined across first-year high school Geometry, Algebra, Latin, and English
[3] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4. Sensitivity Analyses

5.4.1. Univariate and Bivariate Results

Table 6 presents the descriptive characteristics of the samples used in the sensitivity analyses by the outcome, survival. The mean age (at baseline) for the sample restricted only by education (n=364) was 83 years. A majority of the participants (76.1%) did not have any *APOE*-ε4 alleles. While half of the participants had dementia at the last cognitive assessment, 32.7% had definite AD and 26.1% had a high likelihood of AD according to CERAD and NIA-RI neuropathologic criteria, respectively.

The sample was a highly educated group of individuals. To illustrate, 43.13% of the participants had a Bachelor's degree, 42.58% had a Master's degree or higher, while only 14.29% of the participants had a high school or lower level of educational attainment. The samples for Geometry (n=264), Algebra (n=272), Latin (n=250), and English (n=275) were subsamples of the larger sample restricted by education. The quartile ranges for final grades in each of the above first-year high school courses demonstrate that participants in the above samples of academic performance achieved high academic success (see Table 6 for quartile ranges).

Bivariate analyses were conducted between each covariate and the outcome, survival. A significant, inverse relationship existed between baseline age and survival ($r=-0.35$, $p<0.0001$). Cognitive status at baseline was also significantly associated with survival ($p<0.0001$) using ANOVA: individuals with global impairment had 2.71 years shorter survival than those with intact cognition, participants with dementia had 2.93 years shorter survival than those with intact cognition, participants with global impairment had 1.66 years shorter survival than those with mild cognitive impairments,

and participants with dementia had 1.88 years shorter survival than those with mild cognitive impairments. Note that the above differences in means between categories of cognitive status are significant. Furthermore, AD neuropathology, as defined by the CERAD neuropathologic criteria, was significantly associated with survival ($p=0.01$) using ANOVA: individuals without AD had 1.31 years shorter survival in comparison to individuals with probable AD. AD neuropathology, as defined by the NIA-RI neuropathologic criteria, was also significantly associated with survival ($p=0.04$): individuals without AD had 1.36 years shorter survival than those with an intermediate likelihood of AD. Educational attainment, academic performance in Geometry, Algebra, Latin, and English, cognitive function at the last assessment, and *APOE*-ε4 status were not significantly associated with survival.

Table 6: Descriptive characteristics of the samples used in sensitivity analyses

Exposures	n	%	Time to death Mean years (SD)
Educational attainment (n=364)			
Grade school	34	9.34	7.42 (2.78)
High school	18	4.95	7.61 (2.88)
Bachelor's degree	157	43.13	7.79 (3.16)
Master's degree or higher	155	42.58	7.86 (3.16)
Academic performance in Geometry (n=264)			
Quartile 1 (65% - ≤81%)	67	25.38	7.07 (3.09)
Quartile 2 (>81% - ≤88%)	70	26.52	7.78 (3.17)
Quartile 3 (>88% - ≤94%)	61	23.10	8.61 (3.03)
Quartile 4 (>94%)	66	25.00	8.00 (3.12)
Academic performance in Algebra (n=272)			
Quartile 1 (65% - ≤80%)	67	24.63	7.61 (3.28)
Quartile 2 (>80% - ≤88%)	67	24.63	7.66 (3.10)
Quartile 3 (>88% - ≤94%)	51	18.75	8.37 (3.06)
Quartile 4 (>94%)	87	31.99	7.80 (3.10)

Exposures	n	%	Time to death Mean years (SD)
Academic performance in Latin (n=250)			
Quartile 1 (65% - ≤82%)	61	24.40	8.08 (3.37)
Quartile 2 (>82% - ≤89%)	63	25.20	7.88 (3.20)
Quartile 3 (>89% - ≤94%)	64	25.60	7.70 (3.02)
Quartile 4 (>94%)	62	24.80	8.13 (3.18)
Academic performance in English (n=275)			
Quartile 1 (65% - ≤80%)	69	25.09	7.39 (3.46)
Quartile 2 (>80% - ≤86%)	70	25.45	8.23 (3.15)
Quartile 3 (>86% - ≤92%)	65	23.64	8.35 (3.24)
Quartile 4 (>92%)	71	25.82	7.59 (2.69)

Covariates	n	%	Mean (SD)	Median	IQR	Time to death Mean years (SD)
Age at baseline (n=364)**	364	100	83.28 (5.11)	82.53	7.37	7.75 (3.10)
APOE-ε4 alleles (n=364)						
0	277	76.10				7.91 (3.12)
1+	87	23.90				7.25 (2.99)
Cognitive function at baseline**						
Intact cognition[a]	84	23.08				9.04 (2.78)
Mild cognitive impairments[a]	181	49.73				8.00 (3.10)
Global impairment[bc]	37	10.16				6.33 (3.04)
Dementia[bc]	62	17.03				6.11 (2.56)

Covariates	n	%	Mean (SD)	Median IQR	Time to death Mean years (SD)
Cognitive function at last assessment (n=364)					
Intact cognition	38	10.44			8.83 (2.59)
Mild cognitive impairments	63	17.31			7.25 (3.23)
Global impairment	78	21.43			7.78 (3.29)
Dementia	185	50.82			7.69 (3.04)
CERAD neuropathologic criteria (n=364)*					
No NPs[a]	80	21.98			6.93 (3.12)
Possible AD[ab]	38	10.44			7.12 (3.13)
Probable AD[b]	127	34.89			8.24 (3.07)
Definite AD[ab]	119	32.69			7.97 (3.01)
NIA-RI neuropathologic criteria (n=364)*					
Not [likely][a]	78	21.43			6.95 (2.79)
Low [likelihood][ab]	99	27.20			7.72 (3.01)
Intermediate [likelihood][b]	92	25.27			8.31 (3.30)
High [likelihood][ab]	95	26.10			7.90 (3.14)

*p<0.05 **p<0.0001

Academic performance in Geometry, Algebra, Latin and English was defined as quartiles of the final course grade in each of the above four first-year high school courses

a, b, and c reflect significant differences in time to death across CERAD and NIA-RI neuropathologic criteria groups

Abbreviations: AD = Alzheimer's disease; *APOE*-ε4 = Apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; NIA-RI = The National Institute of Aging and Reagan Institute; NP = neuritic plaques

5.4.2. The Association Between Level of Educational Attainment and Survival in the Sample Restricted Only by Education

Tables 7 and 8 present the results of the Cox regression analyses for the association between the level of educational attainment and survival in the sample restricted only by education (n=364).

In unadjusted models, education was not significantly associated with survival (Bachelor's degree vs. high school or less: HR=0.84, 95% CI=0.61-1.15; Master's degree or higher vs. high school or less: HR=0.80, 95% CI=0.58-1.09).

After adjusting for age, *APOE*-ε4 status, and cognitive status, the association between education and survival remained statistically non-significant (Bachelor's degree vs. high school or less: HR= 0.98, 95% CI=0.71-1.34; Master's degree or higher vs. high school or less: HR=1.12, 95% CI=0.81-1.57). In this model, older age (HR=1.08, 95% CI=1.06-1.10) and more impaired cognitive status (HR=1.18, 95% CI=1.06-1.31) were significantly associated with shorter survival.

In models stratified by Alzheimer neuropathology based on the CERAD neuropathologic criteria, education was not significantly associated with survival in either the presence (Bachelor's degree vs. high school or less: HR=0.90, 95% CI=0.63-1.29; Master's degree or higher vs. high school or less: HR=1.02, 95% CI=0.70-1.49) or absence (Bachelor's degree vs. high school or less: HR=2.08, 95% CI=0.94-4.60; Master's degree or higher vs. high school or less: HR=2.15, 95% CI=0.95-4.87) of Alzheimer neuropathology. In the group of participants with Alzheimer neuropathology, older age (HR=1.08, 95% CI=1.06-1.11), the presence of *APOE*-ε4 alleles (HR=1.38, 95% CI=1.06-1.81), and more impaired cognitive status (HR=1.19, 95% CI=1.05-1.36)

were significantly associated with shorter survival, while in the group of participants without Alzheimer neuropathology, only more impaired cognitive status (HR=1.59, 95% CI=1.25-2.03) was significantly associated with shorter survival. Models stratified for Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced similar results overall (see Table 8); one difference from the models stratified based on the CERAD neuropathologic criteria was that in the group of participants without Alzheimer neuropathology according to NIA-RI criteria, older age (HR=1.06, 95% CI=1.02-1.11) was significantly associated with shorter survival.

Table 7: The association between level of education and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=364)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=364)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=364)**	**Yes HR (95% CI) (n=284)**	**No HR (95% CI) (n=80)**
Education (vs. ≤High school)					
Bachelor's degree	0.84 (0.61, 1.15)	0.90 (0.66, 1.24)	0.98 (0.71, 1.34)	0.90 (0.63, 1.29)	2.08 (0.94, 4.60)
Master's degree or higher	0.80 (0.58, 1.09)	1.00 (0.72, 1.39)	1.12 (0.81, 1.57)	1.02 (0.70, 1.49)	2.15 (0.95, 4.87)
Covariates					
Age at baseline	-	**1.09 (1.06, 1.11)**	**1.08 (1.06, 1.10)**	**1.08 (1.06, 1.11)**	1.06 (1.00, 1.11)
APOE-ε4 1+ alleles (vs. 0 alleles)	-	**1.35 (1.05, 1.72)**	1.23 (0.96, 1.59)	**1.38 (1.06, 1.81)**	2.97 (0.92, 9.60)
Cognition	-	-	**1.18 (1.06, 1.31)**	**1.19 (1.05, 1.36)**	**1.59 (1.25, 2.03)**

[1]Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 8: The association between level of education and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=364)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=364)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=364)**	**Yes HR (95% CI) (n=286)**	**No HR (95% CI) (n=74)**
Education (vs. ≤High school)					
Bachelor's degree	0.84 (0.61, 1.15)	0.90 (0.66, 1.24)	0.98 (0.71, 1.34)	0.97 (0.67, 1.40)	1.30 (0.64, 2.66)
Master's degree or higher	0.80 (0.58, 1.09)	1.00 (0.72, 1.39)	1.12 (0.81, 1.57)	1.09 (0.74, 1.61)	1.56 (0.72, 3.39)
Covariates					
Age at baseline	-	**1.09 (1.06, 1.11)**	**1.08 (1.06, 1.10)**	**1.08 (1.05, 1.11)**	**1.06 (1.02, 1.11)**
APOE-ε4 1+ alleles (vs. 0 alleles)	-	**1.35 (1.05, 1.72)**	1.23 (0.96, 1.59)	**1.37 (1.05, 1.79)**	2.04 (0.54, 7.74)
Cognition	-	-	**1.18 (1.06, 1.31)**	**1.20 (1.06, 1.36)**	**1.42 (1.11, 1.81)**

[1]National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4.3. The Association Between Academic Performance in Geometry and Survival

Tables 9 and 10 present the results of the Cox regression analyses for the association between survival and academic performance, as measured by final grades in first-year high school Geometry. In the unadjusted models, some (Quartile 3 vs. Quartile 1: HR=0.64; 95% CI=0.45-0.90) but not all (Quartile 2 vs. Quartile 1: HR=0.75, 95% CI=0.53-1.05; Quartile 4 vs. Quartile 1: HR=0.73, 95% CI=0.52-1.03) categories of Geometry were significantly associated with longer survival.

In the models adjusted for age, *APOE*-ε4 status, and cognitive status, high academic performance in Geometry was significantly associated with longer survival (Quartile 2 vs. Quartile 1: HR=0.69, 95% CI=0.49-0.97; Quartile 3 vs. Quartile 1: HR=0.66, 95% CI=0.47-0.94; Quartile 4 vs. Quartile 1: HR=0.70, 95% CI=0.49-0.99). In this model, older age (HR=1.08, 95% CI=1.05-1.11) and more impaired cognitive status (HR=1.24, 95% CI=1.09-1.40) were also significantly associated with shorter survival.

In models stratified for Alzheimer neuropathology based on the CERAD neuropathologic criteria, academic performance in Geometry was not significantly associated with survival in either the presence or absence of Alzheimer neuropathology. Further, in the group of participants with Alzheimer neuropathology, older age (HR=1.08, 95% CI=1.05-1.12) and more impaired cognitive status (HR=1.25, 95% CI=1.08-1.45) were significantly associated with shorter survival, while in the group of participants without Alzheimer neuropathology, the presence of *APOE*-ε4 alleles (HR=27.82, 95% CI=1.53-505.22) and more impaired cognitive status (HR=1.55, 95% CI=1.17-2.07) were significantly associated with shorter survival. Models stratified by Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced

similar results overall; they differed from models stratified by Alzheimer neuropathology based on the CERAD neuropathologic criteria as they were unable to test the association between academic performance in Geometry and survival in individual without neuropathology after controlling for *APOE*-ε4 status since no individuals in this group were *APOE*-ε4 carriers (see Table 10 for full results).

Table 9: The association between Geometry grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=264)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=264)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=264)**	**Yes HR (95% CI) (n=206)**	**No HR (95% CI) (n=58)**
Geometry (vs. Quartile 1)					
Quartile 2	0.75 (0.53, 1.05)	**0.65 (0.46, 0.92)**	**0.69 (0.49, 0.97)**	0.71 (0.48, 1.05)	0.91 (0.41, 2.01)
Quartile 3	**0.64 (0.45, 0.90)**	**0.64 (0.45, 0.91)**	**0.66 (0.47, 0.94)**	0.71 (0.48, 1.06)	0.71 (0.31, 1.63)
Quartile 4	0.73 (0.52, 1.03)	**0.64 (0.45, 0.90)**	**0.70 (0.49, 0.99)**	0.70 (0.47, 1.06)	0.71 (0.34, 1.49)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.08 (1.05, 1.12)**	1.05 (0.98, 1.12)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.30 (0.97, 1.74)	1.14 (0.84, 1.53)	1.28 (0.93, 1.75)	**27.82 (1.53, 505.22)**
Cognition			**1.24 (1.09, 1.40)**	**1.25 (1.08, 1.45)**	**1.55 (1.17, 2.07)**

[1]Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 10: The association between Geometry grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

Variables	Unadjusted HR (95% CI) (n=264)	Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=264)	Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=264)	Alzheimer neuropathology[1] Yes HR (95% CI) (n=212)	Alzheimer neuropathology[1] No HR (95% CI) (n=52)
Geometry (vs. Quartile 1)					
Quartile 2	0.75 (0.53, 1.05)	**0.65 (0.46, 0.92)**	**0.69 (0.49, 0.97)**	0.71 (0.49, 1.05)	0.83 (0.33, 2.09)
Quartile 3	**0.64 (0.45, 0.90)**	**0.64 (0.45, 0.91)**	**0.66 (0.47, 0.94)**	0.68 (0.46, 1.01)	1.16 (0.45, 3.04)
Quartile 4	0.73 (0.52, 1.03)	**0.64 (0.45, 0.90)**	**0.70 (0.49, 0.99)**	0.69 (0.46, 1.03)	0.80 (0.38, 1.70)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.08 (1.05, 1.11)**	1.06 (1.00, 1.12)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.30 (0.97, 1.74)	1.14 (0.84, 1.53)	1.25 (0.91, 1.71)	--[2]
Cognition			**1.24 (1.09, 1.40)**	**1.25 (1.08, 1.44)**	**1.46 (1.08, 1.98)**

[1] National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4.4. The Association between Academic Performance in Algebra and Survival

Tables 11 and 12 present results of the Cox regression analyses for the association between survival and academic performance in Algebra as measured by final grades in first-year high school Algebra. In the unadjusted models, academic performance in Algebra was not significantly associated with survival (Quartile 2 vs. Quartile 1: HR=0.96, 95% CI=0.68-1.35; Quartile 3 vs. Quartile 1: HR=0.85, 95% CI=0.59-1.22; Quartile 4 vs. Quartile 1: HR=0.87, 95% CI=0.63-1.20).

After adjusting for age, *APOE*-ε4 status, and cognitive function, the relationship between academic performance in Algebra and survival remained statistically non-significant. In this model, older age (HR=1.08, 95% CI=1.05-1.11) and more impaired cognitive status (HR=1.26, 95% CI=1.11-1.42) were significantly associated with shorter survival.

In models stratified by Alzheimer neuropathology based on the CERAD neuropathologic criteria, Algebra was not statistically associated with survival in either the presence or absence of Alzheimer neuropathology. In the group of individuals with Alzheimer neuropathology, older age (HR=1.09, 95% CI=1.06-1.12) and more impaired cognitive status (HR=1.29, 95% CI=1.11-1.49) were significantly associated with shorter survival, while in the group of individuals without Alzheimer neuropathology, the presence of *APOE*-ε4 alleles (HR=31.16, 95% CI=1.73-562.25) and more impaired cognitive status (HR=1.72, 95% CI=1.28-2.29) were significantly associated with shorter survival. Models stratified by Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced similar results overall; they differed from models stratified by Alzheimer neuropathology based on the CERAD neuropathologic criteria as

they were unable to test the association between Geometry and survival in individuals without Alzheimer neuropathology after controlling for *APOE*-ε4 status since no individuals in this group were *APOE*-ε4 carriers (see Table 12 for full results).

Table 11: The association between Algebra grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=272)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=272)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=272)**	**Yes HR (95% CI) (n=214)**	**No HR (95% CI) (n=58)**
Algebra (vs. Quartile 1)					
Quartile 2	0.96 (0.68, 1.35)	0.97 (0.69, 1.37)	1.07 (0.76, 1.51)	1.10 (0.74, 1.63)	1.66 (0.75, 3.65)
Quartile 3	0.85 (0.59, 1.22)	0.89 (0.61, 1.28)	0.97 (0.67, 1.40)	1.05 (0.70, 1.59)	1.05 (0.41, 2.72)
Quartile 4	0.87 (0.63, 1.20)	0.80 (0.57, 1.10)	0.87 (0.62, 1.21)	0.84 (0.57, 1.24)	1.21 (0.60, 2.44)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.09 (1.06, 1.12)**	1.04 (0.98, 1.10)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.31 (0.99, 1.75)	1.14 (0.85, 1.53)	1.28 (0.94, 1.75)	**31.16 (1.73, 562.25)**
Cognition			**1.26 (1.11, 1.42)**	**1.29 (1.11, 1.49)**	**1.72 (1.28, 2.29)**

[1] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 12: The association between Algebra grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

Variables	Unadjusted HR (95% CI) (n=272)	Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=272)	Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=272)	Alzheimer neuropathology[1] Yes HR (95% CI) (n=220)	Alzheimer neuropathology[1] No HR (95% CI) (n=52)
Algebra (vs. Quartile 1)					
Quartile 2	0.96 (0.68, 1.35)	0.97 (0.69, 1.37)	1.07 (0.76, 1.51)	1.09 (0.74, 1.61)	1.31 (0.60, 2.89)
Quartile 3	0.85 (0.59, 1.22)	0.89 (0.61, 1.28)	0.97 (0.67, 1.40)	1.02 (0.69, 1.53)	0.98 (0.28, 3.43)
Quartile 4	0.87 (0.63, 1.20)	0.80 (0.57, 1.10)	0.87 (0.62, 1.21)	0.82 (0.56, 1.19)	1.32 (0.63, 2.76)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.08 (1.05, 1.12)**	1.04 (0.98, 1.10)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.31 (0.99, 1.75)	1.14 (0.85, 1.53)	1.27 (0.93, 1.72)	--[2]
Cognition			**1.26 (1.11, 1.42)**	**1.28 (1.10, 1.48)**	**1.54 (1.15, 2.06)**

[1]National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4.5. The Association between Academic Performance in Latin and Survival

Tables 13 and 14 present the results of the Cox regression analyses for the association between academic performance in Latin as measured by final grades in first-year high school Latin. In unadjusted models, academic performance in Latin was not significantly associated with survival (Quartile 2 vs. Quartile 1: HR=1.05, 95% CI=0.74-1.50; Quartile 3 vs. Quartile 1: HR=1.16, 95% CI=0.82-1.65; Quartile 4 vs. Quartile 1: HR=1.02, 95% CI=0.72-1.46).

After adjusting for age, *APOE*-ε4 status, and cognitive status, the association between academic performance in Latin and survival remained statistically non-significant (Quartile 2 vs. Quartile 1: HR=1.13, 95% CI=0.79-1.62; Quartile 3 vs. Quartile 1: HR=1.27, 95% CI=0.89-1.81; Quartile 4 vs. Quartile 1: HR=1.12, 95% CI=0.78-1.61). In these models, older age (HR=1.08, 95% CI=1.05-1.11) and more impaired cognitive status (HR=1.26, 95% CI=1.11-1.43) were significantly associated with shorter survival.

In models stratified by Alzheimer neuropathology based on the CERAD neuropathologic criteria, academic performance in Latin was not significantly associated with survival in either the presence or absence of Alzheimer neuropathology. In the group of individuals with Alzheimer neuropathology, older age (HR=1.09, 95% CI=1.05-1.12) and more impaired cognitive status (HR=1.27, 95% CI=1.09-1.48) were significantly associated with shorter survival, while in the group of individuals without Alzheimer neuropathology, only more impaired cognitive status (HR=1.75, 95% CI=1.29-2.37) was significantly associated with shorter survival. The models stratified by Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced similar results

(see Table 14 for full results). Furthermore, in the subgroup of individuals without Alzheimer neuropathology (based on both the CERAD and NIA-RI neuropathologic criteria), the effect of *APOE*-ε4 status could not be assessed since no individuals in this group were *APOE*-ε4 carriers.

Table 13: The association between Latin grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=250)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=250)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=250)**	**Yes HR (95% CI) (n=199)**	**No HR (95% CI) (n=51)**
Latin (vs. Quartile 1)					
Quartile 2	1.05 (0.74, 1.50)	1.14 (0.80, 1.63)	1.13 (0.79, 1.62)	1.22 (0.82, 1.81)	0.76 (0.30, 1.90)
Quartile 3	1.16 (0.82, 1.65)	1.21 (0.85, 1.72)	1.27 (0.89, 1.81)	1.23 (0.83, 1.83)	0.99 (0.43, 2.27)
Quartile 4	1.02 (0.72, 1.46)	1.10 (0.77, 1.57)	1.12 (0.78, 1.61)	1.19 (0.80, 1.77)	0.57 (0.24, 1.39)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.09 (1.05, 1.12)**	1.02 (0.95, 1.10)
APOE-ε4 1+ alleles		**1.36 (1.01, 1.83)**	1.18 (0.87, 1.60)	1.36 (0.99, 1.87)	--[2]
Cognition			**1.26 (1.11, 1.43)**	**1.27 (1.09, 1.48)**	**1.75 (1.29, 2.37)**

[1] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 14: The association between Latin grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

Variables	Unadjusted HR (95% CI) (n=250)	Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=250)	Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=250)	Alzheimer neuropathology[1] Yes HR (95% CI) (n=203)	Alzheimer neuropathology[1] No HR (95% CI) (n=47)
Latin (vs. Quartile 1)					
Quartile 2	1.05 (0.74, 1.50)	1.14 (0.80, 1.63)	1.13 (0.79, 1.62)	1.19 (0.80, 1.76)	0.77 (0.31, 1.90)
Quartile 3	1.16 (0.82, 1.65)	1.21 (0.85, 1.72)	1.27 (0.89, 1.81)	1.28 (0.87, 1.88)	1.07 (0.43, 2.69)
Quartile 4	1.02 (0.72, 1.46)	1.10 (0.77, 1.57)	1.12 (0.78, 1.61)	1.19 (0.80, 1.78)	0.55 (0.23, 1.29)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.11)**	**1.08 (1.05, 1.11)**	1.05 (0.99, 1.11)
APOE-ε4 1+ alleles (vs. 0 alleles)		**1.36 (1.01, 1.83)**	1.18 (0.87, 1.60)	1.33 (0.97, 1.83)	--[2]
Cognition			**1.26 (1.11, 1.43)**	**1.25 (1.08, 1.45)**	**1.63 (1.19, 2.22)**

[1] National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4.6. The Association Between Academic Performance in English and Survival

Tables 15 and 16 present the results of the Cox regression analyses for the association between survival and academic performance in English as measured by final grades in first-year high school English. In the unadjusted models, English and survival were not significantly associated (Quartile 2 vs. Quartile 1: HR=0.84, 95% CI=0.60-1.17; Quartile 3 vs. Quartile 1: HR=0.77, 95% CI=0.55-1.08; Quartile 4 vs. Quartile 1: HR=1.07, 95% CI=0.77-1.49).

After adjusting for age, *APOE*-ε4 status, and cognitive status, the association between academic performance in English and survival remained statistically non-significant (Quartile 2 vs. Quartile 1: HR=0.83, 95% CI=0.59-1.16; Quartile 3 vs. Quartile 1: HR=0.87, 95% CI=0.62-1.23; Quartile 4 vs. Quartile 1: HR=1.01, 95% CI=0.72-1.42). In these models, older age (HR=1.07, 95% CI=1.05-1.10) and more impaired cognitive status (HR=1.27, 95% CI=1.12-1.44) were significantly associated with shorter survival.

In models stratified for Alzheimer neuropathology based on the CERAD neuropathologic criteria, academic performance in English was not significantly associated with survival in either the presence or absence of Alzheimer neuropathology. In the group of individuals with Alzheimer neuropathology, older age (HR=1.08, 95% CI=1.05-1.11) and more impaired cognitive status (HR=1.28, 95% CI=1.11-1.49) was significantly associated with shorter survival, while in the group of individuals without Alzheimer neuropathology, the presence of one or more *APOE*-ε4 alleles (HR=21.57, 95% CI=1.18-394.82) and more impaired cognitive status (HR=1.67, 95% CI=1.24-2.24 were significantly associated with shorter survival. Models stratified by Alzheimer

neuropathology based on the NIA-RI neuropathologic criteria produced similar results overall; the one difference with models stratified by Alzheimer neuropathology based on the CERAD neuropathologic criteria was that in the subgroup of individuals without Alzheimer neuropathology based on the NIA-RI neuropathologic criteria, the effect of *APOE*-ε4 status could not be assessed since no individuals in this group were *APOE*-ε4 carriers (see Table 16 for full results).

Table 15: The association between English grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=275)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=275)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=275)**	**Yes HR (95% CI) (n=217)**	**No HR (95% CI) (n=58)**
English (vs. Quartile 1)					
Quartile 2	0.84 (0.60, 1.17)	0.88 (0.63, 1.23)	0.83 (0.59, 1.16)	0.89 (0.61, 1.29)	0.71 (0.30, 1.66)
Quartile 3	0.77 (0.55, 1.08)	0.82 (0.58, 1.15)	0.87 (0.62, 1.23)	0.84 (0.57, 1.26)	0.94 (0.43, 2.05)
Quartile 4	1.07 (0.77, 1.49)	0.99 (0.71, 1.38)	1.01 (0.72, 1.42)	1.06 (0.71, 1.56)	0.68 (0.31, 1.49)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.07 (1.05, 1.10)**	**1.08 (1.05, 1.11)**	1.03 (0.97, 1.10)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.26 (0.95, 1.68)	1.09 (0.81, 1.46)	1.23 (0.90, 1.67)	**21.57 (1.18, 394.82)**
Cognition			**1.27 (1.12, 1.44)**	**1.28 (1.11, 1.49)**	**1.67 (1.24, 2.24)**

[1] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 16: The association between English grades and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=275)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=275)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=275)**	**Yes HR (95% CI) (n=223)**	**No HR (95% CI) (n=52)**
English (vs. Quartile 1)					
Quartile 2	0.84 (0.60, 1.17)	0.88 (0.63, 1.23)	0.83 (0.59, 1.16)	0.85 (0.59, 1.23)	0.86 (0.37, 2.01)
Quartile 3	0.77 (0.55, 1.08)	0.82 (0.58, 1.15)	0.87 (0.62, 1.23)	0.85 (0.58, 1.24)	1.29 (0.51, 3.27)
Quartile 4	1.07 (0.77, 1.49)	0.99 (0.71, 1.38)	1.01 (0.72, 1.42)	1.00 (0.68, 1.47)	0.92 (0.40, 2.12)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.07 (1.05, 1.10)**	**1.08 (1.05, 1.11)**	1.04 (0.98, 1.09)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.26 (0.95, 1.68)	1.09 (0.81, 1.46)	1.21 (0.89, 1.64)	--[2]
Cognition			**1.27 (1.12, 1.44)**	**1.28 (1.10, 1.48)**	**1.56 (1.14, 2.13)**

[1] National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4.7. The Association Between Academic Performance (Tertiles) and Survival

Tables 17 and 18 present the results of the Cox regression analyses for the association of the mean academic performance in first-year high school Geometry, Algebra, Latin, and English (categorized into tertiles) with survival. In the unadjusted models, academic performance was not significantly associated with survival (Tertile 2 vs. Tertile 1: HR=0.78, 95% CI=0.57-1.08; Tertile 3 vs. Tertile 1: HR=0.84, 95% CI=0.61-1.15).

After adjusting for age, *APOE*-ε4 status, and cognitive status, the association between academic performance and survival remained statistically non-significant (Tertile 2 vs. Tertile 1: HR=0.80, 95% CI=0.58-1.10; Tertile 3 vs. Tertile 1: HR=0.93, 95% CI=0.68-1.28). In these models, older age (HR=1.07, 95% CI=1.04-1.10) and more impaired cognitive status (HR=1.24, 95% CI=1.09-1.41) were significantly associated with shorter survival.

In models stratified for Alzheimer neuropathology based on the CERAD neuropathologic criteria, academic performance was not significantly associated with survival in either the presence or absence of Alzheimer neuropathology. In the group of individuals with Alzheimer neuropathology, older age (HR=1.08, 95% CI=1.05-1.12) and more impaired cognitive status (HR=1.26, 95% CI=1.08-1.47) were significantly associated with shorter survival, while in the group of individuals without Alzheimer neuropathology, more impaired cognitive status (HR=1.68, 95% CI=1.23-2.31) was significantly associated with shorter survival. Models stratified by Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced similar results overall (see Table 18 for full results). Furthermore, in the subgroup of individuals without

Alzheimer neuropathology, there was no variation for *APOE*-ε4 status since no individuals in this group were *APOE*-ε4 carriers.

Table 17: The association between academic performance (tertiles) and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=275)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=275)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=275)**	**Yes HR (95% CI) (n=223)**	**No HR (95% CI) (n=52)**
English (vs. Tertile 1)					
Tertile 2	0.78 (0.57, 1.08)	0.77 (0.56, 1.06)	0.80 (0.58, 1.10)	0.80 (0.56, 1.14)	1.08 (0.48, 2.40)
Tertile 3	0.84 (0.61, 1.15)	0.88 (0.64, 1.20)	0.93 (0.68, 1.28)	0.95 (0.66, 1.36)	0.86 (0.41, 1.80)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.07 (1.04, 1.10)**	**1.08 (1.05, 1.12)**	1.02 (0.95, 1.10)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.32 (0.98, 1.80)	1.17 (0.86, 1.60)	1.36 (0.98, 1.89)	--[2]
Cognition			**1.24 (1.09, 1.41)**	**1.26 (1.08, 1.47)**	**1.68 (1.23, 2.31)**

[1] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 18: The association between academic performance (tertiles) and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=275)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=275)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=275)**	**Yes HR (95% CI) (n=223)**	**No HR (95% CI) (n=52)**
English (vs. Tertile 1)					
Tertile 2	0.78 (0.57, 1.08)	0.77 (0.56, 1.06)	0.80 (0.58, 1.10)	0.79 (0.55, 1.13)	1.19 (0.51, 2.81)
Tertile 3	0.84 (0.61, 1.15)	0.88 (0.64, 1.20)	0.93 (0.68, 1.28)	0.94 (0.66, 1.33)	1.03 (0.45, 2.35)
Covariates					
Age at baseline		**1.09 (1.06, 1.12)**	**1.07 (1.04, 1.10)**	**1.08 (1.04, 1.10)**	1.03 (0.97, 1.10)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.32 (0.98, 1.80)	1.17 (0.86, 1.60)	1.33 (0.96, 1.84)	--[2]
Cognition			**1.24 (1.09, 1.41)**	**1.24 (1.06, 1.44)**	**1.55 (1.10, 2.18)**

[1] National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4.8. The Association Between Academic Performance (Dichotomized) and Survival

Tables 19 and 20 present the results of the Cox regression analyses for the association between survival and academic performance, dichotomized into high (i.e., participants achieved at least 90 percent in each of the first-year high school Geometry, Algebra, Latin and English courses) and lower (i.e., less than 90%) academic performance. In the unadjusted models, academic performance was not significantly associated with survival (high vs. lower: HR=1.19, 95% CI=0.80-1.76).

After adjusting for age, *APOE*-ε4 status, and cognitive status, the association between academic performance and survival remained statistically non-significant (high vs. lower: HR=1.23, 95% CI=0.82-1.86). In these models, older age (HR=1.09, 95% CI=1.04-1.14) and more impaired cognitive status (HR=1.22, 95% CI=1.01-1.48) were significantly associated with shorter survival.

In models stratified for Alzheimer neuropathology based on the CERAD neuropathologic criteria, academic performance was not significantly associated with survival in either the presence or absence of Alzheimer neuropathology. In the group of individuals with Alzheimer neuropathology, older age (HR=1.09, 95% CI=1.03-1.15) was significantly associated with shorter survival. Models stratified by Alzheimer neuropathology based on the NIA-RI neuropathologic criteria produced similar results overall (see Table 20 for full results). In the subgroup of individuals without Alzheimer neuropathology, there was no variation for *APOE*-ε4 status since no individuals in this group were *APOE*-ε4 carriers.

Table 19: The association between academic performance (dichotomized) and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: CERAD neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=275)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=275)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=275)**	**Yes HR (95% CI) (n=223)**	**No HR (95% CI) (n=52)**
English (vs. Low)					
High	1.19 (0.80, 1.76)	1.12 (0.75, 1.66)	1.23 (0.82, 1.86)	1.34 (0.82, 2.21)	0.63 (0.27, 1.45)
Covariates					
Age at baseline		**1.11 (1.06, 1.16)**	**1.09 (1.04, 1.14)**	**1.09 (1.03, 1.15)**	1.13 (0.98, 1.30)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.25 (0.79, 1.97)	1.07 (0.66, 1.72)	1.15 (0.69, 1.93)	--[2]
Cognition			**1.22 (1.01, 1.48)**	1.25 (0.99, 1.57)	1.30 (0.82, 2.04)

[1] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

Table 20: The association between academic performance (dichotomized) and time to death in unadjusted models, adjusted models and models stratified by Alzheimer neuropathology: NIA-RI neuropathologic criteria

				Alzheimer neuropathology[1]	
Variables	**Unadjusted HR (95% CI) (n=275)**	**Adjusted for Age and *APOE*-ε4 HR (95% CI) (n=275)**	**Adjusted for Age, *APOE*-ε4, and Cognitive status HR (95% CI) (n=275)**	**Yes HR (95% CI) (n=223)**	**No HR (95% CI) (n=52)**
English (vs. Low)					
High	1.19 (0.80, 1.76)	1.12 (0.75, 1.66)	1.23 (0.82, 1.86)	1.30 (0.82, 2.08)	0.77 (0.25, 2.35)
Covariates					
Age at baseline		**1.11 (1.06, 1.16)**	**1.09 (1.04, 1.14)**	**1.09 (1.03, 1.14)**	1.11 (0.94, 1.31)
APOE-ε4 1+ alleles (vs. 0 alleles)		1.25 (0.79, 1.97)	1.07 (0.66, 1.72)	1.12 (0.68, 1.84)	--[2]
Cognition			**1.22 (1.01, 1.48)**	1.18 (0.96, 1.47)	1.45 (0.77, 2.71)

[1] National Institute of Aging and Reagan Institute (NIA-RI) neuropathologic criteria
[2] In the group without Alzheimer neuropathology, no individuals were *APOE*-ε4 carriers
Abbreviations: *APOE*-ε4 = Apolipoprotein E-ε4; CI = confidence interval; HR = hazard ratio

5.4.9. Additional Bivariate Analyses

5.4.9.1. The Association Between Educational Factors and Age

Bivariate analyses were conducted to assess the associations of educational attainment and academic performance with age at baseline. Educational attainment was significantly associated with age at baseline ($p=0.004$) using ANOVA: individuals with a Master's degree or higher were significantly younger at baseline by 1.98 years in comparison to participants who had a Bachelor's degree. Academic performance was not significantly associated with age at baseline.

5.4.9.2. The Associations of Neuropathologic Criteria with All Study Covariates

Bivariate analyses were conducted for each study covariate by the CERAD and NIA-RI neuropathologic criteria. Analyses with the CERAD neuropathologic criteria showed a significant association with *APOE*-ε4 status ($p<0.0001$). The majority (61%) of participants with 1 or more *APOE*-ε4 alleles had definite AD whereas only 23% of the participants with no *APOE*-ε4 alleles had definite AD. The above results are expected because the presence of *APOE*-ε4 alleles is associated with an increased risk of AD. Cognitive function at the last assessment was also significantly associated with the CERAD neuropathologic criteria ($p<0.0001$). Forty-seven percent of the participants with dementia at the last cognitive assessment had definite AD while 38% of the participants with dementia had probable AD; the above results demonstrate a positive relationship between impairments in cognitive function and severity of AD neuropathology (based on the CERAD neuropathologic criteria). Educational attainment, academic performance,

age at baseline, and cognitive function at baseline were not significantly associated with the CERAD neuropathologic criteria.

Bivariate analyses were also conducted for each covariate with the NIA-RI neuropathologic criteria. *APOE*-ε4 status ($p<0.0001$) and cognitive function at the last assessment ($p<0.0001$) were significantly associated with the NIA-RI neuropathologic criteria and the nature of these associations was similar to those of *APOE*-ε4 status and cognitive function with the CERAD neuropathologic criteria. Cognitive function at the baseline assessment was also significantly associated with the NIA-RI neuropathologic criteria ($p=0.002$): there was a positive association between impairments in cognitive function and severity of AD neuropathology based on the NIA-RI neuropathologic criteria. Further, educational attainment, academic performance, and age at baseline were not associated with AD neuropathology based on the NIA-RI neuropathologic criteria.

6. Discussion

6.1. Summary

The overall objective of the research project was to test the cerebral reserve hypothesis by assessing (1) whether there was a positive relationship of educational attainment and academic performance with survival in the overall population and, (2) whether the above relationships were modified by the presence or absence of Alzheimer neuropathology. Existing literature includes studies that examined the association between education and survival, but this project had a different methodological approach that set it apart from previous research on the topic. Previous studies defined survival as time to death after the diagnosis of AD whereas this study described survival as time from entry into the study until time to death. This difference in how the outcome was defined influenced the nature of the analytic sample. Previous studies only included participants who received a formal diagnosis of AD. This study, on the other hand, included participants with varying cognitive statuses thereby including individuals that might have had Alzheimer neuropathology but were inhibiting the clinical expression of AD symptoms (i.e., participants who had high cerebral reserve). Furthermore, previous studies only examined the relationship between educational attainment and survival while this study also assessed a novel relationship between academic performance and survival.

It was hypothesized that (1) educational attainment and academic performance would be positively associated with survival in the overall population and, (2) the above associations would be modified by the presence or absence of Alzheimer neuropathology. In the presence of Alzheimer neuropathology, high educational factors would be associated with shorter survival (Freels et al., 2002; Stern et al., 1995; Wilson et al.,

2006). The above hypothesis was based on the theory of cerebral reserve: if high educational factors contribute to high reserve, then those with high educational attainment and high academic performance would tolerate more Alzheimer neuropathology before symptom onset, have more severe Alzheimer neuropathology at symptom onset, and have a shorter survival post symptom onset. In individuals without Alzheimer neuropathology, it was hypothesized that high educational factors would be associated with longer survival than lower levels of educational factors, based on literature suggesting that educational attainment is positively associated with survival in the overall population (World Health Organization, 2014a; World Health Organization, 2014b).

The results of the research project did not support the study hypotheses. It was found that (1) educational attainment (Tables 2 and 3) and academic performance (Tables 4 and 5) were not significantly associated with survival in the overall study population and, (2) the above relationships were not modified by Alzheimer neuropathology (see stratified models in Tables 7 and 8).

6.1.1. Explanations For Inconsistencies With Previous Research

Possible explanations for inconsistencies between our results and existing literature are: (1) differences in research methodology; (2) limited variation for educational factors; (3) the association between education and survival is less established in older cohorts, such as the Nun Study population; and (4) educational factors were not associated with survival in a population that is relatively homogeneous for environmental and lifestyle factors throughout adult life.

6.1.1.1. Differences in Research Methodology

The positive association between educational attainment and survival in the overall population (World Health Organization, 2014a; World Health Organization, 2014b) would be expected to be similar to the association between educational factors and survival in the subgroup of individuals without Alzheimer neuropathology, since the overall population should mainly consist of individuals without Alzheimer neuropathology. Contrary to this expectation, however, the majority of the study sample did have Alzheimer neuropathology: 78% of the participants in our analytic sample had Alzheimer neuropathology based on the CERAD neuropathologic criteria while 80% had Alzheimer neuropathology based on the NIA-RI neuropathologic criteria. Thus, because of the nature of the analytic sample, the trend of the association between educational factors and survival should be driven by the subgroup of individuals with Alzheimer neuropathology rather than the subgroup of individuals without Alzheimer neuropathology.

We hypothesized an inverse association between educational factors and survival in individuals with Alzheimer neuropathology (Freels et al., 2002; Stern et al., 1995; Wilson et al., 2006). This hypothesis was based on the theory of cerebral reserve (see Section 6.1.). However, the study results did not support our hypothesis: they illustrated that educational attainment and academic performance were not significantly associated with survival in the subgroup of individuals defined by the presence of AD neuropathology. A possible reason for the inconsistency with previous research is the difference in methodology. In our study the outcome, survival, was defined as time from entry into the study until death (as opposed to survival post-diagnosis of AD as in

previous research) in order to include participants who may have had Alzheimer neuropathology but inhibited the clinical expression of disease symptoms. As discussed in Section 6.1, this definition of the outcome influenced the nature of our analytic sample: our study included participants with varying cognitive statuses while previous studies only included participants who received a formal diagnosis of AD. This difference in how survival was defined also had an impact on the research question. Previous studies examined the association between education and survival post-diagnosis of AD and found conflicting results: some studies reported an inverse association between educational attainment and survival post-diagnosis of AD (Freels et al., 2002; Stern et al., 1995) while others reported no association between these two factors (Bowen et al., 1996; Brehaut et al., 2004; Freels et al., 2002; Fritsch et al., 2001; Geerlings et al., 1997; Helmer et al., 2001; Hier et al., 1989; Larson et al., 2004; Qiu et al., 2001; Stern et al., 1995; Wolfson et al., 2001). Our study, on the other hand, examined a relationship of educational attainment and academic performance (a novel education-related factor) with a different outcome, overall survival, and found that no such statistical association existed.

6.1.1.2. Limited Variation for Educational Factors

The positive association between education and survival in the overall population is well documented (Chappell, Ota, Berryman, Elo, & Preston, 1996; Kunst & Mackenbach, 1994; Lleras-Muney, 2005; Mackenbach, 2015; Smith et al., 1998; Sorlie, Backlund, & Keller, 1995; World Health Organization, 2014a; World Health Organization, 2014b), yet our study was unable to replicate this relationship. A contributing factor to this inconsistency could be that because the Nun Study population

is a highly educated group, there may not have been enough variation in educational attainment to detect the relationship between educational attainment and survival. To demonstrate, only 0.4% of the participants had a grade school level of education while 5.2% had a high school diploma. For this reason, we had to collapse the bottom two categories of grade school and high school into the category high school education or less (which contained 6% of the participants), and this influenced the project's ability to adequately assess the impact of low education on survival.

Further, the relationship between academic performance and survival was expected to be similar to that of educational attainment and survival because academic performance is also an education-related variable. In addition to being highly educated, the Nun Study participants also achieved high academic success. To demonstrate, the lowest mean grade for combined first-year high school Geometry, Algebra, Latin, and English courses was 65%. Since academic performance was not normally distributed, this exposure was categorized into quartiles. On one hand, the categorization of the above variable into quartiles was beneficial in terms of statistical power because there were a similar number of participants in each category, as opposed to the educational attainment exposure where the lowest category of high school or less had only 6% of the total participants. On the other hand, a disadvantage of this categorization was that the quartiles were predefined based on the distribution of grades in this sample. The lowest quartile ranged from 65% to less than or equal to 83%. Although the above range was the lowest category of academic performance in our analytic sample, it may not be representative of low academic performance in the general population.

6.1.1.3. Older Cohort

The association between educational factors and survival is less established in older cohorts (Kaplan et al., 2015) and the Nun Study population is an old cohort, with participants aged 75+ years at baseline. One possibility that could explain the weak association between education and survival in the Nun Study participants is that the beneficial effects (i.e., cognitive stimulation) of high education diminish with time as many years have passed since individuals in this population group completed their formal education (Lauderdale, 2001). Another possibility that could influence the association between education and survival is that some Catholic sisters from the School Sisters of Notre Dame religious congregation died before the Nun Study enrollment began (i.e., these sisters were not included in the study even though they experienced the outcome of interest). A study by Butler and Snowdon (1996) suggests that left truncation would be less severe in the Catholic sisters from the School Sisters of Notre Dame religious congregation, in comparison to the general white, female population in the United States, because the all-cause mortality rate of Catholic sisters that died before they were eligible for the Nun Study (i.e. 75 years) was 73% of that of the general population. Furthermore, another theory suggests that health and economic disparities are reduced in seniors, and this in turn contributes to a weakened association between education and survival in this age group (Cook & Fletcher, 2015; Jones, 1971; Lauderdale, 2001). Factors that contribute to a reduction in health and economic disparities in older cohorts are (1) the presence of insurance programs, such as Medicare, which provide seniors in the United States equal access to healthcare (Lauderdale, 2001), and, (2) the observation that education did not substantially influence economic factors (e.g., occupational attainment)

in older cohorts so individuals in this group could still get a well-paying job in the past despite having a low level of educational attainment (Jones, 1971). Note, however, that while the Nun Study population is a cohort of older women aged 75+ years at baseline, the above theory was not relevant to the Nun Study participants because the Nun Study participants are homogeneous for lifestyle and environmental factors (i.e., for the Nun Study population, the reduction in health and economic disparities was influenced by environmental and lifestyle homogeneity rather than by age group) (see Section 6.1.4). Although not tested directly, this notion presented in the literature that the relationship between education and survival is weakened in old age because of a reduction in health and economic disparities does not support the cerebral reserve hypothesis, which states that high education can contribute to levels of cerebral reserve through (1) measures such as brain size, neuronal count and synaptic density or, (2) mechanisms such as neural reserve (i.e., using remaining areas of the brain in a more efficient manner) or neural compensation (i.e., recruiting additional brain areas to complete a task) (Stern et al., 1995). Rather, it supports an alternate theory that high education may contribute to high socioeconomic status and the accumulation of resources (e.g., income, access to healthcare, strong social networks), thereby having a long-term effect on health outcomes such as survival (Cook & Fletcher, 2015).

6.1.1.4. Homogeneous Population

A feature of the Nun Study that had a major influence on our study findings is that the Nun Study population is relatively homogeneous from mid to late life with regard to many environmental and lifestyle factors (e.g., income, housing, occupation, access to healthcare) and our study found that in such an analytic sample (1) educational

attainment and academic performance were not significantly associated with overall survival and, (2) Alzheimer neuropathology did not modify the above associations. Previous studies examining the association between education and survival in individuals diagnosed with AD did not control for environmental and lifestyle factors (Bowen et al., 1996; Brehaut et al., 2004; Freels et al., 2002; Fritsch et al., 2001; Geerlings et al., 1997; Helmer et al., 2001; Hier et al., 1989; Larson et al., 2004; Qiu et al., 2001; Stern et al., 1995; Wolfson et al., 2001). It is important to account for environmental and lifestyle factors when studying the association between educational factors and survival because these environmental and lifestyle factors are positively associated with educational factors and survival, and are an intermediate step in the causal pathway between educational factors and survival. While the majority of the previous studies did not find an association between education and survival post-diagnosis of AD (Bowen et al., 1996; Brehaut et al., 2004; Fritsch et al., 2001; Geerlings et al., 1997; Helmer et al., 2001; Hier et al., 1989; Larson et al., 2004; Qiu et al., 2001; Wolfson et al., 2001), two studies (Freels et al., 2002; Stern et al., 1995) found a significant association between these two factors of interest. In other words, in addition to presenting conflicting results on the association between education and survival, none of the results in the previous studies were an accurate measure of the association of interest because these previous studies did not control for environmental and lifestyle mediators. Our study attempted to clarify the association between educational factors and survival while controlling for environmental and lifestyle factors, by restriction, and found no significant association of educational attainment and academic performance with survival.

Our finding that educational attainment and academic performance may lose their power to predict survival in a population that is relatively homogeneous for environmental and lifestyle factors throughout adult life raises questions about the mechanism underlying the relationship between these factors of interest (see Section 6.1.3). We hypothesized that in individuals with AD neuropathology, high educational attainment and academic performance would be associated with shorter survival because high educational factors contribute to cerebral reserve; however, the project results did not support our hypotheses because we found no significant association between educational factors and survival in a population that is homogeneous for factors such as income, housing, occupation, and access to healthcare. The lack of a statistical association found in our homogeneous sample supports an alternate theory that educational attainment and academic performance influence survival through the accumulation of economic and social resources because such resources have a long-term effect on the outcome of interest (Cook & Fletcher, 2015). Perhaps it is variation in these environmental and lifestyle factors, which are intervening factors between education and survival, that explains the reported association between education and survival. Further, a study by Kunst and Mackenbach (1994) assessed the association between level of education and a different outcome, inequalities in mortality across different countries. They found small inequalities in mortality, by educational level, in countries such as the Netherlands, Sweden, Denmark, and Norway, but large inequalities in the United States, France and Italy. Mackenbach (2015) conducted a similar study within Europe and found small inequalities in mortality, by education, in Southern Europe but large inequalities in Eastern Europe. The above studies present an interesting finding because they suggest

that education does not have the same effect on inequalities in mortality across different countries. Perhaps there is an external factor that contributes to the differential effect of education on inequalities in mortality. The authors explained that countries with large differences in mortality also have large disparities in income and health conditions (i.e., lung cancer, live cirrhosis). Although this idea needs to be investigated further, the findings of the Kunst and Mackenbach (1994) and Mackenbach (2015) studies suggest that income and health may be intervening factors for the relationship between level of education and inequalities in mortality.

6.2. Study Findings – Bivariate Results

Similar to the multivariate results, some of the bivariate results also did not support the hypotheses. The bivariate results suggested that Alzheimer neuropathology (based on the NIA-RI neuropathologic criteria) was significantly associated with survival ($p<0.05$), although the trend of this association was the opposite of what was expected. Participants without AD had 1.95 years shorter survival when compared to participants who had an intermediate likelihood of AD. The above trend was similar to that of the association between survival and Alzheimer neuropathology, based on the CERAD neuropathologic criteria, although the relationship was not statistically significant. While the trend of the association between Alzheimer neuropathology (based on the NIA-RI neuropathologic criteria) and survival was the opposite of what was expected, the significant association between cognitive function at baseline and survival followed a predictable pattern: participants with global impairment had 2.85 years shorter survival than those with intact cognition, participants with dementia had 3.58 years shorter

survival than those with intact cognition, and participants with dementia had 2.5 years shorter survival than those with mild cognitive impairments.

Supplementary analyses were conducted to investigate why individuals without AD had a shorter survival than those with an intermediate likelihood of AD. There was a possibility that individuals without Alzheimer neuropathology had another disease that influenced their survival. The three most common causes of death in Canada are cancer, heart disease, and cerebrovascular disease (Statistics Canada, 2014). The prevalence of one of the above disorders may contribute to a survival bias where individuals with cancer, heart disease, or cerebrovascular disease may not live long enough to develop AD neuropathology. Another possibility is that the prevalence of cancer, heart disease or cerebrovascular disease may be protective against the development of AD neuropathology. A study by Roe et al. (2010) reported a significant, inverse relationship (HR=0.57, 95% CI=0.36-0.90) between prevalent cancer and the development of AD after adjusting for demographics, *APOE*-ε4 status, and other health conditions (i.e., diabetes, hypertension, coronary heart disease), suggesting that cancer survivors had a reduced risk of AD. Our study was unable to assess the relationship of cancer and heart disease to survival because the Nun Study data do not include information on the above health conditions. The Nun Study data, however, do include information on cerebral infarcts, the pathological markers of stroke, and therefore supplementary analyses were conducted to test whether the association between Alzheimer neuropathology and survival was modified by the presence or absence of cerebral infarcts. The study results showed that infarcts did not modify the association between survival and Alzheimer neuropathology, defined by either the CERAD (p=0.96) or NIA-RI neuropathologic

criteria (p=0.35). Since our study was unable to do so, other research may find it worthwhile to investigate whether cancer and heart disease, the other two common causes of death, modify the relationship between Alzheimer neuropathology and survival.

6.3. Sensitivity Analyses

6.3.1. The Association Between Educational Attainment and Survival

The results from the sample restricted only by education (n=364) suggest that educational attainment was not significantly associated with overall survival, and that Alzheimer neuropathology, as defined by the CERAD and NIA-RI neuropathologic criteria, did not modify this association (Tables 7 and 8).

On one hand, since the above results are similar to those of the reduced, main analytic sample (n=232), they strengthen the conclusion that there is no relationship of level of educational attainment with survival, and that Alzheimer neuropathology does not act as an effect modifier for the above relationship. From another point of view, however, the larger sample that was restricted only by education had the same limitations as the main analytic sample, and this could explain the lack of a statistical association between education and survival in this larger sample. The above sample was also made up of participants from the Nun Study population who were (1) homogeneous throughout adult life for many environmental and lifestyle factors and, (2) a cohort of older women. Furthermore, similar to the main analytic sample, there was reduced variation for the educational attainment exposure in the larger sample: 14% of the participants in the larger sample (as opposed to 6% in the main analytic sample) had a high school or lower level of educational attainment.

6.3.2. The Association Between Academic Performance and Survival

Academic performance was defined in the main analyses as a mean of the final grades in first-year high school Geometry, Algebra, Latin, and English. An alternative definition for academic performance would be the individual final grades in the above four courses (i.e., four different analytic samples, one for each course). The rationale for choosing the former definition of academic performance in the main analyses was that it would be a more stringent measure of academic performance: a participant would need to achieve high final grades in all of the four courses in order to obtain a high mean final grade (i.e., high academic performance). If academic performance for individual courses was assessed, there would be four different analytic samples, one for each of the four courses. This definition of academic performance has two shortcomings: (1) a participant may have had high academic performance in one course but may have performed poorly in the other three courses and, (2) it would not be possible to directly compare the results across the samples because they consist of different participants.

While academic performance was thus defined as a mean of four first-year high school courses in the main analyses, sensitivity analyses were also conducted to assess whether academic performance, as defined by individual final grades in first-year high school Geometry, Algebra, Latin, and English, would produce comparable results to those of the overall academic performance measure. Results from the sensitivity analyses illustrated that academic performance in Algebra (Tables 11 and 12), Latin (Tables 13 and 14), and English (Tables 15 and 16) was not significantly associated with survival in the unadjusted, adjusted or stratified models. However, higher academic performance in Geometry was significantly associated with longer survival in models adjusted for age

and *APOE*-ε4 status and in fully adjusted models, but not in models stratified for Alzheimer neuropathology based on both the CERAD and NIA-RI neuropathologic criteria (see stratified models in Tables 9 and 10).

The results from the sensitivity analyses for academic performance are somewhat comparable to a study by Bezerra et al. (2012), which found that language and math courses were associated with a reduced risk of dementia. Our project tested the association between academic performance and a different outcome, survival, and found that a math course, Geometry, but not language courses were protective of survival in the overall population. Bezerra et al. (2012) proposed that mathematical skills influence the risk of developing dementia in late life because such skills contribute to improved cognition, economic opportunities, and overall quality of life. Since the association between Geometry and survival has not been well explored, further research is required to assess what characteristics of Geometry contribute to survival in the overall population. Furthermore, while the results provide evidence for a novel association between survival and academic performance in first-year high school Geometry in the overall population, they do not support the theory of cerebral reserve because significant results were not found for the stratified models. In other words, our study did not find significant differences in survival, by academic performance in first-year high school Geometry, in individuals with and without Alzheimer neuropathology; this finding is not consistent with the cerebral reserve hypothesis because this hypothesis suggests that individuals with high reserve (i.e., a high academic performance in first-year high school Geometry) should have a shorter survival (see Section 6.1.).

Sensitivity analyses were also conducted using alternate categorization techniques for academic performance: (1) dichotomized into high (i.e., participants achieved at least a 90 percent in all first-year high school Geometry, Algebra, Latin and English courses) versus lower and, (2) categorized into tertiles. The purpose of creating a category of participants that achieved at least 90 percent in each of the four first-year high school courses (Geometry, Algebra, Latin, and English) was that this group of participants would be representative of high academic success. Also, two and three categories for academic performance (as opposed to quartiles in the main analyses) would result in a greater number of participants in each category when compared to the main analyses. The results of the sensitivity analyses for these alternate categorization techniques for academic performance were consistent with those for the main analyses in that academic performance was not associated with survival in: (1) unadjusted models, (2) models adjusted for age and *APOE*-ε4 status, (3) models adjusted for age, *APOE*-ε4 status, and cognitive status and, (4) models stratified by Alzheimer neuropathology (according to both the CERAD and NIA-RI neuropathologic criteria).

6.4. Strengths and Limitations

6.4.1. Strengths

A major strength of the Nun Study is that it includes neuropathologic evaluations for deceased participants. Previous studies on the theory of cerebral reserve used cerebral blood flow and brain glucose metabolism as secondary measures of neuropathology. Since the Nun Study has primary measures of brain damage, the project was able to assess whether Alzheimer-type neuropathology modified the association between educational factors and survival. A second strength is that the Nun Study includes unique

early-life data, particularly on educational factors. The archival records contain high school transcripts, which provided a listing of courses and associated marks achieved by the participants; these transcripts were used to assess academic performance in the project. The high school transcripts provided a more objective measure of academic performance in comparison to the Mehta et al. (2009) study, which used self-assessed school performance as an exposure. Further, the Nun Study collected data on the *APOE*-ε4 status of its participants, and thus the project was able to adjust for this potential effect modifier; previous studies were not able to adjust for genetic factors linked to AD. Additionally, the Nun Study participants were relatively homogeneous from midlife to late life with regard to environment and lifestyle, and thus, these factors could not confound the study results as they may have for past epidemiologic studies. The study had a long duration of follow-up (i.e., up to twelve annual assessments); cognitive status was assessed at each assessment, and thus, the project was able to include this variable as a time-varying covariate. The study design also established a clear temporal relationship between the educational factors and survival.

6.4.2. Limitations

The research project also had some limitations. First, while the Nun Study includes 678 participants, the analytic sample for the project contained a reduced sample of 232 participants; participants were excluded if they were alive or if they had missing data on the covariates of interest. An assessment of non-response bias was conducted to assess if excluded participants differed from the participants in the analytic sample with respect to the study covariates. While there were some significant differences between the excluded participants and analytic sample, these differences were predictable and

followed a logical pattern (see Section 4.3.1.2). Sensitivity analyses were also conducted to test whether a reduced sample size in the main analytic sample contributed to statistically non-significant results. Sensitivity analyses using a larger sample restricted only by education (n=364) produced results similar to the main analytic sample, thus showing that missing data did not have a major influence on the results for the relationship between education and survival in the main analyses. Sensitivity analyses using four different analytic samples for academic performance showed that English, Latin, and Algebra were not statistically associated with survival in unadjusted models; models adjusted for age and *APOE*-ε4 status; and models adjusted for age, *APOE*-ε4 status, and cognitive status. However, high academic performance in Geometry was significantly associated with longer survival in unadjusted models; models adjusted for age and *APOE*-ε4 status; and models adjusted for age, *APOE*-ε4 status, and cognitive status, but not in models stratified by Alzheimer neuropathology. Thus, while the results for academic performance in English, Latin, and Algebra were consistent with those of the overall academic performance measure used in the main analyses, high academic performance in Geometry was protective of survival in the general population and this result was not reflected in the overall academic performance measure used in the main analyses.

Further, another limitation of the project was that there may not have been enough variation in the educational attainment exposure in order to accurately test a key association of interest between educational attainment and survival. Furthermore, information was not available on all desired factors. For example, university-level courses may be more cognitively stimulating than high school courses, and may therefore

more strongly influence levels of cerebral reserve. If the Nun Study had access to university transcripts, sensitivity analyses could be conducted to test the association between survival and academic performance in university-level Geometry, Algebra, English and Latin courses. Note that the above association would have to be tested in sensitivity analyses because the main analyses used the same analytic sample for the two exposures, educational attainment and academic performance. While the educational attainment exposure includes a category of participants who had a high school or lower level of education, by definition, academic performance in university-level courses would omit those whose had a high school or lower level of education, thus leaving an inconsistent sample across the two exposures of interest. Further, homogeneity between study participants with regard to environmental and lifestyle factors was an important feature of the Nun Study that limited the generalizability of the study results. Lastly, our analytic sample included only female participants, and thus, the study results may not be generalizable to males. Differences in male and female brain size could possibly influence the response to brain damage (i.e., since males have a larger brain, they may be able to tolerate more brain damage before expressing symptoms of AD). Future studies could replicate our project using a male population to see if similar results were found.

6.5. Implications and Future Directions

To conclude, existing research on the relationship between educational attainment and survival in individuals with AD is inconsistent: some studies state that an association exists between educational attainment and survival while other studies report no relationship between these two factors. This research project attempted to clarify the relationship between educational attainment and survival and found no such association.

The project further assessed a novel relationship between academic performance and survival and found no association between these factors of interest when academic performance was defined as a mean of final grades in first-year high school Geometry, Algebra, Latin, and English, but sensitivity analyses showed that academic performance in Geometry alone was associated with survival in the overall population. Moreover, this was the first study to my knowledge to assess whether Alzheimer neuropathology modified the relationship between educational factors and survival, and found that Alzheimer neuropathology was not an effect modifier for this relationship of interest. Overall, the study results did not provide evidence for the theory of cerebral reserve.

Although the study results did not support our hypotheses, this study contributed to our understanding of the mechanisms through which educational factors may influence survival. The hypothesis that high educational factors would be associated with shorter survival in individuals with Alzheimer neuropathology was based on the cerebral reserve hypothesis (see Section 6.1); however, the mechanisms through which educational factors influenced survival in the overall population and in the subgroup of individuals defined by the absence of Alzheimer neuropathology were unclear. The results of our study may support an alternate theory for explaining the association between educational factors and survival in the general population and in subgroups defined by either the presence or absence of Alzheimer neuropathology: high educational attainment and academic performance may influence survival through the accumulation of intermediate economic and social factors (e.g., income, occupation, access to healthcare, social networks). Although not explored directly in this study, the above theory may explain why our study did not find an association between educational factors and survival in an older

population that was homogeneous for environmental and lifestyle factors such as income, housing, occupation and access to healthcare. A future study could examine this alternate theory by testing whether environmental and lifestyle factors mediate the association of educational attainment and academic performance with survival.

Furthermore, this study contributed to our understanding of the effect of education on a particular health outcome, survival, and further allowed us to compare the differential effect of education on survival versus other health outcomes. To demonstrate, low education is associated with poor overall health, low self-confidence, high stress, and high mortality; conversely, early-life educational opportunities strongly influence a child's development, chances of survival, and overall health and wellbeing (see Section 2.4.1). Furthermore, previous research in the Nun Study demonstrated an inverse association between education and the risk of developing dementia (see Section 2.2.2.2). Interestingly, using the same dataset (i.e., the Nun Study), our project found that educational factors were not significantly associated with survival. This finding is contrary to existing literature that suggests that higher education is associated with longer survival in the overall population and shorter survival in individuals diagnosed with AD. Our study results are not consistent with previous literature because our study found that in a population homogeneous for environmental and lifestyle factors: (1) education was not significantly associated with survival in the overall population and, (2) there were no significant differences in survival by education in subgroups defined by the presence or absence of Alzheimer neuropathology. The above finding may have implications for the health of individuals living with Alzheimer neuropathology because it suggests that in a population that is homogeneous for environmental and lifestyle factors, there are no

significant differences in survival between subgroups of individuals living with and without Alzheimer neuropathology. Since education is not associated with survival in a population that was homogeneous for factors such as income, housing, and access to healthcare, it may be beneficial to invest resources to provide equal opportunity for individuals with respect to the above variables because reducing disparities with respect to the above environmental and lifestyle factors may help minimize differences in survival, by education, in both the overall population and in subgroups of individuals living with and without Alzheimer neuropathology.

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8. Appendices

Appendix A: Summary of studies examining the relationship between educational attainment and survival post-diagnosis of AD

Primary Author, Year	**Study Objective**	**Exposure**	**Outcome**	**Sample Characteristics**	**Covariates**	**Analysis and Results**
Bowen et al., 1996	To assess the association between different factors and survival in individuals with probable AD	Educational attainment - Categorized into: < high school, high school, > high school	Survival - Date of entry into study until date of death	- n=327 - Participants met NINCDS-ADRDA for probable AD - Exclusion Criteria: Diagnosis of possible AD, non-dementia AD or no dementia	- Age - Gender - Dementia severity (as measured by MMSE score, Blessed dementia rating scale score, Boston naming test score, rate of cognitive decline, and presence of wandering or agitation)	Survival analysis - Cox regression No Association - High school vs. lower than high school: HR 1.0 (95% CI 0.6-1.8) - >High school vs. lower than high school: HR 1.0 (95% CI 0.6-1.7)
Brehaut et al., 2004	To test whether cognitive status is an effect modifier for the relationship	Educational attainment - Categorized into: low (< 8 years), medium (8-12 years), high (> 12) years of formal education	Survival - Date of entry into study until date of death	- n=583 - Data source: Canadian Study of Health and Aging - Participants met NINCDS-ADRDA criteria for AD - Exclusion criteria:	- Age - Gender - Cognitive status (categorized into: no cognitive impairment,	Cox regression No Association

Primary Author, Year	Study Objective	Exposure	Outcome	Sample Characteristics	Covariates	Analysis and Results
	between education and mortality	- High education was the reference category		unavailable information on education & death status	cognitive impairment but no dementia, dementia)	
Freels et al., 2002	To assess predictors of survival in a hospital-based cohort of African-American individuals with AD	Educational attainment - Number of years of formal education	Survival - Date of entry into study until date of death	- n=113 - Inclusion criteria: African-American racial background, English speakers, aged 45 +, company of an informer that knows participant for the last 10 years and who meets participant at a minimum of 3 times a week - Exclusion criteria: comorbid illnesses that can cause death during the follow-up period (e.g., cancer)	- Age - Sex - Educational attainment - Clinical dementia rating, MMSE score (measure of cognitive function) - Hamilton Score (measure of depression) - Medical history (hypertension, diabetes, myocardial infarction, high cholesterol)	Survival analysis - Cox regression Association - HR 1.10 (p=0.01)
Fritsch et al., 2001	To test the relationship between educational	Educational attainment - Highest level of education completed	Survival - Year of entry into study until date of death	- n=258 (99 male, 159 female) - Participants met NINCDS-ADRDA	- Gender - Ethnicity - Year of birth - Year of entry	Cox regression No association - HR 0.97 (95%

Primary Author, Year	Study Objective	Exposure	Outcome	Sample Characteristics	Covariates	Analysis and Results
	attainment and the clinical expression of AD			criteria for AD; 64.7% of participants had mild dementia; 35.3% of participants had moderate dementia - Mean age: 73.4 years; mean level of educational attainment: 12.8 years	into study	CI 0.91 – 1.03)
Geerlings et al., 1997	To test whether higher educational attainment is associated with a greater mortality rate in patients matched for clinical severity	Educational attainment - 8-point ordinal scale (Range: Incomplete primary school education – University degree)	Survival - Date of diagnosis until date of death	- n=66 - Patients met NINCDS-ADRDA criteria for probable AD - Exclusion criteria: unavailable data on mortality and level of education	- Age - Sex	Cox regression No association - HR 0.86 (95% CI 0.63-1.19)
Geerlings et al., 1999	To test whether a positive relationship exists	Educational attainment - Categorized into: ≤ 6 years and ≥ 7 years of formal	- Risk of mortality	-n= 261 - Data source: the Amsterdam Study of the Elderly - Participants met	- Age - Sex - Functional abilities - Depression	- Cox regression -When education was dichotomized,

Primary Author, Year	Study Objective	Exposure	Outcome	Sample Characteristics	Covariates	Analysis and Results
	between cognitive reserve (as measured by level of educational attainment) and mortality rate	education - Number of years of formal education		Geriatric Mental State Schedule criteria for dementia		there was not a difference in survival between those with: ≤ 6 years and ≥ 7 years of formal education - When education was treated as a continuous variable: no association between education and survival HR 1.05 (95% CI 0.97- 1.15)
Helmer et al., 2001	To assess predictors of survival in individuals with dementia	Educational attainment - Categorized into: ≤ primary school level vs. no diploma	Survival - Date of entry into study until date of death	- n=189 - Participants met NINCDS-ADRDA criteria for AD	- Sex - Comorbidity - Activities of daily living scale dependency	No association - HR 0.88 (95% CI 0.54-1.42)
Hier et al., 1989	To assess predictors of survival in individuals with AD	Educational attainment - not specified how this was measured	Survival - Date of initial evaluation until date of death	- n=61 - Inclusion criteria: participants also met NINCDS-ADRDA criteria for AD	- Age - Sex - Race	Cox regression Education was not a significant predicator of

Primary Author, Year	Study Objective	Exposure	Outcome	Sample Characteristics	Covariates	Analysis and Results
						survival in participants with AD
Hui et al., 2003	To assess the relationship between rate of cognitive decline and mortality in individuals with AD	Rate of cognitive decline	Risk of mortality	- n=354 - Inclusion criteria: participants met NINCDS-ADRDA criteria for probable or possible AD	- Age - Sex - Cognitive function - Education	Cox regression - Subgroup with mild cognitive decline vs. subgroup with least decline: RR 3.77 (95% CI 1.80-7.92) - Subgroup with moderately rapid cognitive decline vs. subgroup with least cognitive decline: RR 5.52 (95% CI 2.64-11.55) - Subgroup with rapid cognitive decline vs. subgroup with least cognitive decline: RR 8.88

Primary Author, Year	Study Objective	Exposure	Outcome	Sample Characteristics	Covariates	Analysis and Results
						(95% CI 4.11-19.96)
Larson et al., 2004	To assess predictors of survival post-diagnosis of AD	Educational attainment - Categorized into: <12 years, 12 years, or >12 years of formal education	Survival - Date from diagnosis of AD to date of death	- n=521 - Participants met NINCDS-ADRDA criteria for probable or possible AD	- Did not adjust for age or sex	Cox regression Survival did not vary by level of educational attainment (p>0.2)
Qiu et al., 2001	To assess the relationship between education and AD	Educational attainment - Categorized into: <8 years, ≥ 8 years of formal education	Survival - # Events (death)/ person-years at risk	- n=101 - Participants met DSM-III-R criteria for dementia	- Age (at baseline) - Sex - MMSE score (baseline) - Comorbidity - Socioeconomic status - Clinical dementia rating	Cox regression -Low educational attainment is associated with all-cause mortality RR 2.60 (95% CI 1.50- 4.40) - Low educational attainment is not associated with mortality in individuals with AD HR 1.10 (95% CI 0.50-2.20)
Stern et al., 1995	To test whether	Educational attainment	Survival - Date of initial	- n=246 - Participants met	- Age - Sex	Cox regression

Primary Author, Year	Study Objective	Exposure	Outcome	Sample Characteristics	Covariates	Analysis and Results
	higher educational attainment is associated with a greater mortality rate in patients matched for clinical severity	- Categorized into: ≤ 8 years, > 8 years of formal education - Number of years of formal education	evaluation until date of death	DSM-III-R criteria for dementia (had a comparison group for non-demented participants) - Exclusion criteria: acute stroke or Parkinson's disease diagnosis	- Clinical dementia rating	-When education was dichotomized, > 8 years of formal education was associated with survival HR 1.76 (95% CI 1.11-2.77) -When education was treated as a continuous variable, education was associated with survival HR 1.06 (95% CI 1.01-1.11)
Wilson et al., 2006	To test whether rate of cognitive decline is associated with risk of mortality in individuals	Rate of cognitive decline	Risk of mortality	- n=168 - Participants met NINCDS-ADRDA criteria for AD - 68.6% of the participants were women - Mean age: 78.9	- Age - Sex - Race	Cox regression Participants with slow rate of cognitive decline vs. rapid rate of cognitive decline: HR 0.31 (95% CI

Primary Author, Year	Study Objective	Exposure	Outcome	Sample Characteristics	Covariates	Analysis and Results
	with AD			years; average level of education=11.8 years; average MMSE score=14.4		0.19-0.49)
Wolfson et al., 2001	To assess survival post-diagnosis of AD	Educational attainment - Categorized into: ≤ 8 years, > 8 years of formal education	Survival - Date from diagnosis of AD to date of death	- n=514 - Participants met NINCDS-ADRDA for probable or possible AD - Exclusion criteria: missing data on level of education	- Length bias - Sex - Diagnosis - Age at onset of dementia	Survival analysis Median survival for: - Participants with probable AD: 3.1 years - Participants with possible AD: 3.5 years

Appendix B: Assessment of of non-response bias

Table 1: Test of non-response bias for analytic sample vs. all of the excluded participants

Variable	**Analytic sample (n=232)**	**Excluded participants (n=446)**
Education (%)		
Grade school	0.43	15.02
High school	5.17	5.61
Bachelor's degree	47.84	35.65
Master's degree or higher	46.55	43.72
Academic performance (%)		
Quartile 1	24.14	26.01
Quartile 2	22.84	26.37
Quartile 3	26.29	24.54
Quartile 4	26.72	23.08
Age at baseline		
Mean years (SD)	83.02 (4.89)	83.43 (5.74)
APOE-ε4 status (%)		
0 alleles	75.86	78.04
1 + alleles	24.14	21.96
Cognitive function at baseline (%)		
Intact cognition	27.16	23.87
Mild cognitive impairment	50.43	44.37
Global impairment	8.19	10.36
Dementia	14.22	21.40
Cognitive function at last assessment* (%)		
Intact cognition	11.64	15.70
Mild cognitive impairment	17.67	26.23
Global impairment	21.55	17.04
Dementia	49.14	41.03

*p<0.05 **p<0.0001

Table 2: Test of non-response bias for analytic sample vs. deceased participants

Variable	Analytic sample (n=232)	Deceased participants (n=374)
Education** (%)		
Grade school	0.43	16.58
High school	5.17	6.42
Bachelor's degree	47.84	35.56
Master's degree or higher	46.55	41.44
Academic performance (%)		
Quartile 1	24.14	26.34
Quartile 2	22.84	25.45
Quartile 3	26.29	25.00
Quartile 4	26.72	23.21
Age at baseline*		
Mean years (SD)	83.02 (4.89)	84.25 (5.81)
APOE-ε4 status (%)		
0 alleles	75.86	75.78
1 + alleles	24.14	24.22
Cognitive function at baseline* (%)		
Intact cognition	27.16	18.82
Mild cognitive impairment	50.43	43.28
Global impairment	8.19	12.37
Dementia	14.22	25.54
Cognitive function at last assessment (%)		
Intact cognition	11.64	12.03
Mild cognitive impairment	17.67	24.33
Global impairment	21.55	17.91
Dementia	49.14	45.72
CERAD neuropathologic criteria		
No NPs	21.55	23.57
Possible AD	8.62	12.10
Probable AD	37.50	31.21
Definite AD	32.33	33.12
NIA-RI neuropathologic criteria		
Not [likely]	19.83	23.61
Low [likelihood]	30.60	22.92
Intermediate [likelihood]	23.71	27.08
High [likelihood]	25.86	26.39

*p<0.05 **p<0.0001

Table 3: Test of non-response bias for deceased participants vs. alive participants

Variable	Deceased participants (n=606)	Alive Participants (n=72)
Education** (%)		
Grade school	10.40	6.94
High school	5.94	1.39
Bachelor's degree	40.26	36.11
Master's degree or higher	43.40	55.56
Academic performance (%)		
Quartile 1	25.22	24.49
Quartile 2	24.12	30.61
Quartile 3	25.66	22.45
Quartile 4	25.00	22.45
Age at baseline**		
Mean years (SD)	83.77 (5.50)	79.20 (2.80)
APOE-ε4 status* (%)		
0 alleles	75.81	89.23
1 + alleles	24.19	10.77
Cognitive function at baseline** (%)		
Intact cognition	22.02	50
Mild cognitive impairment	46.03	50
Global impairment	10.76	0
Dementia	21.19	0
Cognitive function at last assessment** (%)		
Intact cognition	11.88	34.72
Mild cognitive impairment	21.78	36.11
Global impairment	19.31	12.50
Dementia	47.03	16.67

*p<0.05 **p<0.0001