Is the Association Between Education and Cognitive Resilience Modified by Brain Weight and Cortical Atrophy?

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

Introduction: Some individuals are able to avoid reaching the threshold for clinical dementia despite the presence of Alzheimer neuropathology. This disparity between the neuropathologic and clinical symptoms required for a diagnosis of AD is often attributed to cognitive resilience, defined in the current study as the combined influence of brain reserve and cognitive reserve. This study assessed how educational attainment (a common measure of cognitive reserve), as well as brain weight and cortical atrophy (measures of brain reserve), may influence the outcome of cognitive resilience independently or through interactions with each other.

Methods: Analyses were based on the Nun Study, a longitudinal study of aging in 678 participants aged 75+ years at baseline. Educational attainment data were available through convent archives while brain weight and cortical atrophy data were collected through post mortem autopsies. Alzheimer neuropathology was assessed through post mortem autopsies and was defined using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and National Institute on Aging and Reagan Institute (NIA-RI) neuropathologic criteria. Finally, dementia status was determined through annual cognitive testing using DSM-IV criteria. Logistic regression analyses were conducted to assess all associations between exposures (educational attainment, brain weight and cortical atrophy) and the outcome (cognitive resilience), controlling for participant age at the time of death and the presence of apolipoprotein E-ε4.

Results: Higher educational attainment and brain weight, and the absence of cortical atrophy were all positively associated with cognitive resilience defined using both CERAD and NIA-RI neuropathologic criteria. However, the negative association between cortical atrophy and cognitive resilience was significant only when brain weights were high. When brain weight and educational attainment were assessed in the same models, the influence of educational attainment

fell below statistical significance. Finally, when educational attainment was assessed in models stratified by cortical atrophy status, it remained significant only in the presence of mild atrophy.

Discussion: It was hypothesized that higher educational attainment, higher brain weight and the absence of cortical atrophy would all be positively associated with cognitive resilience. These hypotheses were supported by findings in the study. Further, it was hypothesized that the impacts of mild atrophy would be more significant among individuals with lower brain weights than among those with higher brain weights, as higher brain weight would act as a buffer against mild atrophy. However, findings were contrary to this hypothesis, with results suggesting that atrophy was only significant when brain weights were high. This non-significant effect is likely partially related to low statistical power in the low brain weight strata. However, this result may additionally be the result of a floor effect whereby low brain weight depletes brain reserve to such an extent that further loss in tissue (through cortical atrophy) is unlikely to result in further impairment. Finally, it was hypothesized that educational attainment would be most strongly associated with cognitive resilience when brain reserve was low (i.e., in the presence of cortical atrophy or low brain weight). This hypothesis was partially supported by findings indicating that when mild atrophy was present, low educational attainment was associated with reduced odds of resilience. Overall, it appears that cognitive reserve factors (educational attainment) are important in reducing the clinical symptoms of AD in late life; however, these positive effects were only found when threats to brain reserve (cortical atrophy, low brain weight) were absent or of mild severity.

Conclusion: Higher levels of education can improve cognitive reserve and help reduce the risk of dementia symptoms despite AD brain changes. These benefits are only realized, however, when low brain weight and cortical atrophy are avoided. This study and future efforts aimed at

better understanding how late-life cognitive resilience is influenced by factors from across the lifespan could inform applications of cognitive resilience theory to clinical and community settings with the goal of offsetting the devastating impacts of AD.

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List of Abbreviations

AD	Alzheimer's Disease
ADL	Activities of Daily Living
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence Interval
DSM-IV	American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
NIA-RI	National Institute of Aging - Reagan Institute
NINCDS-ADRDA	National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NFT	Neurofibrillary Tangle
NP	Neuritic Plaque
OR	Odds Ratio
PSEN1	Presenilin 1
PSEN2	Presenilin 2
SES	Socioeconomic Status

1. Introduction

The rapid aging of the global population represents one of the most significant processes shaping health, social and economic systems around the world. By 2026, over one-fifth of the Canadian population will be over the age of 65 (Schellenburg & Turcotte, 2007), and it is predicted that the majority of babies born in developed countries since 2000 will live past their hundredth birthday (Christensen et al., 2009). In 2013, it was reported that 45 percent of Canadian healthcare expenditures were attributable to those over the age of 65 (Health Canada, 2013), with this number projected to rise as the population continues to age. Thus, the projected aging of the population in the coming decades could pose a considerable liability to Canada's healthcare system (Prince et al., 2013). While some recent research has indicated that healthcare costs associated with population aging may be manageable within the context of a growing economy (Health Canada, 2013), this may largely be dependent on effective management of chronic diseases and compressed morbidity in the last years of life (Canadian Institute for Health Information, 2011).

Of all of the chronic diseases associated with an aging population, dementias are among the most debilitating. Dementing disorders reduce quality and duration of life, negatively impact caregivers and consume a high percentage of healthcare resources (Markesbery, 1998; Prince et al., 2013), making them a primary concern for policy makers and healthcare agencies as the population ages.

Dementia refers to a category of disorders characterized by the deterioration of cognitive abilities (Alzheimer Society of Canada, 2010). Among the dementing disorders, Alzheimer's disease (AD) is the most common, accounting for over half of prevalent cases (Tyas & Gutmanis, 2015).

Presently there is no cure for AD and available pharmaceutical treatments function only to temporarily delay the progression of symptoms (Alzheimer's Association, 2014). However, roughly one-third of all AD cases may be preventable through lifestyle modifications (Norton et al., 2014). Therefore, research has focused on identifying modifiable risk factors for AD with an aim to develop interventions that prevent or delay the onset of symptoms.

A number of lifestyle and socio-economic factors such as education, occupation, physical activity (Hamer & Chida, 2009), and tobacco use (Tyas, White, Petrovich, et al., 2003) may play a role in the development of AD. Of the modifiable factors linked to AD, education has consistently been one of the most important, with evidence indicating that lower levels of educational attainment or fewer years of formal schooling are related to higher risk of dementia in later life (Stern et al., 1994; Fritsch et al., 2002; Tyas, Manfreda, Strain & Mongomery, 2001).

One particular area of interest for research seeking to reduce the burden of dementia is cognitive resilience. Cognitive resilience, comprising two components (brain reserve and cognitive reserve), is a concept that has been used to explain the maintenance of cognitive function despite the development of pathology that would normally be associated with a reduction in cognitive abilities, such as damage indicative of AD (Stern, 2002; Stern, 2009; Stern, 2012). Evidence indicates that among older adults without dementia, as many as 12% show neuropathology consistent with AD (SantaCruz et al., 2011). Although many of these individuals may still exhibit mild cognitive symptoms (SantaCruz et al., 2011), the maintenance of functional ability and independence provided by cognitive resilience significantly improves the quality of life of individuals and reduces the burden placed on families and dementia care resources. A number of factors known to be protective against AD, such as education and occupation, may partially function by promoting higher levels of resilience (Stern, 2012).

Alternatively, several factors are known to reduce cognitive resilience and thus the brain's ability to overcome Alzheimer neuropathology. Cerebral cortical atrophy is suggested to increase the likelihood of dementia symptoms among participants with Alzheimer neuropathology by reducing the brain's level of resilience (Tyas et al., 2008), and this relationship may be particularly strong among individuals with smaller brains (Guo et al., 2013). However, it remains unclear if atrophy interacts with early-life factors, such as education, in the development of cognitive resilience. Better understanding of cognitive resilience, and the factors associated with it, could inform strategies aimed at reducing the personal, social and economic burden associated with AD.

The first aim of the present study was to clarify the relationship between education and cognitive resilience. The second and third aims were to assess the associations of cortical atrophy and brain weight with cognitive resilience. The fourth aim of the study was to assess if the impacts of atrophy on cognitive resilience are modified by brain weight and the final aim of the study was to assess if the effects of education on cognitive resilience were modified by brain weight or cortical atrophy.

Analyses were conducted using secondary data from the Nun Study, a longitudinal study of aging and AD in 678 nuns aged 75+ living in the United States (Snowdon, et al. 1996). Educational attainment data were retrieved through archival records and measured by the highest degree attained. Cognitive status was determined through annual cognitive assessments. Alzheimer neuropathology and cortical atrophy were assessed during post-mortem examination by a pathologist. This study also accounted for a number of confounding variables including age at death and apolipoprotein E-ε4 (*APOE*-ε4).

Success in treating AD with existing pharmaceutical treatments is limited. Thus, the importance of primary AD prevention cannot be overstated. Understanding the impact of factors from across the life-course on cognitive outcomes in older adulthood could inform interventions that may reduce the dementia burden decades later.

2. Literature Review

2.1 Alzheimer's Disease

2.1.1 Epidemiology and Public Health Impact

Dementia refers to a class of symptoms in which individuals experience a loss in cognitive ability and independence in their daily lives (Khachaturian, 1985). Dementing disorders can be broken down broadly into two domains, reversible and irreversible (Alzheimer Society of Canada, 2008). Reversible dementias are usually secondary symptoms of disorders such as thyroid disease, kidney disease or depression. These forms of dementia are treatable through available medical therapies (Alzheimer Society of Canada, 2008). The major concern therefore lies in the irreversible forms of dementia, such as AD.

AD is not a part of normal aging (Alzheimer Society of Canada, 2010). It is, however, a leading cause of morbidity among older adults and is a major driving force in the need for formal institutional care (Wimo, Jönsson, Bond, Prince, & Winblad, 2010). The estimated global prevalence of AD and related dementias was 26.6 million people in 2006, and this number is expected to exceed 100 million by the year 2050 (Brookmeyer et al., 2007). In 2010, the global economic costs of dementia were an estimated 604 billion US dollars (Wimo et al., 2010). If dementia care were a country it would represent the 18th largest global economy, ranking between Turkey and Indonesia (Alzheimer's Disease International, 2010). The largest share of this economic burden impacts North America and Western Europe because of the heavier use of formal institutional care in these regions (Wimo et al., 2010).

Canada is projected to be impacted severely by the growing number of dementia cases. An estimated 1 in 11 Canadians over age 65 are thought to have some form of dementia, with AD responsible for over half of these cases (Alzheimer Society of Canada, 2008; Lindsay, Sykes, McDowell, Verreault, & Laurin, 2004; Tyas & Gutmanis, 2015). Although recent evidence suggests that the incidence rates of dementia may be lower than was previously

projected as a result of improved management of cardiovascular risk factors (Satizabal, Beiser et al., 2016), the aging of the population will still drive the incidence of dementia in Canada, which has been esimated to rise to nearly double current levels to over 250,000 new cases per year by 2038 (Alzheimer Society of Canada, 2008).

Beyond the tremendous societal impact, the impact of AD on those diagnosed, as well as their caregivers, is devastating. While improved symptom management is expected to increase survival among individuals with AD (Jacqmin-Gadda et al., 2013), life expectancy following symptom onset is shortened considerably. Most studies indicate a reduction in lifespan of between three and ten years (Zanetti, Solerte, & Contini, 2009), with evidence that mortality following a diagnosis may be hastened among individuals who are older at the time of diagnosis as well as among males (Todd et al., 2013). In addition to the years of life lost to AD, quality of life is substantially reduced. While some individuals are able to maintain a good quality of life, primarily in the early stages of the disease (Whitehouse, Patterson, & Sami, 2003), advanced AD is associated with a profound decrease in the quality of life among individuals with AD and their families (Logsdon, Gibbons, McCurry & Terry, 1999).

Unfortunately, treatments for AD are limited. Current pharmaceutical treatments serve only to temporarily slow symptom progression, but do not effectively treat the underlying disease (Sink, Holden, & Yaffe, 2005; Small et al., 1997). Canada, therefore, has both a social and economic incentive to invest in interventions that may prevent or delay the onset of AD.

2.1.2 Etiology

Although AD was first described in the early 20th century by Dr. Alois Alzheimer following the autopsy of a patient with memory impairments, a consensus etiologic theory has remained elusive. The first etiologic theory for the development of AD was the cholinergic hypothesis (Francis, Palmer, Snape, & Wilcock, 1999). This theory argues that AD symptoms

develop as a result of reduced acetylcholine signal transmission in the brain. This hypothesis was supported by findings that the brains of individuals with AD showed reduced acetylcholine activity compared to age-matched controls (Perry, Gibson, Blessed, Perry, & Tomlinson, 1977), as well as reduced acetylcholine reuptake (Rylett, Ball, & Colhoun, 1983) and release (Nilsson, Nordberg, Hardy, Wester, & Winblad, 1986). Despite more recent evidence indicating that deficits beyond the cholinergic system underlie the development of AD, the cholinergic hypothesis remains the basis for most common pharmaceuticals used in the treatment of AD.

More recent etiologic theories consider the influence of the hallmark pathologic signs of AD: neuritic plaque (NP) deposits and neurofibrillary tangles (NFT) (Carillo, Thies, & Bain, 2012). NPs are toxic deposits of beta-amyloid protein that occur outside of neurons (Hyman et al., 2012). According to the amyloid hypothesis, these plaques are thought to directly cause synaptic and neuronal damage resulting in a disruption of intercellular communication and are also linked to inflammation that may exacerbate neuronal damage. However, the amyloid hypothesis has several limitations. For example, the number of observed plaques does not strongly correlate with the degree of observed cell death or with the degree of cognitive impairment (Irizarry et al., 1997), and the removal of plaques from brain tissue does not improve clinical symptoms (Holmes et al., 2008). NFTs, the other hallmark Alzheimer neuropathology, are intracellular aggregates of the hyper-phosphorylated tau protein (Grundke-Iqbal et al., 1986), which may underlie the development of AD symptoms. The development of NFTs within neurons results in disruptions in the intracellular transport of molecules. This disruption in cell metabolism ultimately contributes to the loss of neuronal tissue, resulting in cortical atrophy and cognitive symptoms (Hyman et al., 2012). However, despite evidence suggesting that NFT density may better predict cognitive outcomes than NP density (Giannakopoulos et al., 2003), the

theory that tau pathology is the root of AD is limited by a lack of specificity to AD. Despite the limitations of NPs and NFTs as etiologic factors, both remain hallmark neuropathologic markers for AD.

While NPs and NFTs are well established indicators of AD, recent research has suggested that these pathologic changes may develop as a result of vascular damage (de la Torre, 2010). The vascular hypothesis asserts that cardiovascular pathology is the instigator of NP and NFT development (de la Torre, 2010). This hypothesis is supported by a growing body of evidence suggesting that cerebrovascular disease is present in a large number of individuals with AD (Breteler, 2000; Roher et al., 2011), and that comorbid vascular pathology may substantially increase the rate of decline (Snowdon et al., 1997; Mielke et al., 2007). Epidemiological findings that cardiovascular factors (e.g., hypertension, obesity) are strong risk factors for the development of AD (see section 2.1.2.2) further enhance the plausibility of an upstream vascular mechanism initiating AD development. While vascular factors remain important in the study of AD, substantially more evidence is needed to elucidate the precise role these factors play in precipitating symptom onset. While vascular research is ongoing, the presence of NFT and NP remain the most important markers of AD pathogenesis and form the basis of AD neuropathologic evaluation (see section 2.1.3).

2.1.3 Risk Factors for Alzheimer's Disease

Risk factors for AD can be broadly broken down into two types: modifiable and non-modifiable. Non-modifiable risk factors include factors such as age, genetics/family history, and sex. Modifiable risk factors include lifestyle factors, cardiovascular risk factors, educational attainment and occupation.

2.1.3.1 Non-modifiable risk factors

By far the most significant risk factor for dementia and AD is age. The risk of developing dementia grows exponentially with age, with prevalence rates doubling every five years between the ages of 65 and 90 (Jorm, Korten & Henderson, 1987). In fact, the prevalence of dementia reaches as high as 41 percent among centenarians (Carillo, Thies, & Bain, 2012). The strong relationship between increased age and the development of dementia may therefore suggest that dementia is the result of accumulated insults to the brain over time (von Strauss et al., 1999; Selkoe, 2000). The importance of this particular risk factor will continue to rise as the population ages (Alzheimer Society of Canada, 2008).

Genetics and family history represent another major non-modifiable risk factor for development of AD. AD can be classified as either a sporadic form or an autosomal dominant form (Bekris, Yu, Bird & Tsuang, 2010). In sporadic AD, the development of the disease has not been linked to a single causative gene. While several genes may play a role in the development of sporadic AD (see: Bird, 2008), most require further research to determine their true association with AD. Currently, only the apolipoprotein E gene (ε4 allele, *APOE*-ε4) has shown robust consistent associations with AD development (Coon et al., 2007; Schellenberg, 1995; Roses et al., 1995; Selkoe, 2001). While the ε4 allele has a frequency of 20% in the general population, in clinical AD samples as many as 60% of individuals possess this variant (Saunders et al., 1993). The odds of developing AD among Caucasian individuals with 1 or 2 ε4 alleles are 3.2 and 14 times higher respectively versus individuals with no ε4 alleles (Farrar et al., 1997). Although the exact mechanism through which *APOE*-ε4 contributes to AD is not well established, the ε4 allele increases Alzheimer neuropathology by promoting the development of beta-amyloid plaques, ε4-mediated phosphorylation of the tau protein, isoform-specific neural toxicity, and increased tangle formation (Bekris, Yu, Bird, & Tsuang, 2010). Although the

APOE-ε4 allele confers susceptibility to AD, it is not necessary nor sufficient for the development of symptoms. Previous findings have indicated that the presence of an *APOE*-ε4 allele is related to faster cognitive decline, particularly in more educated samples (Seeman et al., 2005). Further, as many as 50% of individuals with *APOE*-ε4 alleles live well into their nineties dementia free, while many individuals without the variant are diagnosed with sporadic AD (Bekris, Yu, Bird, & Tsuang, 2010). This suggests that *APOE*-ε4 may interact with a plethora of lifestyle and environmental factors to produce disease outcomes.

While the vast majority of AD cases are of the sporadic form (Bertram and Tanzi, 2004), three genes have been implicated in the development of autosomal dominant AD. Autosomal dominant AD is a subtype of AD directly linked to particular causal genes. These genes include Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) and amyloid precursor protein (APP) (Bekris, Yu, Bird, & Tsuang, 2010). While these genetic risk factors occur in several hundred families, only 1 percent of AD cases are autosomal dominant. The major distinguishing factor between sporadic and autosomal dominant forms of AD is the age of onset. Where sporadic AD symptoms tend to appear in later life, the first symptoms of autosomal dominant AD typically occur between the ages of 30 and 60 (Bateman et al., 2011).

Some evidence indicates that sex may be a risk factor for AD, as there are far more cases of AD among women than men (Janicki & Schupf, 2010). While this perceived gap between sexes has been explained in terms of its biological plausibility due to hormonal changes in women after menopause (Janicki & Schupf, 2010) and reductions in brain volume among women in late life (Carr, Goate, Phil, & Morris, 1997), it has also been suggested that this difference may be an artifact of women living longer lives and the strong association between age and AD (Dal Forno et al., 2002). In a recent meta-analysis of over 60 studies (including 14 that assessed

incidence rates), while women showed a slightly higher incidence rate of dementia, this was not statistically significant (Fiest et al., 2016). However, despite these non-significant findings, many studies continue to control for sex in their analyses.

2.1.3.2 Modifiable risk factors

While non-modifiable factors are important to the development of AD, a number of modifiable factors in early and mid-life also present significant risk for AD. More than one-third of AD cases can be attributed to modifiable lifestyle factors (Norton et al., 2014), including cardiovascular risk factors (Whitmer et al., 2003), cognitive inactivity (Flicker, 2010), education (Katzman, 1993), and socioeconomic status (SES) (Stern, 1994).

Cardiovascular risk factors such as tobacco use, alcohol consumption, high fat diet and physical inactivity are important to the development of AD. A meta-analysis of 19 studies including over 26 000 participants revealed that tobacco use increased the risk of dementia with tobacco users showing greater yearly declines in MMSE scores versus non-tobacco users (Anstey, von Sanden, Salim, & O'Kearney, 2007). Tobacco use has also been associated with greater NP pathology (Tyas et al., 2003). Norton et al (2014) estimate that 14% of the global AD prevalence is directly related to tobacco use.

Similarly, literature suggesting that physical activity is related to cognitive function and AD continues to grow (Flicker, 2010), with some evidence indicating regular physical activity could reverse symptoms among individuals with early memory complaints (Lautenschlager et al, 2008). It is estimated that as high as 13% of AD cases globally are linked to physical inactivity, with this number climbing to 21% of cases in the USA (Norton et al., 2014).

While some findings show an association between alcohol and AD, such that low levels (1 drink/day) of alcohol consumption are protective against the development of AD (Peters et al., 2008) with potentially deleterious effects at higher levels of intake, the true nature of these

effects is unclear (Panza et al., 2008). Findings on the relationship between alcohol and AD are inconsistent, potentially due to methodological limitations such as confounding by smoking status, selective mortality of heavy alcohol users, and misdiagnosis of alcoholic dementia versus AD (Tyas, 2001).

Dietary factors likely contribute to AD development through cardiovascular pathways. A developing body of literature has indicated a protective influence of the Mediterranean diet (Scarmeas et al., 2006), and decreased consumption of saturated fat (Gillette-Guyonette et al., 2007). However, these findings have tended to be inconsistent or unreplicated (Flicker, 2010).

Finally, medical cardiovascular risk factors from early- and mid-life, such as hypertension, Type 2 diabetes, and obesity, are examples of risk factors that may promote the development of AD through vascular mechanisms (Flicker, 2010). In a systematic review, hypertension in midlife was consistently associated with increased incidence of dementia and AD in late life (Kennelly, Lawlor & Kenny, 2009). This relationship was strengthened by findings indicating that pharmaceutical treatments for hypertension were effective in reducing incidence of dementia (Ligthart et al., 2010). Similarly, diabetes (Lu, Lin & Kuo, 2009) and obesity (Beydoun, Beydoun, & Wang, 2010) are established risk factors for AD that are believed to act through vascular mechanisms (Flicker, 2010). Norton et al. (2014) estimate that if hypertension, diabetes, and obesity were eliminated as risk factors, the global burden of AD would be reduced by 5.1%, 2.9% and 2%, respectively. Fortunately, recent evidence suggests there has been a marked improvement in the management of cardiovascular risk factors, and thus projected incidence rates may begin to decline (Satizabal, et al., 2016).

The most established non-genetic risk factor for AD is the level of educational attainment. Consistent findings have shown that lower levels of educational attainment are

related to higher rates of dementia and AD (Katzman, 1993; Stern, 1994; Fritsch et al., 2002; Tyas, Manfreda, Strain, & Montgomery, 2001). Furthermore, more recent work has found that in addition to low educational attainment, lower academic performance (measured through grades during school) has been associated with increased incidence of AD (Bezerra et al., 2012). Although the literature on these relationships continues to grow, the mechanism underlying the link between educational variables and AD development remains unclear. Some researchers theorize that the protective effect of education is achieved by promoting structural features of the brain that protect against cognitive decline, such as increased brain weight (Coffey et al., 1999), while other research has emphasized educational attainment's association with cognitive flexibility and improved processing that may provide resistance to brain pathology (see Stern, 2012). It has also been suggested that the link between educational success and AD may be confounded by innate intelligence/cognitive ability (Whalley, Dick & McNeill, 2006), such that individuals with better cognitive flexibility and higher functioning throughout the life-course experience increased educational success and reduced risk of dementia. While the mechanism remains unclear, the role of education in cognitive resilience will be discussed further in section 2.2.

Finally, AD incidence is modified by SES (Stern et al., 1994). While higher educational attainment and higher SES are correlated, and this may explain some of the association between SES and dementia (Qiu et al., 2003), SES is also independently predictive of AD with lower SES individuals showing higher levels of exposure to environmental contaminants (Santibanez, Bolumar, & Garcia, 2007), decreased cognitive stimulation at work (Andel et al., 2005), and reduced access to medical resources (Weissman, Stern, Fielding & Epstein, 1991), which limits access to treatment for various vascular AD risk factors such as high blood pressure and diabetes.

2.1.4 Alzheimer's Disease Diagnosis

The gold-standard diagnosis of AD is based on two sets of diagnostic criteria: clinical evaluation during life and neuropathologic assessment after death. Thus, any AD diagnosis given during life is presumptive until confirmed by congruent post-mortem evaluation. Clinical evaluations are used to identify the nature and severity of cognitive and behavioural changes associated with AD. Commonly used clinical criteria include that of the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 2011), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris, Heyman, Mohs & Hughes, 1989), and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, now in its fifth edition (DSM-V) (American Psychiatric Association, 2013). Neuropathologic evaluations are conducted through autopsy to identify physical signs of AD in brain tissues. Common examples of neuropathologic criteria are CERAD (Mirra, Heyman, McKeel, et al., 1991) and the National Institute of Aging and Reagan Institute (NIA-RI) criteria (Hyman et al., 2012). More recent neuropathologic criteria have aimed to assess preclinical evidence of AD in the brain (Jicha et al., 2012; Hyman et al., 2012).

2.1.4.1 Clinical Criteria for the Diagnosis of AD

Clinical assessments during life are used to identify cognitive deficits associated with AD as well as to identify the nature and extent of behavioural changes. While each criterion has unique characteristics, there are a number of common features. DSM-V, CERAD clinical criteria and NINCDS-ADRDA criteria each require a clinical interview including the individual's history of AD symptoms, a physical and neurological exam used to rule out alternative disorders, and a battery of tests assessing multiple domains of cognition.

The NINCDS-ADRDA clinical criterion results in one of three classifications: possible AD, probable AD and definite AD (McKhann et al., 1984; McKhann et al., 2011). Possible AD is used to describe individuals with atypical onset of symptoms, but where AD remains the most plausible explanation. Probable AD is characterized by typical onset of dementia symptoms with the exclusion of alternative explanations for the symptoms. Finally, a classification of definite AD is made when a probable AD label is confirmed by neuropathologic evaluations (McKhann, et al., 2011).

In the DSM-IV and DSM-V criteria, dementia (referred to as a neurocognitive disorder in the DSM-V) is defined by a decline in cognition resulting in the loss of independence (American Psychological Association, 2013). Similar to other clinical criteria, the DSM-IV stipulates that the dementia symptoms cannot be better explained by another disorder. To meet clinical criteria, the individual must show progressive decline in memory in addition to declines in at least one of the following cognitive domains: executive function, agnosia, apraxia, or aphasia (American Psychological Association, 2013).

Finally, the CERAD clinical criteria rely upon demographic, clinical, neurological, and neuropsychological information to confer a diagnosis of possible or probable AD. AD classification is clinically defined by cognitive impairment in any domain severe enough to impact activities of daily living (Morris et al., 1989). The CERAD clinical criteria measure language, memory, praxis and general intellectual status. CERAD neuropathologic measures will be discussed below.

2.1.3.2 Neuropathologic Criteria for the Diagnosis of AD

Similar to clinical assessments, there are a number of evaluative criteria to identify neuropathologic evidence of AD. While a number of non-AD pathological markers may be assessed at autopsy, such as Lewy bodies and vascular damage (Hyman et al., 2012), standard

neuropathologic features assessed in the diagnosis of AD include NFTs and NPs. Two of the major criteria used in the assessment of AD neuropathology, the CERAD neuropathologic criteria and NIA-RI criteria, are discussed.

The CERAD neuropathologic criteria assess NPs through three steps. Step one involves a count of NPs in areas of the neocortex with the highest plaque density. The plaques are then labelled "none", "sparse", "moderate", or "frequent". In step two, this information is integrated with a patient's age at death to derive an age-related plaque score. Finally, because AD diagnosis is based on the combination of both clinical and neuropathologic findings, step three combines plaque scores with results from the clinical battery to determine a diagnostic certainty of "definite AD", "probable AD" or "possible AD" (Mirra, Heyman, McKeel, et al., 1991).

While the CERAD criteria are effective at classifying AD likelihood based on NPs, it fails to consider NFT pathology and therefore does not assess the full spectrum of AD-related changes in the brain. To remedy this limitation, the NIA-RI criteria assess both NP and NFT pathology (NIA-RI Working Group, 1997; Hyman et al., 2012). NP pathology is assessed using a modified CERAD criteria into one of four categories: "no neuritic plaque", "CERAD sparse", "CERAD score moderate" and "CERAD score frequent". NFT severity is assessed through the use of a modified version of the Braak staging method (Braak and Braak, 1991). This method of assessing the severity of NFT pathology is based on observations finding that NFT pathology typically follows a predictable pattern of development. The pathology is graded on one of four levels: 1. no NFTs, 2. NFTs in the entorhinal cortex and related areas (indicative of early NFT development), 3. NFTs abundant in the hippocampus and amygdala and surrounding tissues (indicative of intermediate NFT development) and 4. NFTs distributed widely throughout the cortex (indicative of severe tangle pathology). The scores on NP and NFT pathology are then

combined and an individual is given an AD likelihood of "not", "low", "intermediate", or "high" (Hyman et al., 2012).

While the inclusion of both NP and NFT pathology in the NIA-RI criteria is a major strength, this also presents some challenges to researchers and clinicians. The NIA-RI criteria were developed based on the idea that NP and NFT pathology levels are highly correlated. While this tends to be true (Nelson, Kukull, & Frosch, 2010), in cases where the degree of NP and NFT pathology are incongruent, the subject is unclassifiable. This "unclassified" status may represent as many as 18% of individuals with AD, with most falling into one of two categories: "tangle intensive patients" (those with high NFT density but only moderate NP development) and "plaque intensive patients" (those with high NP density but only moderate NFT development) (Nelson, Kukull, & Frosch, 2010). Presently, no consensus has been reached on how to deal with unclassifiable subjects. This lack of consensus is problematic for both researchers and clinicians faced with making decisions regarding these individuals.

2.2 Cognitive Resilience

The evidence that neuropathology in the brain is related to cognitive function is exceptionally robust. However, the relationship between clinical disease symptoms and neuropathology varies considerably between individuals (SantaCruz et al., 2011). Many older adults have avoided reaching the threshold for clinical dementia, with some managing to avoid any cognitive changes, despite the presence of profound brain pathology (Stern, 2012). The hypothetical construct most commonly employed to explain this disparity between brain pathology and cognitive ability is the reserve hypothesis (Stern, 2012).

Reserve is broadly categorized into two major types: brain reserve and cognitive reserve. The brain reserve hypothesis (Katzman, 1993) considers certain physical features of the brain to be protective entities. This passive model asserts that quantitative structural features of the brain,

such as synaptic density and brain mass, allow an individual to overcome greater levels of brain pathology before reaching the threshold at which cognition begins to decline (Stern, 2012).

Active models of reserve, or cognitive reserve, are not based upon the structural components of the brain but instead emphasize the brain's ability to effectively recruit and utilize existing neuronal networks to maximize cognitive function and compensate for neuropathologic insults. Cognitive reserve is hypothesized by Stern (2002) to take two distinct forms: neural reserve and neural compensation (Stern, 2002).

Individuals with high neural reserve resist the impact of brain pathology as a result of highly efficient neural networks. Evidence has shown between-individual differences in regard to the amount of brain activation required to complete cognitive tasks. Individuals requiring less brain activation to meet a particular demand (i.e., those with more efficient neural networks) may display cognitive reserve as they are able to maintain function with a reduced amount of intact neuronal tissue (Stern, 2012).

Alternatively, neural compensation increases reserve capacity by successfully recruiting new neural networks to compensate for damage in other areas. If neuropathology damages an existing neuronal network, the brain with higher neural compensation can effectively recruit a new network to complete the required task (Stern, 2012). Neural compensation, therefore, equates to increased cognitive flexibility to overcome brain pathology.

The present study considered the impacts of educational attainment, brain weight and cortical atrophy, thus incorporating aspects of both cognitive reserve and brain reserve as defined by Stern (2012). Therefore, the term "cognitive resilience" will be used to capture the influences of both brain reserve and cognitive reserve when resisting the negative impacts of Alzheimer neuropathology.

2.2.1 Cognitive Resilience and Alzheimer's Disease

Perhaps the most studied impact of cognitive resilience is on the clinical expression of AD. Because brain reserve and cognitive reserve may modulate the expression of AD, it can be assumed that promoting the factors that increase cognitive resilience may aid in delaying—or preventing—the onset of AD symptoms. While some patients may experience complete cognitive resilience against AD, where their brains are able to overcome Alzheimer neuropathology to maintain intact cognition, the majority of patients who exhibit resilience show only partial cognitive resilience in that they do not reach the threshold for clinical dementia but may experience some sub-clinical deficits (Santa-Cruz et al., 2011). However, even this partial cognitive resilience may allow individuals to maintain their independence and quality of life (at least temporarily), as well as reducing the negative impacts of dementia on care partners and social systems.

While the underlying mechanism allowing cognitive resilience to confer resistance to AD is not well understood, a number of lifestyle and demographic factors from across the lifespan have been identified as contributors to cognitive resilience in older adulthood. Although lower SES often presents a major barrier to optimizing factors commonly associated with cognitive resilience (such as education and occupational attainment) due to reduced opportunity, given appropriate societal supports these factors are good targets for public health interventions aimed at increasing resilience and reducing the burden of AD decades later.

2.2.1.2 Early-Life Factors Contributing to Resilience Against Dementia

Unlike brain reserve, the emphasis of cognitive reserve is on the brain's processing systems rather than size and density of structures. It is therefore difficult to measure cognitive reserve directly (Jones et al., 2011). Instead, the study of cognitive reserve has largely been conducted by measuring exposure to factors believed to predict cognitive reserve. Factors

considered to be important to cognitive reserve are those linked to an increase in cognitive or intellectual engagement such as multilingualism (Bialystok et al., 2008; Bialystok et al., 2007; Chertkow et al., 2010; Yeung et al., 2014; Hack et al., 2012), written language skills (Riley et al., 2005; Tyas, Snowdon, Desrosiers, Riley, & Markesbery, 2009), education (Stern, 2012), occupation, and social engagement (Stern, 2006). These factors are theoretically linked to the development of complex and robust neural networks that are protective throughout older adulthood (Fillit et al., 2002). The following section addresses the factor most relevant to the current study: education.

2.2.1.3 Educational Factors and Cognitive Resilience

Educational attainment (most commonly measured in years of education or highest level of education achieved) is the most common factor linked to cognitive resilience, with a range of studies finding associations between education and cognitive status in older adulthood (Hall et al., 2007; Stern, 1994; Fritsch et al., 2002; Meng & D'Arcy, 2012). In a recent meta-analysis of 69 studies, low education was found to be linked to a substantial increase in the odds of dementia (pooled Odds Ratio (OR)=2.61, 95% Confidence Interval (CI): 2.10-3.07) (Meng & D'Arcy, 2012). While it is unclear exactly how education modifies the expression of dementia symptoms, three explanations are commonly proposed. First, education may lead to the development of more complex neuronal networks early in life that persist throughout the life-course. Second, education may lead to more cognitive stimulation throughout the life-course via occupational and recreational activities. Third, higher education reduces the risk of detrimental environmental exposures over the life-course (such as smoking, occupational hazards, etc.) (Mortimer & Graves, 1993).

In an effort to directly address the cognitive reserve theory, four studies assessed the role of education in predicting cognitive outcomes while controlling for proxies of brain pathology, using decreased blood flow to the parieto-temporal cortex (Stern et al., 1992; Liao et al., 2005), or decreased glucose metabolism in the parieto-temporal cortex (Garibotto et al., 2008; Kemppainen et al., 2008) to indicate greater brain damage. In all four of these studies, individuals with higher educational attainment showed similar scores on cognitive assessments compared to their less educated counterparts, despite showing vascular or metabolic differences reflecting significantly greater brain damage (Stern et al.,1992; Liao et al., 2005; Garibotto et al., 2008; Kemppainen et al., 2008). These findings provide support for the reserve hypothesis as they indicate that educated individuals are able to maintain their cognitive abilities despite more severe damage. A subsequent study assessed brain damage through the assessment of amyloid deposits in the precuneus region of the brain and compared neuropsychological performance among individuals with varying years of education (Rentz et al., 2010). This study had similar findings to previous work, indicating that while amyloid deposits were strongly related to decreases in cognitive performance, the impact was largely offset by increasing years of education (Rentz et al., 2010). While these findings show consistent links between education and the ability to resist the impacts of brain damage, all five studies were limited by emphasis on a single brain area and lack of gold-standard autopsy data to validate their assessments.

Hall et al. (2007) assessed education's role in cognitive reserve by examining how the development of cognitive deficits varied based on years of education. The results revealed that individuals experienced later onset of symptoms with each additional year of education. Furthermore, it was found that once the onset of symptoms began, individuals with higher education showed more rapid decline in their memory scores than those with less education (Hall

et al., 2007), providing conceptual support for cognitive reserve. While it is counter-intuitive that a protective exposure, such as higher education, would result in faster cognitive decline, educated participants maintain their cognition despite increased evidence of neuropathology. Therefore, when an educated individual's reserve capacity is exhausted and symptoms begin to appear, they are already at a more advanced stage of the disease and thus experience faster deterioration. Indeed, more recent findings have provided marginally significant support for this finding (Cadar, Stephan, Jagger, et al., 2015). Unfortunately, the Hall et al. (2007) study lacked neuropathological data to validate these findings and it is unknown how neuropathology and education interacted to produce cognitive outcomes within the sample.

Finally, educational attainment was tested as a predictor of cognitive reserve by comparing education and dementia status among individuals who posthumously showed neuropathology consistent with AD (Roe, Xiong, Miller & Morris, 2007). This study found that higher education was associated with decreased incidence of dementia in the last year of life, despite evidence of NFT and NP upon autopsy. This study provides robust evidence that education is related to cognitive reserve as it showed that despite the presence of Alzheimer pathology identified using gold-standard diagnostic protocols, educated participants were able to resist showing cognitive symptoms of AD.

While evidence suggests that educational attainment is consistently associated with cognitive reserve, there are a number of limitations to the literature in this field. Most previous findings were conducted on a population in which receiving higher education was less common (Sorlie et al., 1995). Educational attainment among these participants may have been reflective of factors such as SES or geographic location rather than a reflection of cognitive development

and innate intelligence (Stern, 2006). To address this gap in the literature, recent work has assessed the role of academic performance on outcomes of cognitive reserve.

Dekhtyar, Wang, Fratiglioni and Herlitz (2016) assessed rates of incident dementia rates among individuals aged 75+, comparing grades in school at age 9 and 10 and revealing a significant impact of early-life academic performance (based on school archives). Individuals scoring in the lowest quintile for academic performance showed a risk of incident dementia 1.54 times higher than the upper four quintiles. In 2009, a study was published by Mehta et al. to determine whether an individual's perceptions of their school performance were linked to late-life cognitive outcomes. The rates of incident dementia among those who rated their academic performance as "below average" "average" and "above average" were 26%, 12% and 11%, respectively (Mehta et al., 2009). It is important to note that this study is limited by the use of self-report for the measure of academic performance. A later study assessed the association between academic performance and dementia using objective measures of academic performance. This study assessed grades on Portuguese, mathematics and geography tests as indicators of academic performance (Bezerra et al., 2012). The study revealed that even after controlling for a range of lifestyle and socioeconomic factors, high academic performance was related to a decrease in incident dementia (Bezerra et al., 2012). In contrast to the previous work by Mehta et al. (2009) where no gradient between academic performance and dementia was observed, this study revealed some evidence of a gradient between school performance and decreased incidence of dementia. The study showed that each half-point increase in math or Portuguese resulted in decreased dementia risk (Bezerra et al., 2012). However, no such relationship was found for geography grades, indicating that increased abilities in math and language may be particularly protective against dementia.

All of the aforementioned articles considering the influence of academic performance on late-life cognitive outcomes have been limited by their measures of cognitive impairment, which were based on clinical measures and neuropsychological exams. Thus, because AD requires the presence of both clinical and neuropathologic criteria, these studies should not be used to draw conclusions regarding the link between academic performance and cognitive resilience against Alzheimer's disease. However, recent work in the Nun Study has provided some initial insight into this relationship using neuropathologically confirmed AD (Tyas et al., 2016). In this study, individuals with lower grades in high school algebra and English courses were more likely to be diagnosed with neuropathologically confirmed AD compared to those students with higher grades, even when controlling for educational attainment (Tyas et al., 2016). This finding provides initial validation of previous studies on academic performance and AD.

As previously stated, the mechanism underlying education's protective effect on late-life cognition is not well understood. It has been suggested that education may promote cognitive resilience through improved cognitive stimulation through the life-course into older adulthood. In an effort to assess the role of education across the life-course, a recent study assessed whether pursuing higher education in late life could improve cognitive outcomes (Lenehan, Summers, et al., 2016). This interventional study followed adults between 50 and 79 over four years comparing participants assigned to a minimum of 12 months of part-time university study to individuals with no later-life university study. This study found that individuals exposed to additional post-secondary university in the later years of life showed an increase in cognitive performance on neuropsychological testing (Lenehan, Summers, et al., 2016). This study did not assess whether this resulted in decreased rates of dementia and AD further into older adulthood.

Another educational variable that may be linked to cognitive resilience is the educational level of one's parents. While limited, evidence suggests that parental education, particularly maternal education, may be related to late-life cognitive outcomes. A nested case-control study examined the role that parental education played in the development of dementia (Rogers et al., 2009). The study revealed that after controlling for paternal education, individuals whose mothers had less than eight years of formal education were twice as likely to be diagnosed with cognitive impairment or dementia (Rogers et al., 2009).

The role of parental education theoretically could contribute to the promotion of cognitive resilience as highly educated parents may be better equipped to provide the type of stimulation during childhood that improves neuronal network complexity (Guo & Harris, 2000). This early exposure appears to set the framework for continued cognitive stimulation throughout the lifespan (Dollaghan et al., 1999; Flouri & Buchanan, 2004). Higher maternal education has also been found to be associated with larger birth weight, which is a strong predictor of fetal brain development (Shmueli & Cullen, 1999). Lower birth weight was associated with a decrease in gray matter volume in the frontal, temporal and occipital regions at birth (Kessler et al., 2004) that persists throughout the life-course (Walhovd et al., 2012). However, high concordance between parental education and an individual's educational attainment makes it difficult to detect an independent influence of paternal education on reserve outcomes (Rogers et al., 2009). Therefore, individual education and academic performance remain the most relevant educational variables linked to late-life cognitive outcomes.

2.2.2 Cognitive Resilience and Cortical Atrophy

While educational factors from early life are believed to promote cognitive resilience, one's level of resilience is not fixed over time (Stern, 2012). Rather, resilience is likely the

cumulative result of multiple exposures over the life-course. Thus, factors from late life remain critical in the expression of AD symptoms among older adults. One particularly important late-life factor that may be linked to cognitive resilience is cortical atrophy. Cortical atrophy is the loss of neuronal tissue in the cerebral cortex (Fox, Freebourough, & Rossor, 1996). Since NFT pathology is linked to the disruption of cell metabolism and ultimately to neuronal cell death (Hymen et al., 2012), there are causal mechanisms through which Alzheimer neuropathology can directly lead to cortical atrophy (DeCarli, Murphy, McIntosh, Teichberg, Schapiro, & Horwitz, 1995). However, atrophy can also impact individuals through various other disease mechanisms and through the aging process independent of Alzheimer neuropathology (Fox, Freebourough, & Rossor, 1996).

Atrophy may theoretically reduce cognitive resilience as a function of reduced brain reserve. According to brain reserve theory, an individual's level of cognitive resilience should be negatively impacted by cortical atrophy because of decreases in neuronal networks used to overcome Alzheimer neuropathology (Katzman, 1993). This assumption is supported by previous work suggesting that lower brain volume (Stern, 2012; Schofield, Logroscino, Andrews Albert, & Stern, 1997; Katzman et al., 1988) and smaller head circumference (Mortimer, Snowdon & Markesbery, 2003; Bickel et al., 2006; Kim et al. 2008) are associated with higher risk for dementia and AD.

While little research has assessed the impact of cerebral cortical atrophy within the context of cognitive resilience against AD, preliminary evidence suggests the presence of atrophy is strongly and negatively associated with levels of resilience (Tyas et al., 2008). These findings suggest that the presence of atrophy results in a four-fold decrease in the likelihood of

displaying cognitive resilience, with increased severity of atrophy resulting in a reduced likelihood of resilience (Tyas et al., 2008).

Findings providing additional support for the inverse association between cortical atrophy and cognitive resilience were reported in a study by Guo et al. (2013). In this study, cortical atrophy was associated with a reduction in reserve capacity as evidenced by a decrease in cognitive function (Guo et al., 2013). However, brain reserve theory was further supported by the study's finding that larger pre-morbid brain size (measured using intracranial volume as a proxy measure of brain size) was associated with increased reserve in the early stages of atrophy (Guo et al., 2013). An earlier study using head circumference as a proxy measure of premorbid brain size showed similar results (Perneczky et al., 2010). In this study, atrophy was once again strongly linked to cognitive deterioration. However, this relationship was stronger among individuals with smaller head circumferences (Perneczky et al., 2010). These findings indicate that the presence of atrophy is a substantial threat to cognitive resilience and that atrophy may have more severe consequences among individuals with smaller premorbid brains due to their limited initial brain reserve capacity. It is important to note that the protective effects of a large brain were, however, diminished in more advanced atrophy.

One major limitation to these findings was the limited availability of neuropathologic data. Both of these studies (Perneczky et al., 2010; Guo et al., 2013) assessed cortical atrophy as a proxy variable for AD-related neuropathology and did not possess data on the accumulation of hallmark Alzheimer neuropathology (NFTs and NPs). Therefore, the studies were primarily assessing reserve against atrophy itself, rather than reserve against Alzheimer neuropathology.

Addressing this issue, Negash et al. (2013) assessed a biochemical proxy measure for Alzheimer neuropathology (abnormal levels of total tau protein, phosphorylated tau protein and

beta amyloid plaque in cerebrospinal fluid) as well as using imaging to assess cortical atrophy. Similar to Guo et al. (2013), the study also assessed premorbid intracranial volume as a proxy for brain reserve (Negash et al., 2013). While exposure to increased cortical atrophy and amyloid beta plaques were both related to a decrease in cognitive resilience (i.e., led to dementia symptoms), the study also confirmed that higher intracranial volume promoted cognitive resilience (Negash et al., 2013). By including a molecular biochemical proxy measure of Alzheimer neuropathology in the analysis, this study provides a first step in understanding the interacting influences of Alzheimer neuropathology, cortical atrophy and resilience. However, the lack of gold-standard neuropathologic data remains a limitation to be addressed.

In addition to the growing literature on the influence of cortical atrophy on cognitive resilience in AD, research regarding the impact of cortical atrophy within related clinical populations has yielded similar results. In a study of individuals with multiple sclerosis, the degree of cognitive reserve (measured using IQ and level of education) modified the relationship between brain pathology and cognitive function allowing highly educated participants to offset the influence of atrophy (Amato et al., 2013). However, as the severity of atrophy increased, levels of cognitive resilience declined despite high levels of cognitive reserve (Amato et al., 2013).

Research assessing the effects of brain weight, cortical atrophy and educational attainment on cognitive resilience suggests a number of potential interactions. Aforementioned studies suggest that the influence of mild atrophy may be offset by higher pre-morbid brain weight due to higher baseline levels of resilience. Further, evidence suggests that while factors that promote cognitive reserve (such as education) can play a vital role in maintaining cognitive

ability, this impact may be contingent on the maintenance of brain reserve (e.g., avoiding cortical atrophy).

2.2.3 Summary

The concept of cognitive resilience provides a number of opportunities for public health interventions aimed at maintaining cognition broadly, and preventing AD specifically. However, most studies lack gold-standard neuropathologic data required to assess predictors of cognitive resilience. Therefore, further research is required to understand the mechanism through which the plethora of contributing factors may interact to promote positive outcomes. Future efforts aimed at better understanding how factors from across the lifespan interact to influence cognitive resilience could inform applications of cognitive resilience theory to clinical and community settings.

3. Study Rationale

The aims of the present study were to assess the influence of both cognitive reserve (through educational attainment) and brain reserve (through cortical atrophy and brain reserve) on cognitive outcomes in a sample of individuals with autopsy-confirmed neuropathologic evidence of AD. Further, this study assessed how brain reserve and cognitive reserve factors may interact to produce these cognitive outcomes.

The project was completed using data from a population-based cohort with annual clinical assessments as well as post-mortem neuropathologic assessments. The study also included information regarding the educational attainment of its participants as well as data regarding covariates such as *APOE*-ε4, occupation and country of origin. Further, all members of the study were women who had similar lifestyles including similar reproductive histories, access to medical resources, and levels of alcohol and tobacco use. This similarity in participant lifestyles reduces confounding and increases internal validity of the results.

Finally, cognitive resilience is a relatively new concept that has only recently begun to garner attention from the research community. Due to the emerging nature of this research field and the difficulties associated with assessing these outcomes, there are a number of gaps in the field of resilience against AD that the present study addresses, such as the interacting influence of brain reserve (through atrophy and brain weight) and cognitive reserve (through education), as well as including a neuropathologically-derived definition of cognitive resilience providing validation of previous findings.

3.1 Research Questions

1a. Is *educational attainment* related to cognitive resilience?

1b. Does this relationship persist when controlling for age and *APOE*-ε4 status?

2 a. Is the presence or severity of *cortical atrophy* related to cognitive resilience?

2b. Do these relationships persist when controlling for age and *APOE*-ε4 status?

3a. Is brain weight related to cognitive resilience?

3b. Does this relationship persist when controlling for age and *APOE*-ε4 status?

4. Is the effect of *the presence or severity of cortical atrophy* on cognitive resilience modified by *brain weight*?

5. Is the effect of *education* on cognitive resilience modified by *atrophy* or *brain weight*?

3.2 Hypotheses

Based on previous literature, it was hypothesized that:

1. Higher levels of educational attainment would be associated with cognitive resilience because of greater cognitive reserve.

2. Both the presence, and increasing severity, of cortical atrophy would be negatively associated with cognitive resilience because of a reduction in brain reserve.

3. Lower brain weight would be associated with decreased cognitive resilience as a result of a reduction in brain reserve.

4. When stratified by brain weight, individuals with larger brains would be better able to resist the deleterious effects of mild atrophy than those with lower brain weights because higher baseline brain reserve capacity would allow individuals with larger brains to compensate for reductions in brain reserve resulting from mild cortical atrophy.

5. The positive effects of educational attainment would be more strongly associated with cognitive resilience when brain weights were low or atrophy was present, as those with higher brain weights may have reached a ceiling effect for cognitive resilience, and thus the positive influence of education would not be required to maintain cognitive function.

4. Methods

4.1 Literature Search

A literature search on the relationship between educational factors and cognitive resilience was conducted in December 2014 using the PubMed Medline database. A full literature search template can be found in Appendix A. The literature search was restricted to peer reviewed articles written in English or French and included the search terms "educational attainment" or "years of education" or "education level" AND "cognitive reserve [MeSH]" OR "cognitive reserve [all fields]" or "cognitive resilience [all fields]" or "Alzheimer disease [MeSH]" or "Alzheimer's disease [all fields]" or "dementia" or "cognitive impairment[TIAB]" AND "Aged [MeSH]" or "older adult[TIAB]". The search returned 824 results before exclusions. Articles were excluded if: i) cognitive resilience was not the outcome of interest; ii) education was not the primary exposure assessed; iii) they did not use participants aged 65 or over; or iv) education was only incorporated into the analysis as part of a composite measure of SES. Subsequent searches were conducted in October 2015 and September 2016 to identify more recently published articles. After exclusion criteria were applied, no additional studies were retrieved in the October 2015 search. However, one review article was identified. The reference list of the review article was searched manually but did not yield any previously unidentified results. The September 2016 search yielded two additional articles.

A second literature search was conducted using the PsycINFO database in January 2015. A full literature search template can be found in Appendix A. This search used the index terms "education" or "academic achievement" and descriptor terms "educational attainment" or "education" or "level of education" in conjunction with the index term "Alzheimer's disease" and the descriptor terms "Alzheimer disease" or "dementia" or "cognitive impairment" or "cognitive reserve" or "cognitive resilience". This search was restricted to articles written in

English or French and using human participants. This search returned 34 articles and the same exclusion criteria were applied to searches in this database. Once again subsequent identical searches were conducted in October 2015 and September 2016. No additional articles were retrieved from either of these searches.

Overall, ten articles were retrieved from PubMed Medline and five articles were retrieved from PsycINFO. After duplicates were deleted, nine articles remained for full review. A summary of the nine reviewed articles can be found in Appendix B.

Following extraction of the relevant articles, reference lists were searched manually for relevant citations. While no additional articles were added to the formal literature search, several background articles were retrieved.

An additional review was conducted on the role of education in relation to Alzheimer's disease more broadly, using PubMed Medline and PsycINFO databases. This search was conducted using title and abstract searches for the search terms "educational attainment" or "years of education" as well as "dementia" or "Alzheimer* disease" using "all fields" searches. This review was used to provide information more generally on education's influences on late-life cognition, and was not intended to be comprehensive. Rather, this search was used to supplement the literature review to provide a framework for how education may be related to late-life cognition.

A subsequent review was conducted on the relationship between cortical atrophy and cognitive resilience. The literature search was conducted in November of 2015 using the PubMed Medline database. The literature search was restricted to peer reviewed articles written in English or French and included the search terms "cortical atrophy" or "brain atrophy [all fields]" or "Brain tissue loss [all fields]" and "cognitive reserve [MeSH]" or "cognitive reserve

[all fields]" and "Alzheimer's Disease" [MeSH]. This search returned 71 articles. Articles were excluded if i) cognitive resilience was not the outcome of interest; ii) atrophy was not the primary exposure assessed; iii) they did not use participants aged 65 or over. Following exclusions, five articles remained for full review. Summaries of the five articles can be found in Appendix B.

4.2 The Nun Study

The Nun Study is a longitudinal study of aging aimed at investigating risk factors and underlying mechanisms involved in the development of AD. The study originally began in 1986 as a pilot study of aging assessing members of the Minnesota-based School Sisters of Notre Dame. The study was expanded between 1991 and 1993 to include members of the School Sisters of Notre Dame religious congregation from other areas of the United States.

4.2.1 Sample

The Nun Study recruited members of the School Sisters of Notre Dame aged 75 years or older. Of the 1031 eligible members of the School Sisters of Notre Dame, 678 (66%) agreed to participate in all aspects of the study. This included consent to a review of medical and archival records, annual cognitive and physical assessments, and brain donation upon death (Snowdon et al., 1996). Participants and non-participants did not differ significantly by mean age, country of birth, annual mortality rate or race (Snowdon et al., 1996).

The Nun Study participants were exposed to similar lifestyle and environmental risk factors throughout their adult lives, which greatly minimizes common confounding variables that impact many epidemiological studies (Tyas et al., 2007). All participants had consistent social support, did not smoke or drink heavily, had equal access to medical resources and had the same marital and reproductive histories. Additionally, participants had similar occupations, with the

majority working as teachers and most of the remaining participants working as house sisters (with one sister who worked as a nurse's aide). The impact of occupation on analyses was likely modest because little variance in occupation existed and, in addition, would likely be of smaller magnitude than among the general population as economic outcomes were identical regardless of occupation. However, because those sisters with higher levels of education were more likely to be teachers than house sisters, occupational status may partially mediate the association between education and late-life cognition as an effect of cognitive stimulation over the life course.

4.2.2 Data Collection

Cognitive and physical assessment data were collected from Nun Study participants annually following study enrollment. Cognitive function was assessed using the CERAD battery of neuropsychological tests (including the Mini Mental State Exam (MMSE), Boston Naming, Word List Memory, Word List Recall, Word Recognition, constructional praxis and Verbal Fluency tests) (Morris et al., 1998) and standard Activities of Daily Living (ADL) measures. ADL measures (e.g., feeding and dressing) were assessed using performance measures (Kuriansky & Gurland, 1976), reducing biases associated with self-reported ADL measures (Riley et al., 2002; Tyas et al., 2007).

Nun Study neuropathologic evaluations of Alzheimer neuropathology, brain weight and cortical atrophy were conducted by a neuropathologist who was blinded to the cognitive status of participants (Riley et al., 2002). Brain areas were cut into sections that were 8 microns thick to quantify the plaques and tangles. The assessments of *APOE* genotypes were conducted on brain tissue for deceased participants and on buccal cells for living participants (Mortimer, Snowdon, & Markesbery, 2009). Laboratory methods were previously discussed in Saunders, Hullette et al.(1996).

Additional data were collected through archival records. Archival records included level of educational attainment, birth certificates, hand-written autobiographies, and high school transcripts (Patzwald & Wildt, 2004).

4.3 The Analytic Sample

Because the study required neuropathological data, the analytic sample was restricted to deceased participants with completed neuropathologic assessments. Participants were excluded from the analytic sample if they were missing data on educational attainment (n=0), age at death (n=0), *APOE*-ε4 status (n=8), brain weight (n=21), and cerebral cortical atrophy status (n=21) (see Figure 1). Finally, because the study assessed factors that predict the ability to overcome the deleterious effects of Alzheimer neuropathology, only participants showing evidence of Alzheimer neuropathology based on post-mortem evaluations were included in the analytic sample. This resulted in the further exclusion of living participants (n=72), individuals for whom an autopsy had not been completed (n=217), and individuals whose autopsies did not result in a classification of "probable AD" for the CERAD sample (n= 126) or a classification of "intermediate" or "high" likelihood of AD for the NIA-RI sample (n=179) . This left a total analytic sample of 213 for the CERAD sample and 160 for the NIA-RI sample. When non-response bias was assessed to determine the impact of the reduced sample size for the analytic sample, differences between groups were identified; however, these differences were predictable and were unlikely to influence the internal validity of the study. See Appendix C for further information regarding the assessment of non-response.

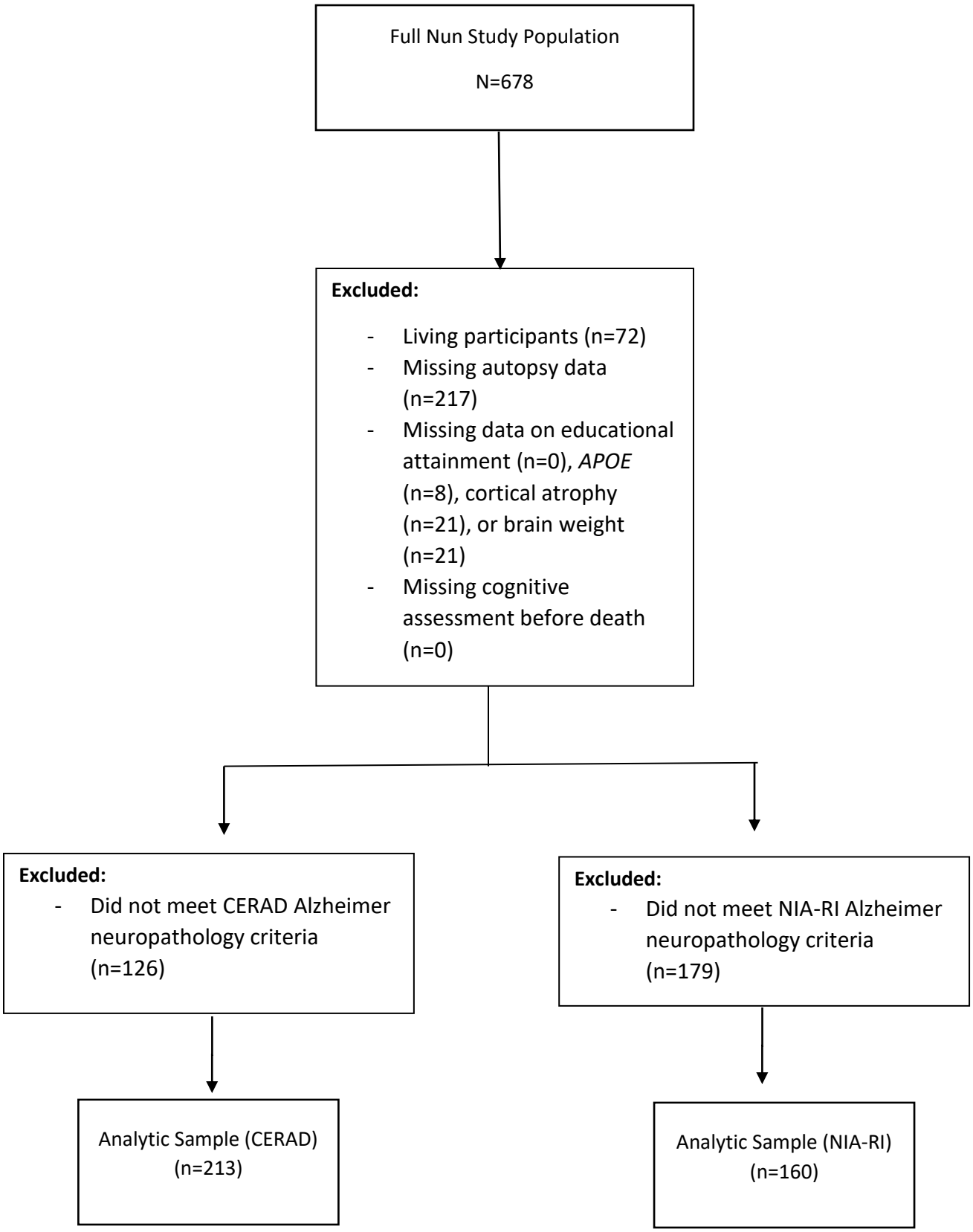

Figure 1. *Flowchart of analytic sample*

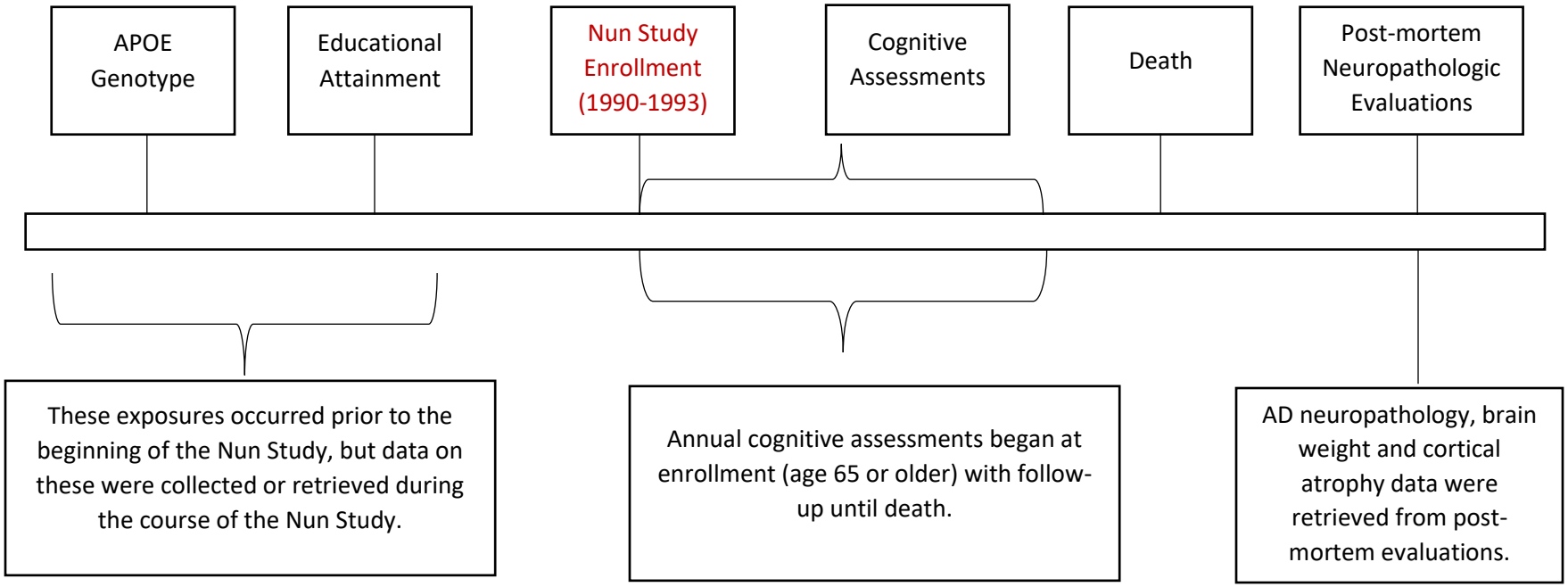

Figure 2. *Timeline of data collection*

4.4 Measures

4.4.1 Exposures

The exposure variable, educational attainment, was self-reported through a survey conducted in 1983 and was previously coded. Highest level of educational attainment was categorized as less than high school, high school, Bachelor's degree, and Master's degree or higher.

Cortical atrophy data were collected during neuropathologic evaluations, which were conducted by a single senior board-certified neuropathologist. These data were then coded for the presence and severity of atrophy. The coding for cortical atrophy presence was a simple yes or no response indicating if cortical atrophy was identified. A second set of analyses assessed the severity of atrophy by coding atrophy into four groups: no atrophy, mild atrophy, moderate atrophy or severe atrophy. The severity of atrophy was noted by brain regions, and for the purpose of the present study, the classification of severity was based on the most severely impacted brain region. Although the severity of atrophy was initially categorized into four categories with moderate and severe atrophy representing distinct groups, these groups were collapsed to provide sufficient sample sizes in this stratum.

Formalin-fixed brain weight, measured in grams, was collected during autopsy assessments. These data were not coded prior to the current study. Data were retrieved from autopsy narrative dictations and entered into a data base as a continuous measure based on weight in grams, which was later categorized into quartiles and tertiles.

4.4.2 Outcomes

The outcome of interest in the proposed investigation was the presence of cognitive resilience. Cognitive resilience was defined as avoiding dementia despite the presence of Alzheimer neuropathology. This outcome was operationalized as not reaching the threshold of

clinical dementia using DSM-IV criteria at the last assessment before death, despite neuropathologic assessments of "probable" AD on the CERAD neuropathologic criteria. (Those with a diagnosis of "definite" AD on the CERAD criteria could not, by definition, be included in this definition as they would have been diagnosed with clinical dementia) (Mirra, Heyman, McKeel, et al., 1991). Because evidence of "possible" AD equates to neuropathologic uncertainty underlying disease processes, and thus would result in a significantly increased risk of measurement error, "possible" AD cases were not included in the sample. The outcome of cognitive resilience was also assessed using NIA-RI neuropathologic criteria of "intermediate" or "high" likelihood of AD (Hyman et al., 2012).

4.4.3 Covariates

APOE-ε4 status was treated as a dichotomous variable: *APOE*-ε4 present (1 or 2 ε4 alleles) and *APOE*-ε4 absent (0 ε4 alleles). Age was restricted as a function of the study design as individuals under the age of 75 were excluded from the Nun Study sample. Additionally, multivariate regression models adjusted for the participant's age at death. As a function of the study population, gender was restricted to females only.

4.5. Analysis

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

4.5.1. Descriptive Analyses

Univariate and bivariate analyses were conducted to summarize and describe the analytic sample. Univariate analyses evaluated the central tendency and frequency distributions of individual variables in the project. Bivariate analyses, which included t-tests and chi-square tests, were performed to evaluate the relationship between pairs of variables in the project. The t-tests assessed the relationship between continuous and dichotomous variables. Chi-square tests

assessed the relationship between sets of categorical variables, with Fisher's exact test used when necessary due to low cell sizes in stratified samples in question 4.

4.5.2 Multivariable Analyses

Logistic regression analyses were used to assess the five research questions under investigation. Models were adjusted for *APOE*-ε4 and age at death. All first-order interactions between covariates and the exposure were assessed and when significant interactions were found, models were stratified. When models failed to run due to incomplete separation of data points, exact logistic regression models were run.

The Hosmer-Lemeshow goodness of fit test (LACKFIT command in PROC LOGISTIC) was used to determine if observed values matched those expected based on the model. Models that had a p-value of less than 0.05 on the Hosmer-Lemeshow goodness of fit test were determined to have poor fit and were investigated. All final models were additionally subjected to diagnostic testing, including assessment of values for C, CBAR, and DFBETA. DFBETA is the standardized difference in the parameter estimate when an observation is deleted from the model. C and CBAR values assess the displacement of the confidence interval after an observation is deleted. Observations with DFBETA, C, and CBAR values exceeding ±1.96 (p=0.05) were considered to be influential outliers. However, no significantly influential observations were identified in final models.

To identify issues with multicollinearity, variance inflation factors (VIF command in PROC REG) were assessed in all final models. Models with VIFs ≥ 10 were considered to be impacted by multicollinearity (Belsley, Kuh, & Welsch, 1980). No significant multicollinearity was identified in final models.

5.0 Results

5.1 Descriptive Analyses

A summary of the descriptive characteristics for the analytic sample by the outcome, cognitive resilience, defined using CERAD criteria (n=213) is found in Table 1a and using NIA-RI criteria (n=160) in Table 1b. In the CERAD analytic sample, the mean age at the time of death was 91.5 years and 39.9% of participants (n=85) were cognitively resilient prior to death. The NIA-RI sample, with a mean age of 91.7 years, showed lower rates of cognitive resilience, with only 28.8% of participants (n=46) displaying cognitive resilience.

Both samples were highly educated. Within the CERAD sample only 15.5% of participants were in the "low education" group receiving a high school diploma or less, 45.1% of participants were in the "moderate education" group receiving a Bachelor's degree, and 40.4% of participants were in the "high education" group receiving a Master's degree or higher. These numbers were similar in the NIA-RI sample where 15.6% of participants were in the low education group, 46.9% in the moderate education group and 37.5% of participants in the high education group.

In both the CERAD and NIA-RI samples, the majority of the participants did not possess any *APOE*-ε4 alleles. However, approximately three-quarters of the participants possessed some level of cortical atrophy, with approximately half of both samples showing mild atrophy.

Bivariate analyses were conducted between each variable and the outcome, cognitive resilience. Within both samples, chi-square tests revealed a significant positive association between higher educational attainment and cognitive resilience (CERAD: $p=0.036$, NIA-RI: $p=0.029$). Chi-square tests also revealed significant negative relationships between cognitive resilience and both the presence of atrophy ($p<0.001$) and the severity of atrophy ($p<0.001$) for both samples. Brain weights were, on average, significantly higher among those with cognitive

resilience than those without resilience (CERAD: 1139g vs 1068g, $p<0.001$; NIA-RI: 1138g vs. 1060g, $p<0.001$). When brain weight was categorized in tertiles, Pearson chi-square tests again showed a statistically significant association with cognitive resilience in both samples (CERAD: $p=0.001$; NIA-RI: $p<0.003$).

Marginally significant associations with cognitive resilience were found for *APOE*-ε4 status ($p=0.055$) and age at death ($p=0.077$) among the CERAD sample, with no significant associations identified in the NIA-RI sample (*APOE*-ε4: $p=0.47$; age at death: $p=0.11$).

Table 1a. Descriptive characteristics of the analytic sample by cognitive resilience status (CERAD criteria)

Characteristic	Cognitive Resilience (CERAD) Yes (n=85)	No (n=128)	Total (n=213)
Exposures			
Educational attainment*			
High school or less	7.1%	19.5%	15.5%
Bachelor's degree	47.1%	43.8%	45.1%
Master's degree or higher	45.9%	36.7%	40.4%
Brain weight (grams), mean (SD) **	1139 (96.04)	1068 (115.00)	1097 (113.11)
Brain weight (quartiles)**			
Tertile 1	20.0%	43.0%	33.8%
Tertile 2	38.8%	32.8%	35.2%
Tertile 3	41.2%	24.2%	31.0%
Presence of atrophy **			
No	37.7%	13.3%	23.0%
Yes	62.3%	86.7%	77.0%
Severity of atrophy**			
None	37.7%	13.3%	23.0%
Mild	52.9%	50.8%	51.6%
Moderate	8.2%	23.4%	17.4%
Severe	1.2%	12.5%	8.0%
Covariates			
Age at death in years, mean (SD)	90.80 (4.87)	92.05 (5.11)	91.55 (5.04)
APOE-ε4 status			
No ε4 alleles	76.5%	64.1%	69.0%
1+ ε4 alleles	23.5%	35.9%	31.0%

* significantly associated with cognitive resilience at $p<0.05$

** significantly associated with cognitive resilience at $p<0.01$

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

Table 1b. Descriptive characteristics of the analytic sample by cognitive resilience status (NIA-RI criteria)

Characteristic	Cognitive Resilience (NIA-RI) Yes (n=46)	No (n=114)	Total (n=160)
Exposures			
Educational attainment*			
High school or less	4.4%	20.2%	15.6%
Bachelor's degree	47.8%	46.5%	46.9%
Master's degree or higher	45.8%	33.3%	37.5%
Brain weight in grams, mean (SD) **	1138 (92.98)	1060 (116.50)	1083 (115.54)
Brain weight quartile**			
Tertile 1	15.2%	41.2%	33.8%
Tertile 2	39.1%	30.7%	33.1%
Tertile 3	45.7%	28.1%	33.1%
Presence of atrophy **			
No	41.3%	14.1%	22.5%
Yes	58.7%	85.1%	77.5%
Severity of atrophy**			
None	41.3%	14.9%	22.5%
Mild	52.2%	44.7%	46.9%
Moderate	6.5%	26.3%	20.6%
Severe	0.0%	14.0%	10.0%
Covariates			
Age at death in years, mean (SD)	90.76 (4.19)	92.06 (4.81)	91.69 (4.67)
APOE-ε4 status			
No ε4 alleles	67.4%	61.4%	63.1%
1+ ε4 alleles	32.6%	38.6%	36.9%

* significantly associated with cognitive resilience at the $p<0.05$ level

** significantly associated with cognitive resilience at the $p<0.01$ level

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

5.2 Question 1: The influence of educational attainment on cognitive resilience

Table 2 presents the results of the logistic regression analyses assessing the association between educational attainment and cognitive resilience for both the CERAD and NIA-RI samples. Within the CERAD sample, logistic regression analyses revealed that individuals with low education (high school or less) were significantly less likely to be cognitively resilient compared to those with high education (Master's degree or higher) in unadjusted models (OR=0.29, 95% CI=0.10-0.74). This relationship remained significant after adjusting for covariates age at death and *APOE*-ε4 (OR=0.30, 95% CI=0.10-0.81). There was no statistically significant impact of moderate education (Bachelor's degree) versus high education in unadjusted or adjusted models.

Logistic regression analyses revealed significant effects of education on cognitive resilience in the NIA-RI sample. Low (versus high education) was significantly associated with cognitive resilience in unadjusted (OR=0.15, 95% CI=0.02-0.57) and adjusted models (OR=0.16, 95% CI=0.02-0.65). No statistically significant differences existed between moderate and high education on the outcome of cognitive resilience, nor was there a relationship between age at death and cognitive resilience. The effect of *APOE-ε4* on cognitive resilience also fell below significance in the adjusted model, likely as a result of reduced power.

Table 2. The association between level of education and cognitive resilience

Variables	CERAD Criteria (n=213)		NIA-RI Criteria (n=160)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposure				
Education (vs. ≥ Master's degree)				
≤ High school	**0.29 (0.10-0.74)**	**0.30 (0.10-0.81)**	**0.15 (0.02-0.57)**	**0.16 (0.02-0.65)**
Bachelor's degree	0.86 (0.48-1.55)	0.96 (0.51-1.79)	0.72 (0.35-1.48)	0.78 (0.36-1.69)
Covariates				
Age at death	-	0.95 (0.89-1.01)	-	0.96 (0.88-1.04)
1+ *APOE*-ε4 allele	-	**0.46 (0.24-0.86)**	-	0.62 (0.29-1.31)

Abbreviations: APOE-ε4 = apolipoprotein E- ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

5.3 Question 2: The influence of cortical atrophy on cognitive resilience

Table 3 presents the results of the logistic regression analyses for the association between the presence of cortical atrophy and cognitive resilience for both the CERAD and NIA-RI samples. In these models, the presence of atrophy was consistently negatively associated with cognitive resilience in both unadjusted (OR=0.25, 95% CI=0.13-0.49) and adjusted (OR=0.28, 95% CI=0.14-0.54) models for the CERAD sample. Similarly, in the NIA-RI sample, the presence of atrophy was negatively associated with cognitive resilience in both unadjusted (OR=0.25, 95% CI=0.11-0.54) and adjusted models (OR=0.24, 95% CI=0.10-0.53).

Table 4a presents the results of logistic regression analyses for the association between the severity of cortical atrophy and cognitive resilience in the CERAD sample. In unadjusted models, compared to those with no atrophy, both mild atrophy (OR= 0.36, 95% CI=0.18-0.73) and moderate to severe atrophy (OR= 0.09, 95% CI=0.03-0.23) were significantly negatively associated with cognitive resilience.

Because model diagnostics identified a significant interaction between the severity of atrophy and *APOE*-ε4 status, adjusted models are presented stratified by *APOE*-ε4 status. When adjusted for age at death and stratified by *APOE*-ε4, mild atrophy was significantly negatively associated with cognitive resilience only among *APOE*-ε4 carriers (OR=0.14, 95% CI=0.02-0.71). Among non-carriers, this association fell short of significance (OR=0.51, 95% CI=0.23-1.11). Moderate/severe atrophy was significantly negatively associated with cognitive resilience regardless of *APOE*-ε4 status.

In the NIA-RI sample, both mild and moderate to severe atrophy were strongly associated with cognitive resilience in both unadjusted and adjusted models (Table 4b).

Table 3. The association between the presence of cortical atrophy and cognitive resilience

Variables	CERAD Criteria (n=213)		NIA-RI Criteria (n=160)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposure				
Presence of atrophy (vs. 'No atrophy')				
Atrophy present	**0.25 (0.13-0.49)**	**0.28 (0.14-0.54)**	**0.25 (0.11-0.54)**	**0.24 (0.10-0.53)**
Covariates				
Age at death	-	0.95 (0.89-1.01)	-	0.92 (0.85-1.00)
1+ *APOE*-ε4 allele	-	0.56 (0.29-1.07)	-	0.89 (0.40-1.94)

Abbreviations: APOE-ε4 = apolipoprotein E- ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 4a. The association between severity of cortical atrophy and cognitive resilience, using CERAD criteria

Variables	CERAD Criteria (n=213)		
		Adjusted	
	Unadjusted OR (95% CI)	APOE-ε4 Non-carrier OR (95% CI)	APOE-ε4 Carrier OR (95% CI)
Exposures			
Severity of atrophy (vs. 'No atrophy')			
Mild atrophy	**0.36 (0.18-0.73)**	0.51 (0.23-1.11)	**0.14 (0.02-0.71)**
Moderate/severe atrophy	**0.09 (0.03-0.23)**	**0.19 (0.06-0.54)**	**0.01 (<0.01-0.08)**
Covariates			
Age at death	-	0.95 (0.89-1.02)	0.87 (0.73-1.02)

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 4b. The association between severity of cortical atrophy and cognitive resilience, using NIA-RI criteria

Variables	NIA-RI Criteria (n=160)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**
Exposure		
Severity of atrophy (vs. 'No atrophy')		
Mild atrophy	**0.42 (0.18-0.95)**	**0.40 (0.17-0.93)**
Moderate/severe atrophy	**0.06 (0.01-0.20)**	**0.04 (0.01-0.16)**
Covariates		
Age at death	-	**0.89 (0.80-0.98)**
1+ *APOE*-ε4 allele	-	1.03 (0.45-2.35)

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

5.4 Question 3: The influence of brain weight on cognitive resilience

Tests of the association between brain weight and cognitive resilience are presented with brain weight assessed as a continuous variable in Table 5 and in tertiles in Tables 6 and 7. When considered as a continuous variable, individuals with higher brain weight (measured in grams) were significantly more likely to be cognitively resilient in both adjusted and unadjusted models. This finding was consistent for both the CERAD and NIA-RI samples.

When brain weight was categorized into tertiles, compared to the highest tertile, individuals in the lowest brain weight tertile were significantly less likely to be cognitively resilient in both unadjusted and adjusted models for both NIA-RI and CERAD samples. No significant association was found between brain weight tertile 2 (versus tertile 3) and cognitive resilience for either sample (CERAD: adjusted OR=0.72, 95% CI=0.37-1.42; NIA-RI: adjusted OR=0.83, 95% CI=0.37-1.72), suggesting that much of the association between brain weight and cognitive resilience was driven by reduced odds of resilience among those with lower brain weight rather than higher odds of resilience in the top tertile. Therefore, to improve statistical power, analyses were also completed comparing low brain weight (lowest brain weight tertile) versus higher brain weight (the upper two tertiles). Results of these analyses are summarized in Table 7. Consistent with previous results, individuals with low brain weight were significantly less likely to be cognitively resilient in both unadjusted and adjusted models among both CERAD (adjusted OR=0.21, 95% CI=0.09-0.45) and NIA-RI (adjusted OR=0.07, 95% CI=0.01-0.24) samples.

Table 5. The association between brain weight as a continuous variable and cognitive resilience

Variables	CERAD Criteria (n=213)		NIA-RI Criteria (n=160)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposure				
Brain weight (in grams)	**1.006 (1.004-1.009)**	**1.006 (1.004-1.009)**	**1.007 (1.003-1.01)**	**1.007 (1.003-1.01)**
Covariates				
Age at death	-	0.94 (0.89-1.01)	-	0.92 (0.84-1.00)
1+ *APOE*-ε4 allele	-	**0.52 (0.26-0.99)**	-	0.76 (0.34-1.64)

Abbreviations: APOE-ε4 = apolipoprotein E- ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 6. The association between brain weight tertile and cognitive resilience

Variables	CERAD Criteria (n=213)		NIA-RI Criteria (n=160)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposures				
Brain Weight Tertile (vs. Tertile 3)				
Tertile 1	**0.27 (0.13-0.56)**	**0.28 (0.13-0.59)**	**0.23 (0.08-0.57)**	**0.22 (0.08-0.56)**
Tertile 2	0.70 (0.36-1.35)	0.72 (0.37-1.42)	0.78 (0.35-1.73)	0.83 (0.37-1.72)
Covariates				
Age at death	-	**0.94 (0.87-0.99)**	-	**0.92 (0.84-0.99)**
1+ *APOE*-ε4 allele	-	**0.51 (0.26-0.96)**	-	0.80 (0.37-1.72)

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 7. The association between low brain weight and cognitive resilience

Variables	CERAD Criteria (n=213)		NIA-RI Criteria (n=160)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposure				
Low Brain Weight (tertile 1 vs. 2 and 3)				
Low brain weight	**0.23 (0.10-0.47)**	**0.21 (0.09-0.45)**	**0.09 (0.01-0.31)**	**0.07 (0.01-0.24)**
Covariates				
Age at death	-	**0.93 (0.87-0.99)**	-	**0.90 (0.81-0.98)**
1+ *APOE*-ε4 allele	-	**0.50 (0.26-0.96)**	-	0.63 (0.28-1.37)

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

5.5 Question 4: The influence of cortical atrophy on cognitive resilience, stratified by brain weight

5.5.1 The influence of the presence of atrophy on cognitive resilience, stratified by brain weight

To assess the *a priori* hypothesis that the effects of cortical atrophy would be modified by brain weight, models were developed including the interaction term presence of cortical atrophy by brain weight [higher brain weight (upper two tertiles) versus low brain weight (lowest tertile)]. While the interaction between cortical atrophy and brain weight fell short of significance in models predicting cognitive resilience (CERAD: p=0.39; NIA-RI: p=0.41), to fully explore potential effect modification by brain weight, subsequent analyses were conducted on models stratified into low and higher brain weight groups. The results of these analyses are summarized in Table 8a for the CERAD sample and Table 8b for the NIA-RI sample.

Within the CERAD sample, low brain weight and the presence of atrophy were significantly negatively associated with cognitive resilience in both unadjusted and adjusted models. When these models were stratified, the presence of atrophy only remained significantly negatively associated with cognitive resilience when brain weights were higher (OR= 0.27, 95% CI= 0.12-0.60). When brain weights were low, this effect did not reach statistical significance (OR=0.75, 95% CI=0.14-5.72).

While the non-significant finding among those with lower brain weights may in part be due to low power in the models, bivariate analyses were used to investigate this relationship further. Among participants with higher brain weights, cognitive resilience was present in 71.4% of those without cortical atrophy and only 38.4% of individuals with cortical atrophy ($p<0.01$) (see Fig. 3). These data suggest that when brain weights are high, the influence of atrophy is substantial. Conversely, among those with low brain weights, 28.5% of individuals without atrophy were resilient versus 23.1% of individuals with atrophy (p=0.53). This suggests that

when brain weight is low, the odds of cognitive resilience are reduced regardless of atrophy status.

Within the NIA-RI sample, low brain weight and the presence of atrophy were significantly negatively associated with cognitive resilience in both adjusted and unadjusted models. In stratified models, the presence of atrophy remained significantly associated with cognitive resilience when brain weights were in the upper two tertiles only (OR=0.26, 95% CI= 0.10-0.64), with models in the lower strata failing to run.

Similar to the CERAD sample, bivariate analyses were used to investigate the stratified relationships further. Among participants with higher brain weights, cognitive resilience was present in 59.3% of those without cortical atrophy and only 27.2% of individuals with cortical atrophy ($p<0.01$) (see Fig. 4). However, within the low brain weight stratum (n=54), only seven individuals were cognitively resilient, none of whom were in the "no atrophy" group. Thus, logistic regression analyses failed to run due to complete separation of data points, and this issue persisted when using exact logistic regression models. When bivariate analyses were conducted to test for an association between atrophy and cognitive resilience in this sample, no statistically significant relationship was revealed using Fisher's exact test ($p=0.56$) in this stratum, likely due to the low number of participants with low brain weight who did not have atrophy (n=4).

Table 8a. The effects of brain weight on the association between the presence of atrophy and cognitive resilience (CERAD criteria)

Variables	CERAD Criteria (n=213) Unstratified OR (95% CI)	Unstratified, Adjusted OR (95% CI)	Adjusted, Stratified Low Brain Weight OR (95% CI) (n=72)	Adjusted, Stratified Higher Brain Weight OR (95% CI) (n=141)
Exposures				
Low brain weight (tertile 1 vs tertiles 2 and 3)	**0.41 (0.21-0.78)**	**0.41 (0.21-0.78)**	--	--
Presence of atrophy	**0.30 (0.15-0.60)**	**0.33 (0.16-0.66)**	0.75 (0.14-5.72)	**0.27 (0.12-0.60)**
Covariates				
Age at death	-	0.95 (0.89-1.01)	0.94 (0.83-1.05)	0.95 (0.88-1.02)
APOE-ε4 status	-	0. 56 (0.29-1.09)	0.67 (0.18-2.18)	0.51 (0.23-1.13)

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; OR = Odds ratio

Note: Bold font represents statistically significant result

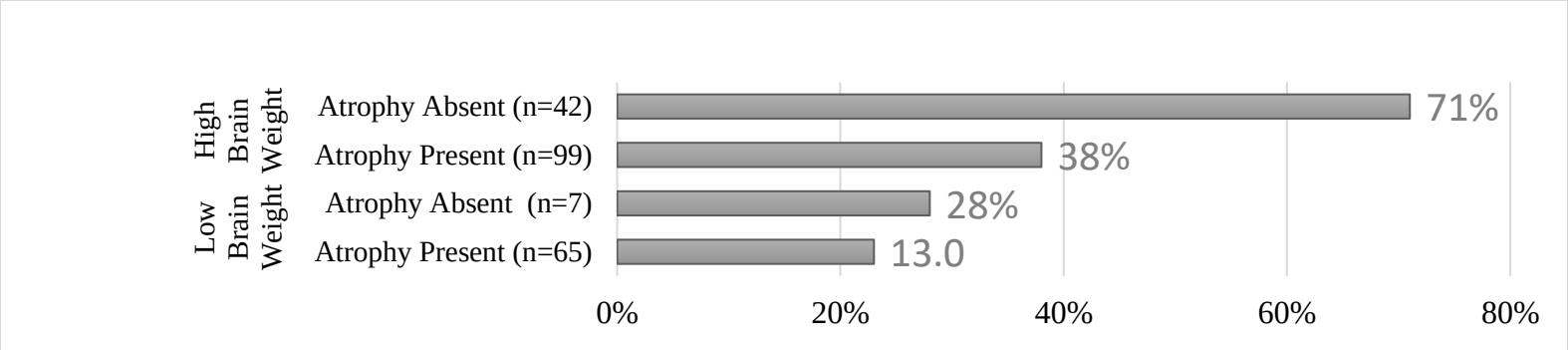

Figure 3. *The percentage of participants who were cognitively resilient by brain weight and atrophy status in the CERAD sample*

Table 8b. The effect of brain weight on the association between the presence of atrophy and cognitive resilience (NIA-RI criteria)

Variables	NIA Criteria (n=160)			
	Unstratified OR (95% CI)	**Unstratified, Adjusted OR (95% CI)**	**Adjusted, Stratified low brain weight OR (95% CI) (n=54)**	**Adjusted, Stratified higher brain weight OR (95% CI) (n=106)**
Exposures				
Low brain weight (tertile 1 vs 2 and 3)	**0.33 (0.14-0.71)**	**0.30 (0.11-0.73)**	--	--
Presence of Atrophy	**0.32 (0.12-0.79)**	**0.30 (0.13-0.69)**	##	**0.26 (0.10-0.64)**
Covariates				
Age at death	-	**0.91 (0.83-0.99)**	##	**0.90 (0.80-0.99)**
APOE-ε4 status	-	0. 97 (0.43-2.15)	##	0.53 (0.19-1.37)

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

= model unable to run due to quasi complete separation of data points

Note: Bold font represents statistically significant result

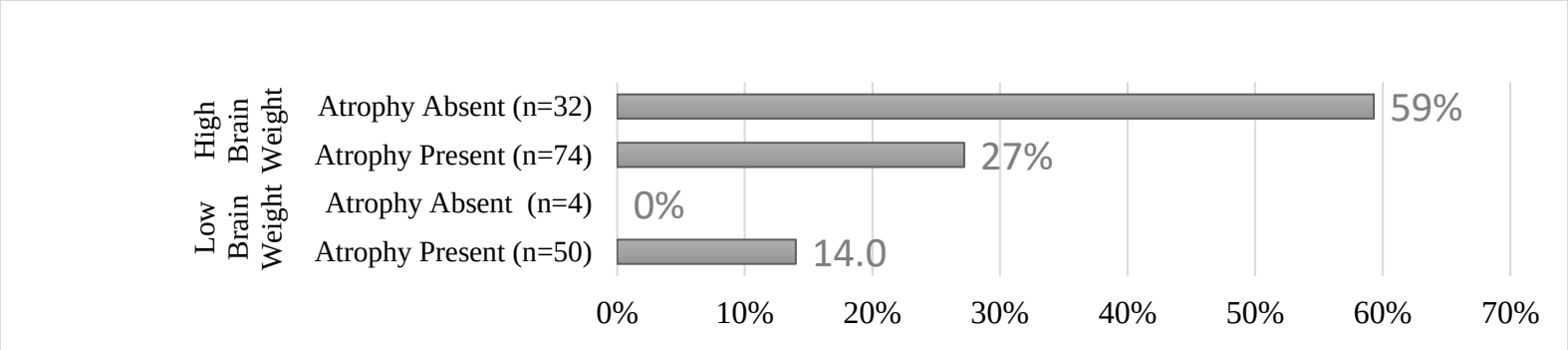

Figure 4. The percentage of participants who were cognitively resilient by brain weight and atrophy status in the NIA-RI sample

5.5.2 The influence of the severity of atrophy on cognitive resilience, stratified by brain weight

The results of multivariate analyses assessing the impact of brain weight on the relationship between the *severity* of atrophy and cognitive resilience are summarized in Table 9a for the CERAD sample and Table 9b for the NIA-RI sample. Within the CERAD sample in unstratified models, low brain weight, mild atrophy (vs. no atrophy) and moderate to severe atrophy (vs. no atrophy) were all significantly negatively associated with cognitive resilience in both unadjusted and adjusted models.

When brain weights were high, individuals with either mild or moderate to severe cortical atrophy (versus no atrophy) were significantly less likely to display cognitive resilience (Table 9a). Among individuals with low brain weights, no significant associations were found. However, this non-significant finding for the effect of severe atrophy may be related to low power in the models, as confidence intervals were wide (mild atrophy vs no atrophy: OR=1.33, 95% CI=0.24-10.50; moderate/severe atrophy vs no atrophy: OR=0.26, 95% CI=0.03-2.41).

In the NIA-RI sample, when brain weight and the severity of atrophy were considered together in models, moderate to severe cortical atrophy remained significantly negatively associated with cognitive resilience in both unadjusted (OR=0.08, 95% CI=0.02-0.28) and adjusted models (OR=0.14, 95% CI= 0.06-0.22) (Table 9b). However, the effects of mild atrophy on cognitive resilience fell short of statistical significance in both the unadjusted and adjusted models, as did the effect of low brain weight, although this may be the result of low statistical power.

When NIA-RI models were stratified by brain weight, both mild and moderate/severe cortical atrophy were significantly negatively associated with cognitive resilience among the higher brain weight tertiles. Within the lowest brain weight tertile, logistic regression models did

not run due to small cell sizes, and this issue persisted when using exact logistic regression. While this was an issue for model convergence, it likely reflects the strength of the relationship between brain weight and cognitive resilience as so few individuals with low brain weight were able to display cognitive resilience. In an effort to understand the effects within brain weight strata, bivariate analyses were conducted. Within the low brain weight tertile, Fisher's exact tests revealed that there was a significant increase in the chances of cognitive resilience among individuals with mild atrophy (where 27% of individuals displayed cognitive resilience) versus those with moderate to severe atrophy (where only 3.6% showed cognitive resilience) ($p=0.046$).

Table 9a. The impact of brain weight on the association between the severity of atrophy and cognitive resilience (CERAD criteria)

Variables	CERAD Criteria (n=213) Unstratified OR (95% CI)	Unstratified, Adjusted OR (95% CI)	Adjusted, Stratified Low Brain Weight OR (95% CI) (n=72)	Adjusted, Stratified Higher Brain Weight OR (9B5% CI) (n=141)
Exposures				
Lower brain weight (tertile 1 vs tertiles 2 and 3)	**0.49 (0.25-0.96)**	**0.49 (0.24-0.97)**	--	--
Severity of Atrophy (vs. none)				
Mild	**0.41 (0.20-0.82)**	**0.44 (0.21-0.89)**	1.33 (0.24-10.50)	**0.33 (0.14-0.74)**
Moderate	**0.12 (0.04-0.31)**	**0.14 (0.05-0.34)**	0.26 (0.03-2.41)	**0.13 (0.03-0.40)**
Covariates				
Age at death	-	0.94 (0.88-1.00)	0.94 (0.82-1.05)	0.95 (0.88-1.02)
APOE-ε4 status	-	0. 62 (0.31-1.23)	0.75 (0.20-2.54)	0.57 (0.25-1.26)

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 9b. The impact of brain weight on the association between the severity of atrophy on cognitive resilience (NIA-RI criteria)

Variables	NIA-RI Criteria (n=160) Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted, Stratified Low Brain Weight OR (95% CI) (n=54)	Adjusted, Stratified Higher Brain Weight OR (95% CI) (n=106)
Exposures				
Lower brain weight (tertile 1 vs tertiles 2 and 3)	0.44 (0.16-1.09)	0.39 (0.14-1.03)		--
Severity of Atrophy (vs. None)				
Mild	0.48 (0.21-1.09)	0.45 (0.19-1.07)	##	**0.33 (0.14-0.74)**
Moderate	**0.08 (0.02-0.28)**	**0.14 (0.06-0.22)**	##	**0.13 (0.03-0.40)**
Covariates				
Age at death	-	**0.88 (0.80-0.97)**	##	0.95 (0.88-1.02)
APOE-ε4 status	-	1.15 (0.49-2.69)	##	0.57 (0.25-1.26)

= model unable to run due to quasi- complete separation of data points

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

5.6.1 Question 5A: The effect of brain weight on the association between education and cognitive resilience

To assess if the effects of education on cognitive resilience were modified by brain weight, logistic regression analyses were conducted assessing education in a model either adjusted for or stratified by brain weight. Summaries of these results are presented in Table 10a (CERAD sample) and Table 10b (NIA-RI sample).

Within the CERAD sample, individuals with moderate educational attainment were not significantly less likely to display cognitive resilience in either unadjusted or adjusted models than those with high educational attainment, nor were individuals with low versus high educational attainment. However, the effect of low educational attainment approached a significant negative association with cognitive resilience in both unadjusted (OR=0.39, 95% CI=0.13-1.03) and adjusted (OR=0.42, 95% CI=0.13-1.16) models. When stratified by brain weight, no significant impacts of educational attainment were identified in either the high brain weight or low brain weight strata. However, the effects of low educational attainment (versus high educational attainment) approached significance among those with higher brain weights (OR=0.33, 95% CI=0.07-1.29).

Within the NIA-RI sample, in unadjusted models the effect of low versus high education was significantly negatively associated with cognitive resilience (OR=0.20, 95% CI= 0.03-0.78) (Table 10b). After adjusting for covariates, the effect of low versus high education remained marginally significant (OR=0.23, 95% CI=0.03-1.00). Within the upper two brain weight tertiles, the impact of education on cognitive resilience was not statistically significant. In the lowest tertile of brain weight, models assessing the impact of education on cognitive resilience failed to run due to complete separation of data points. While this does reflect low sample size in this stratum (n=54), it is also related to the strength of the association between education and

cognitive resilience in this sample as zero participants with low educational attainment achieved cognitive resilience, while 15% of those with moderate educational attainment and 22% of those with high educational attainment displayed cognitive resilience. Although no significant association was found between educational attainment and cognitive resilience using Fisher's exact test ($p=0.15$), the relationship between educational attainment and cognitive resilience ran in the expected direction.

Table 10a. The impact of brain weight on the association between education and cognitive resilience (CERAD criteria)

Variables	CERAD Criteria (n=213) Unstratified OR (95% CI)	Unstratified, Adjusted OR (95% CI)	Adjusted, Stratified Low Brain Weight OR (95% CI) (n=72)	Adjusted, Stratified Higher Brain Weight OR (95% CI) (n=141)
Exposures				
Lower brain weight (tertile 1 vs tertiles 2 and 3)	**0.38 (0.19-0.72)**	**0.38 (0.19-0.73)**		--
Level of Education (vs ≥ Master's degree)				
≤ High school	0.39 (0.13-1.03)	0.42 (0.13-1.16)	0.53 (0.09-2.64)	0.33 (0.07-1.29)
Bachelor's degree	0.91 (0.50-1.66)	1.04 (0.55-1.98)	0.90 (0.26-3.28)	1.14 (0.54-2.46)
Covariates				
Age at death	-	0.95 (0.89-1.01)	0.95 (0.84-1.07)	0.94 (0.87-1.01)
APOE-ε4 status	-	**0. 48 (0.24-0.91)**	0.61 (0.16-1.99)	**0.43 (0.19-0.92)**

Abbreviations: *APOE*-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 10b. The impact of brain weight on the association between education and cognitive resilience (NIA-RI criteria)

Variables	NIA-RI Criteria (n=160)			
	Unstratified OR (95% CI)	**Unstratified, Adjusted OR (95% CI)**	**Adjusted, Stratified Low Brain Weight OR (95% CI) (n=54)**	**Adjusted, Stratified Higher Brain Weight OR (95% CI) (n=106)**
Lower brain weight (tertile 1 vs tertiles 2 and 3)	**0.30 (0.11-0.70)**	**0.28 (0.10-0.68)**	-	-
Level of Education (vs ≥ Master's degree)				
≤ High school	**0.20 (0.03-0.78)**	0.23 (0.03-1.00)	##	0.37 (0.05-1.86)
Bachelor's degree	0.69 (0.33-1.45)	0.81 (0.36-1.80)	##	0.84 (0.34-2.12)
Covariates				
Age at death	-	0.94 (0.85-1.02)	##	0.92 (0.82-1.01)
APOE-ε4 status	-	**0.73 (0.33-1.57)**	##	0.41 (0.15-1.01)

Model failed to run: Quasi-complete separation of data

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

5.6.2 Question 5B: The influence of cortical atrophy on the association between education and cognitive resilience

To assess if the effects of education on cognitive resilience were modified by cortical atrophy, logistic regression analyses were conducted assessing education in models adjusting for and stratifying by cortical atrophy. The results of these analyses assessing the presence of cortical atrophy are found in Tables 11a (CERAD sample) and 11b (NIA-RI sample), and results of analyses assessing the severity of atrophy are found in Tables 12a (CERAD) and 12b (NIA-RI).

The presence of atrophy and low (vs high) educational attainment were significantly negatively associated with cognitive resilience in both unadjusted and adjusted models for both the CERAD and NIA-RI samples. Moderate educational attainment was not significantly associated with cognitive resilience in either CERAD or NIA-RI samples.

When stratified by the presence of atrophy, the impact of low education was only significant when atrophy was present for both the CERAD and NIA-RI samples. The lack of a significant association among those without cortical atrophy may be reflective of weak statistical power due to the smaller number of participants without any cortical atrophy.

Similar trends were identified when assessing the severity of atrophy. Within both the CERAD (Table 12a) and NIA-RI samples (Table 12b), significant negative associations were identified between low educational attainment and cognitive resilience, with no association found for moderate versus high educational attainment. For both samples, the negative influence of a low education only remained significant among individuals with mild atrophy, although once again this may be partially explained by lower sample sizes in “no atrophy” and “moderate to severe atrophy” strata.

Table 11a. The impact of cortical atrophy status on the association between education and cognitive resilience (CERAD criteria)

Variables	CERAD Criteria (n=213) Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted, Stratified No Atrophy OR (95% CI) (n=49)	Adjusted, Stratified Atrophy Present OR (95% CI) (n=164)
Exposures				
Cortical Atrophy Present	**0.25 (0.12-0.49)**	**0.27 (0.13-0.54)**		--
Level of Education (vs ≥ Master's degree)				
≤ High school	**0.27 (0.09-0.72)**	**0.28 (0.09-0.78)**	0.35 (0.03-3.08)	**0.29 (0.08-0.91)**
Bachelor's degree	0.81 (0.44-1.50)	0.89 (0.46-1.70)	0.95 (0.21-4.24)	0.82 (0.39-1.73)
Covariates				
Age at death	-	0.96 (0.90-1.02)	0.89 (0.74-1.04)	0.98 (0.91-1.05)
APOE-ε4 status	-	**0. 51 (0.26-0.99)**	1.85 (0.35-14.34)	**0.39 (0.17-0.82)**

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 11b. The impact of cortical atrophy status on the association between education and cognitive resilience (NIA-RI criteria)

Variables	NIA-RI Criteria (n=160) Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted, Stratified No Atrophy OR (95% CI) (n=36)	Adjusted, Stratified Atrophy Present OR (95% CI) (N=124)
Exposures				
Cortical Atrophy Present	**0.24 (0.10-0.53)**	**0.24 (0.10-0.55)**	--	--
Level of Education (vs ≥ Master's degree)				
≤ High school	**0.14 (0.02-0.57)**	**0.17 (0.02-0.71)**	0.28 (0.01-3.83)	**0.13 (0.01-0.75)**
Bachelor's degree	0.62 (0.29-1.33)	0.71 (0.31-1.60)	0.63 (0.10-3.61)	0.71 (0.27-1.82)
Covariates				
Age at death	-	0.95 (0.87-1.04)	0.92 (0.73-1.14)	0.96 (0.87-1.05)
APOE-ε4 status	-	0.80 (0.36-1.76)	2.28 (0.37-19.41)	0.61 (0.24-1.51)

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 12a. The impact of the severity of atrophy on the association between education and cognitive resilience (CERAD criteria)

Variables	CERAD Criteria (n=213) Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted, Stratified No Atrophy (n=49)	Adjusted, Stratified Mild Atrophy (n=110)	Adjusted, Stratified Moderate to Severe Atrophy (n=54)
Exposures					
Cortical Atrophy Status (vs No atrophy)					
Mild atrophy	**0.36 (0.17-0.72)**	**0.38 (0.18-0.79)**	--	--	--
Moderate/severe atrophy	**0.09 (0.03-0.23)**	**0.10 (0.04-0.25**	--	--	--
Level of Education (vs ≥ Master's degree)					
≤ High school	**0.27 (0.09-0.72)**	**0.28 (0.09-0.78)**	0.35 (0.03-3.08)	**0.26 (0.05-0.99)**	0.54 (0.02-5.92)
Bachelor's degree	0.74 (0.39-1.39)	0.83 (0.43-1.61)	0.95 (0.21-4.24)	0.87 (0.37-2.04)	0.31 (0.04-1.92)
Covariates					
Age at death	-	0.96 (0.90-1.02)	0.89 (0.74-1.04)	0.99 (0.90-1.07)	0.89 (0.73-1.05)
APOE-ε4 status	-	0.56 (0.28-1.11)	1.85 (0.35-14.34)	0.55 (0.23-1.30)	**0.07 (0.01-0.56)**

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; OR = Odds ratio

Note: Bold font represents statistically significant result

Table 12b. The impact of the severity of atrophy on the association between education and cognitive resilience (NIA-RI criteria)

Variables	NIA-RI Criteria (n=160) Unadjusted OR (95% CI)	Adjusted for Age at death and *APOE* OR (95% CI)	Adjusted, Stratified No Atrophy (n=36)	Adjusted, Stratified Mild Atrophy (n=75)	Adjusted, Stratified Moderate to Severe Atrophy (n=49)
Exposures					
Cortical Atrophy Status (vs No atrophy)					
Mild atrophy	**0.41 (0.17-0.94)**	**0.41 (0.17-0.98)**	--	--	--
Moderate/severe atrophy	**0.05 (0.01-0.18)**	**0.04 (0.01-0.16)**	--	--	--
Level of Education (vs ≥ Master's degree)					
≤ High school	**0.13 (0.02-0.53)**	**0.16 (0.02-0.70)**	0.28 (0.01-3.83)	**0.12 (0.01-0.81)**	**
Bachelor's degree	0.49 (0.22-1.10)	0.62 (0.26-1.45)	0.63 (0.10-3.61)	0.54 (0.18-1.59)	**
Covariates					
Age at death	-	0.96 (0.90-1.02)	0.92 (0.73-1.14)	0.93 (0.82-1.04)	**
APOE-ε4 status	-	0.89 (0.38-2.06)	2.28 (0.37-19.41)	0.76 (0.26-2.15)	****

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

5.7 Sensitivity Analysis

Several results from the present study were impacted by small sample sizes resulting in non-significant effects and wide confidence intervals. One major problem area was in the "no cortical atrophy" strata in models for research questions 4 and 5b. In an effort to address this issue, the coding of cortical atrophy variables was reconsidered.

Nun Study cortical atrophy data were collected through autopsy reports, with notes indicating the presence and severity of cortical atrophy used to inform coding within the project. In an effort to avoid information bias, the analytic sample excluded participants whose autopsy reports did not explicitly state cortical atrophy information. However, as autopsy reports are intended to include all relevant pathologic information, the absence of explicit cortical atrophy information might be reasonably interpreted as an indication that no evidence of cortical atrophy was identified. Therefore, in an effort to improve sample sizes, several key relationships were reassessed with participant autopsy reports that did not mention cortical atrophy coded as "no atrophy present". The analytic samples with the new coding increased in size from 213 to 226 participants in models using CERAD neuropathologic criteria and from 160 to 167 participants in models using NIA-RI neuropathologic criteria. Tables of results from these analyses are included in Appendix D.

This sensitivity analysis was undertaken with three research questions. These included the assessments of the association between education and cognitive resilience (Question 1), the association between cortical atrophy (both presence and severity) and cognitive resilience (Question 2), and the impact of brain weight on the relationship between cortical atrophy and cognitive resilience (Question 4). Sensitivity analyses were not relevant for Question 3 as there was no issue with statistical power for this question. For each of the three research questions

analyzed using the new coding, results were consistent with those from the primary analysis for both the CERAD and NIA-RI analytic samples.

However, despite similar results to the primary analysis, there was a consistent widening of confidence intervals for both CERAD and NIA-RI samples across all analyses, in both unadjusted and adjusted models. This suggested that the new coding may have introduced some degree of measurement error to the sample. Furthermore, despite contributing to a marginal increase in sample sizes for both samples, the modified coding of atrophy data did not improve sample sizes in the low brain weight strata and thus did not address the major limitations of low model power and model failure to converge in stratified samples. As a result, the original coding was used for the primary analyses.

6.0 Discussion

Based on previous research and the theory of cognitive reserve (Stern, 2011), it was hypothesized that individuals with higher educational attainment would be more likely to display cognitive resilience (Stern, 2011). In addition, it was hypothesized that individuals with cortical atrophy and lower brain weight would experience decreased odds of cognitive resilience due to reduced brain reserve capacity (Katzman, 1993). Further, we hypothesized that when the influence of cortical atrophy was assessed in models stratified by brain weight, individuals with higher brain weight might be able to resist the negative influences of mild cortical atrophy, because higher baseline brain reserve capacity would allow individuals with larger brains to compensate for reductions in brain reserve resulting from mild cortical atrophy. Finally, it was hypothesized that the influence of education on cognitive resilience would be stronger among individuals with lower brain weights and those with cortical atrophy. The rationale for this hypothesis was based on the interaction between cognitive reserve and brain reserve, where when brain reserve was high, the positive influence of higher education (and higher cognitive reserve) may not be additionally beneficial (i.e., a ceiling effect). Alternatively, as brain reserve declines (due to low brain weight or the presence of cortical atrophy), the presence of higher cognitive reserve (reflected by higher educational attainment) may effectively differentiate between those who are resilient versus those who showed dementia symptoms.

6.1 Summary of Findings

The present study sought to examine the independent and interacting effects of education, brain weight and cortical atrophy on the outcome of cognitive resilience. While existing literature has examined many of these relationships, it has often relied on proxy measures of resilience (such as time to dementia) with neuropathologic definitions of cognitive resilience being comparatively rare and typically using less well validated measures, such as glucose

metabolism (Garibotto et al., 2008), in place of gold-standard autopsy data. This project's ability to use gold-standard neuropathologic data from autopsy to measure the outcome was a key asset that allowed this study to validate previous findings and provide support for the theory of cognitive resilience. Further, previous studies did not have direct measures of exposure variables including brain weight and cortical atrophy. Reliance on proxy measures for brain weight (such as head circumference or intracranial volume) and imaging for the presence of atrophy was a major limitation to the literature that this study sought to address.

While several hypotheses were confirmed, findings were mixed. A brief summary of findings from each research question is included in Table 13 below.

Table 13. Summary of findings on the association between exposures of interest and cognitive resilience using CERAD and NIA-RI criteria

Question #	Associated Results Table	Exposure	Model Type	Results	
				CERAD	NIA-RI
1	Table 2	High school education or less (vs. Master's degree or higher)	Unadjusted	↓	↓
			Adjusted	↓	↓
		Bachelor's degree (vs. Master's degree or higher)	Unadjusted	×	×
			Adjusted	×	×
2a	Table 3	Presence of cortical atrophy	Unadjusted	↓	↓
			Adjusted	↓	↓
2b	CERAD: Table 4a	Mild cortical atrophy	Unadjusted	↓	↓
			Adjusted	--	↓
	NIA-RI: Table 4b		Stratified: *APOE*-ε4 present	↓	--
			Stratified: *APOE*-ε4 absent	×	--
		Moderate to severe cortical atrophy	Unadjusted	↓	↓
			Adjusted	--	↓
			Stratified: *APOE*-ε4 present	↓	--
			Stratified: *APOE*-ε4 absent	↓	--
3a	Table 5	Brain weight (continuous)	Unadjusted	↑	↑
			Adjusted	↑	↑
3b	Table 7	Low brain weight (lowest versus upper two tertiles)	Unadjusted	↓	↓
			Adjusted	↓	↓
4a	CERAD: Table 8a	Low brain weight	Unadjusted	↓	↓
			Adjusted	↓	↓
	NIA-RI: Table 8b	Presence of atrophy	Unadjusted	↓	↓
			Adjusted	↓	↓
			Stratified: Low brain weight	--	--
			Stratified: High brain weight	↓	↓
4b	CERAD: Table 9a	Low brain weight	Unadjusted	↓	×
			Adjusted	↓	×
	NIA-RI: Table 9b	Mild atrophy	Unadjusted	↓	×
			Adjusted	↓	×
			Stratified: Low brain weight	--	--
			Stratified: High brain weight	↓	↓
		Moderate to severe atrophy	Unadjusted	↓	↓
			Adjusted	↓	↓
			Stratified: Low brain weight	--	--
			Stratified: High brain weight	↓	↓

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria
"--" indicates that the model was not run in that sub-sample
Note: Arrows indicating direction of significant association (upward arrows indicating a positive association; downward facing arrows indicating a negative association); X indicates a non-significant finding

Question #	Associated Results Table	Exposure:	Model Type:	Statistically Significant?	
				CERAD[1]	NIA-RI[2]
5A	CERAD: Table 10a NIA-RI: Table 10b	Low brain weight	Unadjusted	↓	↓
			Adjusted	↓	↓
		High school or less (versus Masters degree or Higher)	Unadjusted	×	↓
			Adjusted	×	×
			Stratified: low brain weight	×	×
			Stratified: high brain weight	×	×
		Bachelor's degree (versus Masters degree or Higher)	Unadjusted	×	×
			Adjusted	×	×
			Stratified: low brain weight	×	×
			Stratified: high brain weight	×	×
5B-1	CERAD: Table 11a NIA-RI: Table 11b	Presence of Atrophy	Unadjusted	↓	↓
			Adjusted	↓	↓
		High school or less (versus Masters degree or Higher)	Unadjusted	↓	↓
			Adjusted	↓	↓
			Stratified: no atrophy	×	×
			Stratified: atrophy present	↓	↓
		Bachelor's degree (versus Masters degree or Higher)	Unadjusted	×	×
			Adjusted	×	×
			Stratified: no atrophy	×	×
			Stratified: atrophy present	×	×
5B-2	CERAD: Table 12a NIA-RI: Table 12b	Mild cortical atrophy	Unadjusted	↓	↓
			Adjusted	↓	↓
		Moderate to severe cortical atrophy	Unadjusted	↓	↓
			Adjusted	↓	↓
		High school or less (versus Masters degree or Higher)	Unadjusted	↓	↓
			Adjusted	↓	↓
			Stratified: no atrophy	×	×
			Stratified: mild atrophy	↓	↓
			Stratified: moderate to severe atrophy	--	--
		Bachelor's degree (versus Masters degree or Higher)	Unadjusted	×	×
			Adjusted	×	×
			Stratified: no atrophy	×	×
			Stratified: mild atrophy	×	×
			Stratified: moderate to severe atrophy	×	--

Abbreviations: APOE-ε4 = Apolipoprotein E- ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria
"--" indicates that the model was not run in that sub-sample
Note: Arrows indicating direction of significant association (upward arrows indicating a positive association; downward facing arrows indicating a negative association); X indicates a non-significant finding

6.1.1 Question 1: Education and cognitive resilience

Results from the project supported the hypothesis that lower educational attainment would be linked with decreased odds of cognitive resilience. The association between education and cognitive resilience was found when comparing the highest (Master's degree or higher) versus lowest educational level (high school diploma or less) and this effect was consistent across both samples (CERAD and NIA-RI). However, the findings did not reach statistical significance when comparing moderate educational attainment (Bachelor's degree) to high educational attainment. While this lack of a significant dose-response relationship is partially inconsistent with previous research on the link between education and AD that found additional years of education are beneficial, even among the highly educated (see Xu, Tan, Wang, et al., 2015), this non-significant finding may be related to the exceptionally high levels of education within the sample overall. Because one of the primary missions of the School Sisters of Notre Dame is education, roughly 85% of the analytic sample had received a university degree. Due to this high level of education, "moderate educational attainment" reflected receiving an undergraduate degree, a level far beyond the average educational attainment in previous studies. Therefore, it is possible that individuals in the moderate and high educational attainment groups were approaching a ceiling effect whereby the additional benefit of continued education was modest.

Results from the current project supported findings from several previous studies. While earlier research found that education may mitigate the impacts of brain damage on cognition during the life-course (Garibotto et al., 2008; Liao et al., 2005), it was unclear if these relationships persisted up to the time of death or if they delayed symptom onset only temporarily. The current finding that education was positively associated with cognitive resilience at the last cognitive assessment prior to death provided additional support for the potentially life-long

importance of education in cognition. This finding is consistent with research using autopsy data showing that the impacts of NFT and NP on cognition may be reduced by higher education (Roe, Xiong, Miller & Morris, 2007).

Further, this study expands on previous work by providing some initial insight into how education may function to predict cognitive resilience, through improved cognitive reserve. Previous work on the impact of education has resulted in a number of hypotheses regarding the mechanism through which education may be protective against AD. These include educational attainment's contribution to more complex neuronal networks in early life, more intellectual stimulation over the life-course, less exposure to dangerous work conditions less educated individuals may be subjected to, and higher SES throughout one's adult life (Mortimer & Graves, 1993). One of the unique aspects of the Nun Study population is that the study subjects lived as members of a religious order for nearly the entirety of their adult lives. This homogeneity of the Nun Study sample during their adult lives uniquely positions the present study to provide insight into the mechanism through which education may promote cognitive resilience. Unlike previous epidemiologic studies on the link between early-life education and late-life cognitive outcomes, this project is free of several major confounds. All study participants experienced equivalent economic status (similar living conditions, access to food, access to health care, etc.). Therefore, the presence of significant relationships between educational attainment and cognitive resilience suggests cognitive resilience is not solely the result of improved socio-economic conditions.

In contrast, the study design in the current project supports the hypothesis that the association between educational attainment and cognitive resilience is related to cognitive development in early life or education laying the foundation for continued cognitive stimulation

over the life-course, either by contributing to life-long learning, or promoting a more cognitively stimulating occupation (such as teaching at a higher learning institution versus working in domestic labor), even when controlling for the economic differences usually associated with these levels of employment. Further research attempting to unpack the mechanism(s) through which education contributes to cognitive resilience is warranted, including conducting analyses on the association between education and cognitive resilience that control for measures of cognitive stimulation throughout adult life.

6.1.2 Question 2: Cortical atrophy and cognitive resilience

Findings from the project (summarized in Table 13) provided support for the hypothesis that the presence of cortical atrophy would be negatively associated with cognitive resilience, with increased severity further reducing the odds of cognitive resilience. These findings, coupled with previous research on the impact of cortical atrophy on cognitive outcomes (Tyas et al., 2008; Guo et al., 2013; Perneczky et al., 2010; Negash et al., 2013), provide strong support for the presence of cortical atrophy being a critical predictor of brain reserve. With the exception of one preliminary analysis, derived from the same data set as the current project (Tyas et al., 2008), no prior assessment of cortical atrophy's influence on cognitive resilience has used gold-standard diagnostic criteria (autopsy data) for both the exposure and outcome variable. Thus, the present study provides both support for previous findings and brain reserve theory.

One interesting finding revealed by the present study was that the severity of atrophy significantly interacted with *APOE*-ε4 within the CERAD sample. Within this sample, the effects of mild atrophy were only significant among *APOE*-ε4 carriers. The cause of this effect modification may lie in differences of the location of cortical atrophy between *APOE*-ε4 carriers and non-carriers. Mixed findings have found that *APOE*-ε4 carriers (versus noncarriers) tend to

develop atrophy in the medial temporal lobe/ hippocampal region, an area associated with memory and thus strongly associated with our outcome of cognitive resilience (Lehtovirta et al., 1995; Agosta et al., 2009; Pievani et al., 2011). While some conflicting evidence has been found (Jack et al., 1998; Basso et al., 2006), it remains plausible that when mild loss of brain tissue occurs, this impact may be more likely to affect critical memory structures among those with *APOE*-ε4, and thus may be more strongly associated with an increase in clinical symptoms of dementia. *APOE*-ε4 non-carriers, conversely, may be impacted by mild atrophy in areas of the brain less directly related to memory. Therefore, while the impact of mild atrophy among *APOE*-ε4 non-carriers may still result in cognitive deficits, these deficits may not present as clinical dementia as commonly and thus were not captured by the definition of cognitive resilience in the present study. Alternatively, the interaction between mild atrophy and A*POE*-ε4 may be explained as the cumulative impact of the two exposures, whereby the brain is able to overcome either exposure on its own, but when both are present the resilience levels may fall below the threshold where dementia occurs. The interaction between *APOE*-ε4 status and the location of cortical atrophy may represent a potential area of future research efforts.

6.1.3 Question 3: Brain weight and cognitive resilience

The hypothesis that brain weight would be positively associated with cognitive resilience was supported in the present study. While consistent evidence has indicated that smaller brain size may be related to increased risk of AD, fewer studies had directly assessed brain weight as a predictor of reserve capacity specifically. Findings from the current study (summarized in Table 13) were consistent with previous cognitive resilience literature suggesting that low brain weight represents a limitation to brain reserve capacity and thus is linked to decreased odds of cognitive resilience (Mori, Hirono, Yamashita et al., 1997). Within the present study, when brain weight

was categorized as a continuous variable, each one-gram increase in brain weight was associated with a significant increase in the odds of cognitive resilience. However, when brain weight was categorized into tertiles, the effects of brain weight on cognitive resilience were largely centered on risk among those with low brain weight rather than a protective influence of higher brain weight. This finding provides support for the brain reserve hypothesis. According to the brain reserve hypothesis (Katzman, 1993), individuals with lower brain weights possess less surplus brain tissue available to be drawn upon when compensating for Alzheimer neuropathology and therefore would be at increased risk of developing AD symptoms.

6.1.4 Question 4: Cortical atrophy, brain weight and cognitive resilience

Findings from the project reveal some support for the hypothesis that the association between cortical atrophy and cognitive resilience would be modified by brain weight. However, evidence of effect modification was minimal and did not occur in the expected direction. It was hypothesized that the influence of cortical atrophy, particularly mild cortical atrophy, may be offset among individuals with larger brains due to an abundance of brain reserve in these individuals, as was found in previous studies (Perneczky et al., 2010; Guo et al., 2013). Instead, in the CERAD sample, negative impacts of cortical atrophy (both mild and severe) were found among those with higher brain weights with no significant impact among those with lower brain weights. However, conclusions based on these findings are questionable due to low statistical power resulting in wide confidence intervals. In an effort to better understand this relationship, additional bivariate analyses were conducted to assess the nature of the relationship between cortical atrophy and cognitive resilience when stratified by brain weight. These analyses revealed that among those with low brain weights, the odds of cognitive resilience were extremely low and did not vary substantially based on atrophy status. While increasing severity of atrophy led to a decreased likelihood of resilience among those with lower brain weight, the added risk of

severe versus mild atrophy was reduced among the low brain weight strata. One hypothesis for this effect was that there was a floor effect for cognitive resilience where brain weight is of primary importance. Low brain weight appeared to diminish brain reserve to such an extent that any further reductions in brain reserve (through atrophy) were unlikely to result in additional detrimental effects. While this was not the expected relationship, this finding is consistent with the theory of brain reserve as it suggests that low brain weight, regardless of cortical atrophy status, results in inadequate brain reserve to overcome the effects of Alzheimer neuropathology.

6.1.5.1 Question 5A: The influence of brain weight on the association between education and cognitive resilience

The hypothesis that education would be more highly associated with cognitive resilience among those with lower brain weights was not supported by findings in the current study. Rather, results from the study (summarized in Table 13) revealed that when brain weight and educational attainment were considered simultaneously, the effect of educational attainment on cognitive resilience fell below significance, despite no significant interaction between the two variables. While it is worth noting that there was a suggestion of a dose-response relationship between increasing educational attainment and increased brain weight, the lack of a significant relationship suggests that the maintenance of brain reserve factors (in this case brain weight) is independently associated with resilience and is likely of primary importance in promoting cognitive resilience, with cognitive factors (such as education) supporting these benefits. Thus, this finding provides some insight into the importance of higher brain weights in maintaining cognitive function.

However, the lack of significant findings for education when controlling for brain weight is likely due to a reduction in power resulting from the inclusion of an additional variable, although the point estimates reflect a strong protective effect (e.g., high school education or less:

OR=0.23, 95% CI=0.23-1.00, Table 10b). This lack of power becomes evident in the stratified models in which confidence intervals widened substantially, particularly among the low brain weight tertile. Even though the hypothesis was not supported in the present study, the interacting influence of predictors of cognitive reserve (such as education) and brain reserve (such as brain weight) remain an interesting area for research and warrant continued research with larger data sets.

6.1.5.2 Question 5B: The influence of cortical atrophy on the association between education and cognitive resilience

The hypothesis that education would be more highly associated with cognitive resilience in the presence of cortical atrophy was not confirmed in the present study. In both the NIA-RI and CERAD samples, the impact of education only remained significant in the presence of mild atrophy. When cortical atrophy was absent or moderate/severe atrophy was present, this effect fell below significance. It was predicted that when high levels of brain reserve were present (as reflected by the absence of cortical atrophy), the cognitive reserve conferred by educational attainment would not be additionally beneficial in promoting cognitive resilience. Further, it was predicted that when insults to brain reserve were severe (as reflected by moderate/severe cortical atrophy), the resilience capacity of the brain would be profoundly reduced to the point where even significant cognitive reserve (through high levels of education) would be unable to prevent the emergence of dementia symptoms. While, as predicted, the impact of education on cognitive resilience was most significant in the presence of mild atrophy, evidence in support of this hypothesis was limited by insufficient power in ‘no atrophy’ and ‘moderate/severe atrophy’ strata. Due to this low power, confidence intervals were too wide to provide meaningful support for the hypothesis. To clarify these relationships, subsequent studies should assess the impact of

cortical atrophy on the relationship between education and cognitive resilience using larger databases with greater numbers of participants in non-atrophic and severely atrophic subgroups.

6.2 Limitations

While there are several strengths of the proposed study, a few limitations must be addressed. Firstly, because early-life data from the study were retrospectively collected, several factors that may be relevant to the present study were not available. For example, several measures indicative of early-life advantage, such as childhood nutrition and SES, were not assessed. These could confound the relationship between educational attainment and cognition in late life through various mechanisms and would have been useful in assessing the nature of the relationship between education and cognitive resilience. For example, participants with higher parental SES (particularly higher education) may have been exposed to more early-life cognitive stimulation and better nutrition, which may have improved brain and cognitive development and increased the likelihood of higher educational attainment as well as improved cognitive health outcomes in older adulthood.

Secondly, there are limitations in assessing Alzheimer neuropathology. The CERAD neuropathologic criterion used in the study does not assess the development of neurofibrillary tangle pathology in AD. Therefore, this criterion used only one of the two hallmark biomarkers for AD, and may be assessing cognitive resilience against neuritic plaque pathology rather than against Alzheimer neuropathology more broadly. While caution should therefore be used when generalizing findings from the CERAD sample to individuals with AD, the study did attempt to address this limitation by re-running all analyses with cognitive resilience defined using the NIA-RI criterion (which considers both NFT and NP pathologies). While the analytic sample using NIA-RI criteria is considerably smaller due to several participants being unclassifiable because of atypical Alzheimer pathology development (see section 2.1.4), using this second

analytic sample was integral to validating conclusions from the CERAD sample. Throughout the project, the general associations between exposure variables and cognitive resilience were consistent across the two samples. Where minor differences were found, the inconsistent results could largely be explained by the lower sample size and corresponding reduction in statistical power in the NIA-RI sample. A more general limitation of the criterion used in the assessment of Alzheimer neuropathology is that this association between AD neuropathology and dementia is less robust among older individuals where the presence of non-Alzheimer neuropathology is much higher. This is because an older sample would have accumulated significantly more insults to the brain than a younger sample, and thus the impact of non-Alzheimer neuropathology may indeed be causing the cognitive impairments more than the Alzheimer pathology. This may contribute to a conclusion that Alzheimer neuropathology led to a reduction in cognitive resilience directly, when this influence was in fact due to non-Alzheimer brain pathology.

Non-response was also a limitation of the present study. From the School Sisters of Notre Dame religious congregation, 678 of the 1031 eligible sisters agreed to participate in the study. While this may have introduced selection biases to the study, participants and non-participants did not differ significantly on mortality, age, country of birth or race. The Nun Study sample was further reduced from 678 participants to the analytic sample of 213 participants for the CERAD sample and 160 participants in the NIA-RI sample. Participants were excluded if they did not have Alzheimer neuropathology or were missing covariates of interest. An assessment of non-response bias was conducted to assess if excluded participants differed from the participants in the analytic samples 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) and were unlikely to explain the findings in the study.

Another key limitation of the project was that the sample was somewhat homogeneous on key covariates making it difficult to accurately test associations of interest in multivariable models. This limitation impacted models assessing education and cortical atrophy in particular. Within the educational attainment exposure, few participants received only a high school diploma or less (<16% of participants in both samples). The implication of this highly educated sample was that low statistical power resulted in wide confidence intervals for measures assessing the impact of low education. However, despite the reduced statistical power, the effects of low education still reached statistical significance, suggesting that the true effect of education on cognitive resilience is large. Similarly, in models incorporating cortical atrophy, less than 25% of participants were free from atrophy at the time of death. However, this was not surprising as individuals of advanced age and those with Alzheimer neuropathology are at heightened risk for atrophy. Because of this lack of variability in atrophy, there are concerns that when education predicted cognitive resilience in models that did not control for atrophy, this effect could be driven largely by the mild atrophy strata. However, in stratified models, the impact of education appeared to remain important in all strata and consistently trended in the same direction. Ultimately, the low numbers of participants in the "no atrophy" strata resulted in reductions in statistical power and may have led to a type II error where the true impact of education on resilience in the no atrophy strata was not identified.

While the use of brain weight at autopsy was used to help validate previous findings using MRI (Mori, Hirono, Yamashita et al., 1997), head circumference (Graves, Mortimer, Larson, et al., 1996) and intracranial volume (Guo et al., 2013), this measure is not without

limitations. Because brain weights were collected after death, these measures were not independent from cortical atrophy. In fact, only 22% of the NIA-RI sample and 23% of the CERAD sample were free from cortical atrophy, and thus the measured brain weight of participants at autopsy did not reflect the pre-morbid brain weight (or baseline brain reserve). This is problematic as brain weights at death likely would have been systematically lower among those with more advanced atrophy, another known risk factor for dementia, but not for participants without atrophy. Therefore, brain weight measurements may have partially reflected loss of tissue due to cortical atrophy. However, models assessing both brain weight and cortical atrophy simultaneously found that these factors were independently associated with cognitive resilience. There was no statistically significant interaction between brain weight and the presence or severity of cortical atrophy, or evidence of multicollinearity between these exposures in model diagnostics. Therefore, the effects of these variables in the study are likely valid. However, subsequent studies would benefit from the inclusion of a valid estimate of pre-morbid brain weight.

The Nun Study population differs from the general population in a number of ways that may impact generalizability. First, because the sample is female only, generalizability of findings to males may be limited. While there is no compelling evidence in the literature suggesting Alzheimer neuropathology and cortical atrophy impact males and females differentially, consistent findings from the literature indicate that males have higher brain weights, and thus the impact of atrophy and low brain weight may have impacted our sample more severely than it would the general population. Additionally, because the sample is from a religious order, participants differ from the general public in a number of ways, including marital status, tobacco

use, and alcohol consumption that may impact outcomes of interest. These differences, while contributing to higher internal validity, decrease the generalizability of the findings.

Lastly, this study began follow up at age 75. While this minimum age at baseline is a methodological strength as it filtered out the majority of the cases of early-onset forms of AD, this could potentially introduce survivor bias as individuals with higher susceptibility to outcomes of interest (AD, dementia) may have died before reaching age 75.

6.3 Strengths

Despite the limitations, the proposed research possesses several important strengths for the study of cognitive resilience. Participants in the Nun Study are largely free from many factors that confound other epidemiologic studies, including tobacco use, heavy alcohol consumption, and unequal access to medical resources throughout adulthood. Several of these factors were major confounding variables that were not adjusted for in previous studies on the link between education and cognitive resilience. By largely controlling for these variables through sample selection, the present study was able to present a clearer relationship between the exposure variables and cognitive resilience.

While the vast majority of studies assessing cognitive resilience have been conducted on clinic samples, the Nun Study is a population-based cohort. The use of a population sample provides a number of strengths to the current study. Because the focus of the current investigation is to identify factors that promote cognitive resilience, the use of a clinic sample would not be feasible as clinic samples by definition would only include symptomatic cases. Additionally, the Nun Study is longitudinal. The availability of archived early-life data coupled with follow up over 12 annual cognitive assessments allows for temporal relationships to be clearly established. This is a distinct advantage over previous research on cognitive resilience which, due to practical considerations, typically relied upon cross-sectional data.

Finally, the present study used assessments of cortical atrophy, brain weight, Alzheimer neuropathology, and cognitive resilience that were based on neuropathologic assessment via autopsy. Although the measures of neuropathology are imperfect (as noted in the limitations), the use of autopsy data is the gold-standard diagnostic methodology. While previous studies have approximated neuropathologic data through glucose metabolism assessments, cerebral blood flow measurements, and imaging, little research in this area has been conducted using the definitive gold-standard criteria utilized in the Nun Study. The availability of *APOE*-ε4 genotype data was also a critical advantage over previous studies that were unable to control for this potential effect modifier.

6.4 Implications and Future Directions

To conclude, the body of literature attempting to understand how variables from across the life-course can predict cognitive resilience in late life remains in its infancy. While several studies have assessed how early-life factors may promote cognitive resilience, the literature largely lacked robust methodologic assessments and findings were unclear. This project addressed this issue by using a neuropathologically-derived definition of cognitive resilience to support previous findings.

The study was also among the first of its kind to assess brain reserve factors (brain weight and cortical atrophy) on cognitive resilience in late life using gold-standard autopsy data instead of proxy measures. While there are limitations of the autopsy data (see section 6.2), this study provided validation of earlier work on both the direct relationships between brain reserve factors and cognitive resilience as well as providing new insights into how different brain reserve factors from across the life-course may interact to produce cognitive outcomes. However, due to limitations of the present study, subsequent cohort studies assessing late-life cognition would

benefit strongly from the inclusion of measures of premorbid brain weight through the use of MRI data or validated head size measurements.

Finally, findings from this study suggested the potential for interacting effects of cognitive reserve and brain reserve in the development of late-life cognitive resilience. The availability of both early- and late-life data provided the unique opportunity to assess how education from early life interacted with later-life brain weight and cortical atrophy to impact cognition among individuals with Alzheimer neuropathology. This study provided a critical first step in understanding the link between these life-course factors and the development of cognitive resilience.

These contributions to the cognitive resilience literature have a number of practical and theoretical implications. Primarily, these findings will lay the groundwork for future research in this area. Results indicating that variables from across the life-course may interact to produce cognitive resilience provide a critical step in untangling the complex life-course development of cognitive resilience. Future research is needed to clarify several potential relationships revealed in the present study, including the interaction between *APOE*-ε4 status and cortical atrophy, the potential interacting effects of brain weight and cortical atrophy, and the relative importance of brain reserve and cognitive reserve.

One contribution of these findings is the potential to prioritize intervention strategies. For example, because there was some evidence that insults to brain reserve capacity may offset the cognitive reserve benefits of education, prioritizing research and interventions focused on the maintenance of brain reserve may successfully maximize cognitive resilience. Some previous literature has suggested that there are nutritional interventions that can maximize brain weight across the life-course and improve cognitive outcomes (see: Alzheimer's Disease International,

2014; Wang et al., 2012). Further, improved control over cardiovascular risk factors, such as hypertension (Salerno, Murphy et al., 1992) and diabetes (Knopman, Mosley et al., 2005), may reduce late-life cortical atrophy. Indeed, reductions in incident cases of AD that have been attributed to better control of cardiovascular risk factors (Satizabal, Beiser et al., 2016) may partially contribute to reduced incident AD through heightened brain reserve.

Finally, because this study found that education was associated with cognitive resilience in a population largely free from differences in SES, housing, and health care access, these findings support the continued investment in education as a fundamental determinant of health that functions beyond improved access to the aforementioned variables.

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Appendix A
Literature search strategy

Table A1. Literature Search Strategy

Data Base	Education	Cognitive Reserve	Age
PubMed/Medline	education [MeSH] educational attainment [tiab] OR education level [tiab] OR years of education	cognitive reserve [MeSH] OR cognitive reserve [all fields] OR brain reserve [all fields] OR cognitive resilience [Tiab] OR Alzheimer disease [MeSH] OR Alzheimer's disease [tiab]	aged [MeSH] OR older adult [all fields] OR elderly [all fields] OR seniors [all fields]
PsycINFO	**Index:** education OR academic achievement **Title and Any Field:** {education} OR {educational attainment} OR {education level} OR {educational level}	**Index: {**Alzheimer's Disease} **Title or Any Field:** {cognitive reserve} OR {brain reserve} OR {Alzheimer disease} OR {Alzheimer's disease}	

Appendix B
Summary of literature search articles

Table B1. Summary findings on the association between education and cognitive resilience.

Study	Measure of education	Assessment of brain damage	Assessment of cognitive ability	Findings
Bezerra et al., 2012	Academic performance (high school grades in Portuguese, mathematics and geography)	None	Incidence of dementia	Higher academic performance was linked to decreased incident dementia
Dekhtyar et al., 2016	Archival records of school grades at age 9 and 10	Not done	Incidence rates of dementia (comprehensive clinical exam)	Low school performance at ages 9/10 was associated with increased incidence of dementia independent of educational attainment and occupational attainment
Garibotto et al., 2008	Years of education	Glucose metabolism in parietotemporal cortex and cognitive testing	Neuropsychological test performance	Education was related to higher cognitive performance despite increased brain damage
Hall et al., 2007	Years of education	None	Incidence of dementia	Higher education delayed the onset of symptoms, led to faster deterioration upon symptom onset (compression of morbidity)
Kemppainen et al, 2008	High education vs. low education	Glucose metabolism in parietotemporal cortex	Neuropsychological test performance	Education was related to higher cognitive performance despite increased damage
Liao et al, 2005	Years of education	Blood flow in parietotemporal cortex	Neuropsychological test performance	Education was related to decreased AD symptoms despite increased brain damage
Mehta et al. 2009	Self-reported academic performance in high school ("below average", "average", "above average")	None	Incidence of dementia	Lower rates of dementia among those with higher self-reported academic performance
Rentz et al., 2010	Years of education	Amyloid deposits in the precuneus	Neuropsychological test performance	The relationship between amyloid deposits and decreased cognitive ability was reduced in highly educated participants
Roe et al., 2007	Years of education	Autopsy assessment of Alzheimer neuropathology	Incidence of dementia	Education was protective against dementia despite the presence of Alzheimer neuropathology, regardless of neuropathologic criteria
Stern et al.,	Years of education	Blood flow in	Neuropsychological	Despite more severe brain

1992		parietotemporal cortex	test performance	damage, highly educated participants experienced the same clinical severity as their less educated counterparts.

Table B2. Summary of findings on the association between cortical atrophy and cognitive resilience.

Study	Measures of atrophy	Covariates assessed	Measure of cognition	Main findings
Amato et al., 2013	MRI scan of normalized total brain volume and cortical brain volume	Level of cognitive reserve (IQ and education)	Neuropsychological test scores (Rao's brief repeatable battery)	Cognitive reserve modified the relationship between atrophy and cognition: High cognitive reserve provided resistance to cognitive impacts of atrophy in mild but not severe atrophy
Guo et al., 2013	MRI scan of brain volume Intracranial volume	APOE-ε4	Dementia status (Intact, MCI, AD) Neuropsychological performance (MMSE)	Atrophy was inversely associated with cognitive performance. Larger intracranial volume was associated with preservation of cognitive ability
Negash et al., 2013	MRI scan of cortical volume Intracranial volume	Cerebral spinal fluid test of amyloid beta plaque (AD marker),	Clinical Dementia Rating score (measures of	Intra-cranial volume was associated with the ability to resist the impacts of atrophy and amyloid beta
Perneczky et al., 2010	MRI scan of cortical volume	Head circumference, APOE-ε4	MMSE performance, Dementia status (DSM-IV)	Inverse association between atrophy and cognitive ability. Larger head circumference was protective against the effects of mild atrophy
Tyas et al., 2008	Autopsy evidence of cortical atrophy	Pathologic evidence of AD	Dementia status (DSM-IV)	Those with cortical atrophy were 4 times less likely to resist AD-related brain changes and avoid dementia

Appendix C
Assessment of Non-Response Bias

Sensitivity analyses included an assessment of non-response bias. In this assessment, the analytic sample using CERAD criteria (n=213) was compared to the following samples of excluded participants: participants who were excluded as they were still living (n=72), deceased participants who did not meet neuropathologic criteria for AD based on CERAD criteria (n=126) and individuals excluded due to missing data (n=50). For a summary comparison of these groups see Table C1. The sample defined using the NIA-RI neuropathologic criteria (n=160) was also compared to a group of individuals who were still living (n=72), a group of participants who were deceased but did not meet neuropathologic criteria for AD based on NIA-RI criteria (n=184), and participants who were excluded due to missing exposure or covariate data (n=32). For a summary comparison of these groups see Table C2.

The results of the assessment of non-response showed that living participants were significantly less likely to be demented at their last cognitive assessment than participants in the analytic sample for both NIA-RI ($p<0.001$) and CERAD samples ($p<0.001$), and were less likely to possess APOE-ε4 alleles ($p=0.002$). Because the analytic sample was limited to those individuals with AD neuropathology, these significant impacts were expected. Further, participants who were living differed significantly from our sample on measures of education in the NIA-RI sample ($p=0.03$), and showed a marginally significant difference in the CERAD sample ($p=0.06$). Again, given the relationship between educational attainment and longevity, it was not surprising that living participants would be more highly educated. Finally, no statistically significant differences were found between the analytic sample and living participants on age at the last cognitive assessment (CERAD: $p=0.21$, NIA-RI: $p=0.36$).

Comparisons between the analytic sample and deceased participants who were excluded because they did not show evidence of AD neuropathology upon autopsy examination showed several predictable differences. Individuals without AD neuropathology had larger brains (CERAD: $p<0.032$, NIA-RI: $p<0.001$), were less likely to possess APOE-ε4 alleles (CERAD: $p<0.001$, NIA-RI: $p<0.001$), and were less likely to be demented at their last cognitive assessment (CERAD: $p<0.001$, NIA-RI: $p<0.001$). Further, participants without AD neuropathology were also younger at the time of their last cognitive assessment before death. No significant differences were found on educational attainment (CERAD: $p=0.44$, NIA-RI: $p=0.40$).

Finally, comparisons between our sample and participants who, despite meeting the AD neuropathology criteria, were excluded from our sample due to missing data indicated that the loss of these participants did not likely systematically alter our analyses. No differences between our sample and participants with missing data existed for cognitive status at the last assessment (CERAD: $p=0.79$), NIA-RI: $p=0.94$), educational attainment (CERAD: $p=0.97$, NIA-RI: $p=0.21$), APOE- ε4 status (CERAD: $p<0.54$, NIA-RI: $p=0.81$), brain weight (CERAD: $p=0.09$, NIA-RI: $p=0.13$) or age at the last cognitive assessment before death (CERAD: $p<0.21$, NIA-RI: $p=0.60$).

Because the outcome measure and analytic samples were based on a definition of cognitive resilience requiring the presence of AD neuropathology, differences between the analytic samples and those without AD neuropathology are neither surprising, nor would they impact our ability to generalize our findings to the broader target population (those with AD neuropathology). The lack of significant differences between the analytic sample and those who

were excluded strictly due to missing data indicates that non-response likely did not systematically influence our analyses.

Table C1. Test of non-response bias for analytic sample (CERAD) vs. excluded participants.

Variable	CERAD analytic sample (n=213)	Excluded Participants: Living participants (n=72)	Excluded Participants: Deceased, without AD pathology (n=126)	Excluded Participants: Missing covariate data (n=50)
Educational attainment				
High school or less	15.5%	8.3%	13.5%	14.0%
Bachelor's degree	45.1%	36.1%	41.3%	44.0%
Master's degree or higher	40.4%	55.6%	45.2%	42.0%
Dementia status at last assessment				
Yes	60.1%	16.7%**	33.3%**	58.0%
No	39.9%	83.3%**	66.7%**	42.0%
Age at last cognitive assessment	90.80 (5.13)	91.59	89.11 (5.24)**	91.78 (3.85)
APOE-ε4 alleles present	31.0%	10.4%**	10.5%**	26.2%[1]
Brain weight in grams [Mean (SD)]	1097.20 (113.10)	--	1125.3 (113.6)*	1142.10 (96.84)[2]

*significant differences from the Analytic sample at the p<0.05 level

** significant differences from the analytic sample at the p<0.01 level

[1] Analysis of the influence of non-response on APOE-ε4 status was based on a value of n=42 for "missing covariate data" group

[2] Analysis of the influence of non-response on brain weight was based on a sample of n=20 for the "missing covariate data" group.

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

Table C2. Test of non-response bias for analytic sample (NIA-RI) vs. excluded participants.

Variable	NIA-RI analytic sample (n=160)	Excluded Participants		
		Living participants (n=72)	Deceased, without Alzheimer neuropathology (n=126)	Missing covariate data (n=50)
Educational attainment				
High school or less	15.6%	8.3%*	13.0%	15.6%
Bachelor's degree	46.9%	36.1%*	42.4%	31.3%
Master's degree or higher	37.5%	55.6%*	44.6%	53.1.0%
Dementia status at last assessment				
Yes	71.3%	16.7% **	23.3%**	71.9%
No	28.7%	83.3%**	70.7%**	28.1%
Age at last cognitive assessment	90.95 (4.72)	91.59 (5.30)	89.39 (5.30)**	91.41 (4.04)
1+ *APOE*-ε4 allele	36.9%	10.8%**	9.5%**	39.3%[1]
Brain weight in grams [Mean (SD)]	1082.9 (115.5)	--	1130.5 (107.9)**	1136.80 (109.00)[2]

*significant differences from the analytic sample at the p<0.05 level

** significant differences from the analytic sample at the p<0.01 level

[1] Analysis of the influence of non-response on APOE status was based on a value of n=28 for "missing covariate data" group

[2] Analysis of the influence of non-response on brain weight was based on a sample of n=11 for the "missing covariate data" group

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

Appendix D
Results for sensitivity analysis: 'No atrophy information' coded as no atrophy

As addressed in section 5.7, Nun Study cortical atrophy data were collected through autopsy reports, with notes indicating the presence and severity of cortical atrophy used to inform coding within the project. In an effort to avoid information bias, the analytic sample excluded participants whose autopsy reports did not explicitly state cortical atrophy information. However, it is reasonable to interpret the absence of explicit cortical atrophy information as an indication that no evidence of cortical atrophy was identified in assessments of participant brain tissues. Therefore, key relationships were reassessed with participants whose autopsy reports did not mention cortical atrophy coded as "no atrophy present". The analytic samples with the new coding increased from 213 to 226 participants in models using CERAD neuropathologic criteria and from 160 to 167 participants in models using NIA-RI neuropathologic criteria. As previously alluded to in section 5.7, the results for models assessing educational attainment and its impact on cognitive resilience (Table D1), models assessing the role of atrophy presence on cognitive resilience (Table D2), and models assessing the influence of the severity of atrophy on cognitive resilience (Table D3a and Table D3b) revealed trends identical to those in the primary analysis. However, these results showed consistent widening of confidence intervals versus the primary analysis despite larger sample sizes. This suggested the potential introduction of error and thus the primary analysis was maintained.

Table D1. The association between level of education and cognitive resilience among CERAD and NIA-RI samples, recoded to include the absence of cortical atrophy data as "no atrophy present".

Variables	CERAD Criteria (n=226)		NIA-RI Criteria (n=167)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposure				
Education (vs. ≥ Master's degree)				
≤ High school	**0.28 (0.10-0.71)**	**0.29 (0.10-0.75)**	**0.26 (0.06-0.84)**	**0.26 (0.06-0.92)**
Bachelor's degree	0.96 (0.54-1.70)	1.06 (0.58-1.94)	0.80 (0.39-1.63)	0.84 (0.39-1.82)
Covariates				
Age at death	-	0.95 (0.89-1.01)	-	0.96 (0.88-1.04)
APOE-ε4 status	-	**0.45 (0.24-0.83)**	-	0.58 (0.27-1.20)

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

Table D2. The association between the presence of cortical atrophy and cognitive resilience among CERAD and NIA-RI samples, recoded to include the absence of cortical atrophy data as "no atrophy present".

Variables	CERAD Criteria (n=226)		NIA-RI Criteria (n=167)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposure				
Presence of atrophy (vs. 'no atrophy')				
Atrophy present	**0.32 (0.18-0.59)**	**0.35 (0.19-0.65)**	**0.32 (0.15-0.67)**	**0.33 (0.15-0.70)**
Covariates				
Age at death	-	0.95 (0.89-1.01)	-	0.94 (0.87-1.02)
APOE-ε4 status	-	0.55 (0.29-1.01)	-	0.73 (0.34-1.54)

Abbreviations: APOE-ε4 = apolipoprotein E-ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result

Table D3a. The association between severity of cortical atrophy and cognitive resilience, using CERAD criteria, recoded to include the absence of cortical atrophy data as "no atrophy present".

	CERAD Criteria (n=226)		
		Adjusted	
Variables	**Unadjusted OR (95% CI)**	**APOE-ε4 non-carrier OR (95% CI)***	**APOE-ε4 carrier OR (95% CI)***
Exposures			
Severity of atrophy (vs. 'no atrophy')			
Mild atrophy	**0.47 (0.25-0.88)**	0.59 (0.28-1.21)	0.30 (0.07-1.14)
Moderate/severe atrophy	**0.12 (0.05-0.28)**	**0.22 (0.08-0.60)**	**0.01 (<0.01-0.15)**
Covariates			
Age at death	-	0.96 (0.89-1.02)	0.88 (0.74-1.01)

Abbreviations: APOE-ε4 = apolipoprotein E- ε4; CERAD = Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria; CI = confidence interval; OR = Odds ratio

Note: Bold font represents statistically significant result

*Stratified by *APOE*-ε4 status due to a significant interaction between severity of atrophy and *APOE*-ε4 in model diagnostics

Table D3b. The association between severity of cortical atrophy and cognitive resilience, using NIA-RI criteria, recoded to include the absence of cortical atrophy data as "no atrophy present".

	NIA-RI Criteria (n=167)	
Variables	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Exposure		
Severity of atrophy (vs. 'no atrophy')		
Mild atrophy	0.54 (0.25-1.10)	**0.57 (0.26-0.1.26)**
Moderate/severe atrophy	**0.08 (0.02-0.25)**	**0.07 (0.01-0.23)**
Covariates		
Age at death	-	**0.91 (0.84-0.99)**
APOE-ε4 status	-	0.80 (0.36-1.75)

Abbreviations: APOE-ε4 = apolipoprotein E- ε4; CI = confidence interval; NIA-RI = National Institute on Aging-Reagan Institute neuropathologic criteria; OR = Odds ratio

Note: Bold font represents statistically significant result