Emotional expressivity in early adulthood as a predictor of dementia and Alzheimer's disease in late adulthood

by

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Author's Declaration

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

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Abstract

Background: As the global population ages, the prevalence of age-related disorders, such as dementia, is increasing. Dementia is a condition of progressive deterioration of cognitive ability that leads to functional deficits. The primary subtype of dementia is Alzheimer's disease (AD). Currently, there is no cure for AD or other major forms of dementia (e.g., vascular dementia) so prevention is the best approach for reducing the burden of these conditions. Emotions experienced across the lifespan may affect the development of dementia and AD, given their high involvement in cognitive, cardiovascular and psychosocial processes. Emotions may be neuroprotective by promoting the development of cognitive resources that allow resistance to pathologic changes in the brain. Alternatively, emotions may be neuropathogenic by contributing to vascular risk factors and evoking the stress response. The objective of this study is to investigate a potential novel association of emotional expressivity in early adulthood with dementia and AD in late life.

Methods: Data from the Nun Study, a longitudinal study of 678 religious sisters who were aged 75+ at baseline in 1991, were used for the investigation. Data include annual cognitive and physical assessments, post-mortem brain autopsies and historical documents obtained from convent archives. Archival autobiographies handwritten in early adulthood (mean age=22) were available for 180 U.S.-born participants. Autobiographies were scored for emotional expressivity, as well as for idea density, a measure of written language skills known to be associated with dementia and AD. Emotional expressivity was classified as high (i.e., top two quartiles) or low (i.e., bottom two quartiles) based on within-convent ranking of number of emotion words. Dementia was diagnosed if individuals displayed an inability to perform activities of daily living, and cognitive impairment on a battery of neuropsychological tests, according to standard criteria. A diagnosis of AD required evidence of dementia and AD neuropathology. Samples were selected for the analysis of dementia (n=149) and AD (n=85) based on the availability of data on dementia, AD neuropathology and all covariates of interest, and on restriction by low education.

Positive, negative, and overall emotional expressivity (i.e., the sum of positive and negative emotion words) were investigated in association with both dementia and AD using multivariate logistic regression analysis. Additional analyses were performed to investigate the association of emotional expressivity with dementia. These included dividing the negative emotional expressivity variable into three (as opposed to two) categories, and testing the interaction between positive and

negative expressivity in association with dementia. All final models were stratified by idea density and adjusted for age and apolipoprotein E-ε4 (*APOE*-ε4).

Results: The association of emotional expressivity with dementia and AD was modified by idea density. Among individuals with high idea density, those with high emotional expressivity, regardless of valence (i.e., overall, positive and negative), were consistently at an increased risk of dementia and AD compared to those with low emotional expressivity. In particular, overall emotional expressivity was significantly associated with dementia in this subgroup (odds ratio [OR]=2.60, 95% confidence interval [CI]=1.04-7.11). Among individuals with low idea density, those with high overall and negative emotional expressivity were at a decreased risk of dementia and AD compared to individuals with low emotional expressivity. Positive emotional expressivity was associated with an increased risk of dementia and AD. None of the associations of emotional expressivity with dementia or AD were significant in the low idea density subgroup.

The associations did not reach statistical significance among individuals with low idea density in the additional analysis of emotional expressivity with dementia. However, among individuals with high idea density, moderate, but not high, negative emotional expressivity was associated with an increased risk of dementia (OR=3.59, 95% CI=1.13-11.89). Furthermore, high negative emotional expressivity was associated with an increased risk of dementia among individuals with low positive emotional expressivity (OR=8.17, 95% CI=1.66-58.96).

Discussion: The results support emotional expressivity in early adulthood as a potential predictor of dementia and AD in late adulthood. Idea density, a known risk factor of dementia and AD, modifies the association. High emotional expressivity, regardless of valence, is associated with an increased risk of dementia and AD when cognitive risk is otherwise low (i.e., high idea density), whereas overall and negative expressivity are associated with a decreased risk of dementia and AD when cognitive risk is high (i.e., low idea density). Furthermore, as predicted, the effect of negative emotional expressivity was modified by positive emotional expressivity: negative expressivity was only associated with an increased risk of dementia when positive expressivity was low, suggesting that positive emotions may counteract the adverse effects of negative emotions. Taken all together, the results provide evidence for a potential association of emotional expressivity in early adulthood with dementia and AD in late life. These findings suggest the importance of emotional expressivity as a predictor of long-term health outcomes, including dementia and AD. As such, emotions may serve as a potential target for future dementia and AD prevention strategies.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

3MS	Modified Mini-Mental State Exam
Aβ	Beta-amyloid (plaques)
AD	Alzheimer's disease
ADLs	Activities of daily living
APA	American Psychiatric Association
APOE-ε4	Apolipoprotein E epsilon 4 allele
APP	Amyloid precursor protein
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Cdk5	Cyclin-dependent protein kinase
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence interval
CRH	Corticotropin releasing hormone
CSF	Cerebrospinal fluid
DSM	Diagnostic Statistical Manual of Mental Disorders
GDS	Global Deterioration Scale
Gsk3b	Glycogen synthase kinase
HIS	Hachinski Ischemic Scale
ICD	International Classification of Diseases
MCI	Mild cognitive impairment
MID	Multi-infarct dementia
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
NFT	Neurofibrillary tangle
NINDS-AIREN	National Institute of Neurologic Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement et Neurosciences
NIA-RI	National Institute on Aging and the Reagan Institute
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association
OR	Odds ratio
PiB	Pittsburgh compound B
PS	Presenilin
SD	Standard deviation
SSND	School Sisters of Notre Dame
UN	United Nations
VaD	Vascular dementia
VIF	Variance inflation factor

Chapter 1
Introduction

As the global population ages, the prevalence of age-related disorders, such as dementia, is increasing. In 2008, half a million Canadians suffered from dementia (Alzheimer Society of Canada, 2010), a medical syndrome defined by substantial cognitive deterioration that leads to loss of function and subsequently, loss of independence (American Psychiatric Association [APA], 2013). Within the next 25 years, the number of people with dementia is projected to more than double, with the associated annual care costs estimated to reach $153 billion (Alzheimer Society of Canada, 2010). Currently, the leading subtype of dementia is Alzheimer's disease (AD), a neurodegenerative disease that involves progressive loss of neuronal structure and function within the brain (APA, 2013). Vascular dementia (VaD) is the second most common subtype of dementia and sometimes co-occurs with AD (i.e., mixed dementia), given the large vascular involvement in both diseases (APA, 2013). Despite no known cure for these underlying forms of dementia, several factors that affect risk have been identified. In particular, factors pertaining to cognitive development (e.g., Middleton & Yaffe, 2010), psychosocial behaviour (e.g., Fratiglioni & Wang, 2007; Rothman & Mattson, 2010) and cardiovascular function (e.g., Snowdon et al., 1997) are associated with the risk of dementia, AD and VaD. Investigation of such factors informs prevention strategies in an effort to lessen the burden of dementia on affected individuals and society as a whole.

Emotions play a pivotal role in cognitive, psychosocial and cardiovascular aspects of health and as a result may be associated with the development of dementia, AD and VaD over the long term. Emotional experiences may contribute to these outcomes in two ways. First, emotions affect cognitive development and may have a neuroprotective effect to resist pathologic changes to brain tissues. In particular, positive emotions broaden attention, exploration and social networking, which enrich cognitive resources (Fredrickson, 2004) and may in turn enhance the ability to maintain cognitive function even if neurodegeneration occurs. Second, emotions affect cardiovascular and endocrine activity and may have a neuropathogenic effect that contributes to the development of AD and VaD pathology: negative emotions tend to elevate cardiovascular function and evoke the stress response, leading to conditions that are known risk factors for AD and VaD. Taken all together, cognitive, social and physical aspects of emotional experiences across the lifespan have the potential to either protect against the development of dementia, or cause the neurodegeneration associated with AD and VaD.

The aim of the current research is to investigate the association of emotional expressivity in early adulthood with the risk of dementia and AD. Previous literature on this association is limited so the objective of the current study is to establish if an association exists, based on hypothesized mechanisms. Measures of emotional expressivity will be based on single autobiographical entries written in young adulthood that were obtained through a longitudinal study on health and aging called the Nun Study. Previous literature suggests that isolated events of emotional expressivity, such as an autobiography or a photograph, are indicative of long-term emotional tendencies that affect late-life health outcomes (Danner, Snowdon, & Friesen, 2001; Harker & Keltner, 2001; Pennebaker, 1997). Thus, emotional expressivity scores from the Nun Study autobiographies, as a reflection of emotional tendencies, will be studied in relation to the development of dementia and AD. The potential influence of vascular and genetic risk factors will also be assessed in order to clarify the association. Low prevalence of VaD in the sample population prevents the investigation of its relationship with emotional expressivity separately; however, it is included in the classification of all-cause dementia and is closely associated with AD neuropathology. As such VaD will be discussed in the literature review in parallel with AD to support the argument of a potential effect of emotional expressivity on development of dementia and its subtypes.

Given the relative novelty of the current investigation, the primary objective is to establish whether emotional expressivity contributes to the development of dementia and its most prevalent subtype, AD. Such findings will set the stage for future studies to investigate the mechanisms underlying any observed associations. Advancement in the understanding of risk factors associated with dementia and AD could help to inform prevention strategies, which are especially important in the case of these devastating diseases. There is currently no cure for these conditions so efforts to avoid their onset are crucial. Effective strategies that help to prevent or delay the onset of dementia and AD could significantly reduce the projected burden of these diseases at both individual and societal levels.

Chapter 2
Literature Review

2.1 The Aging Population and Age-Related Diseases

Globally, the population of older adults, aged 60 years and older, is growing rapidly. Over the first half of this century, the number of adults over the age of 60 is expected to triple and it is estimated to surpass 2 billion by 2050 (United Nations [UN], 2013). A similar trend can be seen in the Canadian population: projections suggest that the number of Canadians aged 65 and over will increase from 4.7 million in 2009 to between 11.9 and 15.0 million by 2061 (Statistics Canada, 2010). The population of very old persons, aged 80 and over, is experiencing the fastest growth of any age group worldwide. While the population of those aged 60 and older is expected to triple by 2100, the number of people aged 80 and over will increase seven-fold over the same time period (UN, 2013). By 2050, 1 in 5 persons aged 60 or over will be above the age of 80 (UN, 2013). In Canada, the number of individuals aged 80 years or older is expected to reach 5.1 million by 2061 (Statistics Canada, 2010). These statistics indicate a major, never-before-seen shift in age distribution. This will be the first time in history that the greatest proportion of the global population is at or above mid-life.

The trend toward an increased proportion of older adults globally has serious implications. With old age comes increased risk of disability, the loss of cognitive or physical function that causes difficulties in activities of daily living. Disability results from changes in structure and function of the body that may be determined by genetics, or by lifestyle factors such as physical activity, social engagement, cognitive stimulation, and habits formed across the lifespan. Lifetime experiences, which accumulate to influence the state of bodily functions, determine disability. Although disability is not inevitable, risk increases with age.

An especially devastating, and increasingly prevalent, form of disability among the aging population is dementia, a syndrome characterized by progressive loss of cognitive function. Dementia is caused by disruption of normal physiological processes within the brain resulting in loss of memory, recognition, and the ability to communicate and learn new information (see section 2.2.1). In 2010, the overall estimate of worldwide prevalence of dementia was 4.7% of those aged 60 and older, although this number was between 5 and 7% in the majority of regions (Prince et al., 2013). Prevalence of dementia is highly dependent on age (Prince et al., 2013). Thus, a shift in the world population toward older ages suggests an increase in dementia cases over the coming decades.

Projections of global dementia prevalence are alarming. Currently, there are 35.6 million cases of dementia worldwide (Prince et al., 2013). By 2050, this number is expected to rise to 115.4 million, with the highest rate of growth in low- to moderate-income countries (Prince et al., 2013). This is cause for concern because caring for older adults who are not able to carry out activities of daily living and who may have behavioural symptoms, such as aggression and wandering, can be costly. Between 2008 and 2038, the cumulative cost associated with dementia care is projected to reach $872 billion in Canada alone (Alzheimer Society of Canada, 2010), putting great demands on the economy. This trend will be seen worldwide.

Of equal importance to the price tag of formal dementia care, the personal time spent by caregivers in assisting dementia patients with daily tasks and other services is substantial. In 2008, Canadians provided 231 million hours of informal (unpaid) care to people living with dementia. This time demand is expected to triple by 2038 (Alzheimer Society of Canada, 2010). Furthermore, the upward shift in age distribution over time will result in a larger proportion of the population being affected by dementia. In Europe, the number of "working-aged" persons (aged 15-64) is expected to decrease from 69 to 21 for every individual with dementia over the next forty years (Wancata, Musalek, Alexandrowicz, & Krautgartner, 2003), leaving fewer people in younger generations to provide care. The shifting of the proportion of eligible caregivers to dependents could have dire implications on society as a whole, and requires immediate attention to slow or reverse the expected impact.

Efforts to reduce the threat of dementia can be improved through better understanding of the etiologic factors that contribute to the disorder. Currently, the two leading subtypes of dementia are Alzheimer's disease (AD) and vascular dementia (VaD), respectively contributing approximately 60-80% (Alzheimer's Association, 2010) and 16% (van der Flier & Scheltens, 2005) of dementia cases in adults aged 65 or over. AD and VaD are both neurodegenerative diseases of characteristic damage to brain tissue that lead to functional decline and dementia (see subsequent sections for further details). The pathologic changes characteristic of these two conditions have been found to overlap in some cases of dementia (see section 2.5.1). Similar to dementia, risk of AD and VaD increases significantly with age. As such, prevalence of both is expected to increase as the population ages. By 2050, 1 in 85 individuals worldwide will have AD, 8.8 million of whom will be living in North America (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). The prevalence of AD and VaD is doubling every 4.3 and 5.3 years, respectively (Ganguli, 2011). Given the large contribution of these subtypes to the overall prevalence of

dementia, exploration of mechanisms by which they affect brain function and cognition will help to advance the overall understanding of dementia.

Further awareness of the etiology of dementia will guide development of interventions to decrease the forecasted threat. Projections have shown that efforts to delay onset or slow the progression of dementia could significantly reduce the prevalence of dementia in the future (Jorm, Dear, & Burgess, 2005). A global intervention to effectively delay onset of AD by one year would result in 11.8 million fewer cases than is estimated for 2050 if the current trends continue (Brookmeyer et al., 2007). Recent studies have shown that improvements in education and better prevention of risk factors such as vascular disease may help to reduce incidence rates (Larson, Yaffe, & Langa, 2013). Such estimations are promising and are a driving force behind efforts to identify causes of these conditions. A better understanding of dementia and its underlying diseases will contribute to the development of strategies to limit the looming global epidemic.

2.2 Dementia

2.2.1 Overview

Dementia is a complex clinical syndrome characterized by progressive deterioration of cognition from a previous level of ability, leading to a wide range of functional deficits. Dementia is most commonly associated with memory impairment, but also includes decline of executive function as well as loss of functionality in language, speech, motor skills and coordination (APA, 2013). As symptoms increase in severity, individuals frequently experience behavioural and psychological symptoms, such as agitation, aggression, disinhibition, sleep disturbance, and wandering (Mirakhur, Craig, Hart, McIlroy, & Passmore, 2004). Depression, anxiety and other affective disorders are also common comorbidities found in individuals living with dementia (Burns & Iliffe, 2009).

Dementia can be reversible or irreversible, depending on the underlying cause. Symptoms of reversible dementia subside if the underlying cause is identified and successfully treated (Tripathi & Vibha, 2009). In contrast, irreversible dementias are untreatable, although some interventions slow the progression of decline. Eventually, cognitive faculties decline to the point where assistance is required for basic activities of daily living (ADLs), such as eating, dressing and bathing. Manifestation of symptoms varies widely and depends on factors such as individual experience, coexisting health factors and the underlying cause.

2.2.2 Etiology of Dementia

Dementia, itself, is not a definitive diagnosis; rather, it is a set of symptoms (i.e., a syndrome) that warrant further investigation to determine its cause. As such, all-cause dementia is an umbrella term often used to describe all dementias when the causes are unspecified. Abnormalities in the brain that lead to dementia can result from a wide range of diseases and disorders featuring distinct pathologies. Potentially reversible causes of dementia include neurosurgical conditions (e.g., subdural hematoma), neuroinfections and inflammations (e.g., meningitis), metabolic conditions (e.g., hypothyroidism), and other causes (e.g., depression, drugs and alcohol, sleep apnea) (Tripathi & Vibha, 2009). The four leading subtypes of irreversible dementia, which account for 90% of all dementia cases, are AD, VaD, frontotemporal dementia and Lewy body dementia (Grand, Caspar, & MacDonald, 2011; Tedeschi, Cirillo, Tessitore, & Cirillo, 2008). Of these, AD and VaD are the most prominent and will be discussed in more detail elsewhere (AD, section 2.3; VaD, section 2.4). Each subtype of dementia causes a distinct pattern of decline, useful in differentiating one from another in a clinical setting.

The rate and pattern of dementia progression are dependent on the underlying disease and specific neuropathology causing the dementia. For example, dementia associated with AD appears gradually and decline is progressive, while the onset of VaD is sudden and decline is stepwise (Grand et al., 2011). These patterns coincide with the effect of each disease on brain tissue: AD features gradual build-up of protein deposits, while VaD results from acute incidents of brain infarcts or other vascular lesions. Such variations in disease progression are helpful in forming diagnoses in a clinical setting.

In addition, cognitive and behavioural deficits in individuals with dementia occur based on the area of the brain that is affected. Dementia can be divided into two main types (i.e., cortical and subcortical), which correspond to the affected region and clinical manifestation. Cortical dementia is defined by early and severe memory disturbances, aphasia, apraxia and agnosia, and is consistent with AD diagnosis (Román, 2005). AD pathology appears first in the hippocampus, amygdala and posterior cingulate gyrus of the temporal and parietal lobes, coinciding with brain regions controlling memory, language and perception (Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012; Tedeschi et al., 2008). Conversely, subcortical dementia is distinguished by slowed cognitive and motor function as well as dysfunction of gait, speech, affect and mood, symptoms that may be associated with VaD (Román, 2005). These examples illustrate how clinicians move beyond the initial diagnosis of dementia to identify the underlying cause.

2.2.3 Diagnosis of Dementia

Early detection of dementia is important for effective planning and, when appropriate, administration of therapeutic treatment (Burns & Iliffe, 2009; Mathias & Burke, 2009). In addition, early detection and treatment of potentially reversible dementias provides the best chance for successful recovery (Feldman et al., 2008). Typically, an initial complaint by the patient or a caregiver of memory loss or some other aspect of mental decline will prompt a series of global cognitive screening tests. These tests determine deficits in various domains of cognition and may include the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) or the elongated version, the modified MMSE (3MS; Teng & Chui, 1987); the Global Deterioration Scale (GDS; Reisberg, Ferris, de Leon, & Crook, 1982); or the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). In addition to cognitive assessments, the diagnostic process relies on assessment of patient history, caregiver interview, physical examination, basic laboratory tests and neuroimaging (Feldman et al., 2008). As dementia is a syndrome with various etiologies, many of these tests are used to identify the cause and to rule out other explanations for the decline that are unrelated to dementia.

Diagnostic criteria for dementia, such as those outlined in the Diagnostic and Statistical Manual of Mental Disorders, now in the fifth edition (DSM-5; APA, 2013), and in the International Classification of Diseases, 10th edition (ICD-10; World Health Organization, 1992), are used to identify dementia. However, the DSM-5 and the ICD-10 criteria are not typically used alone because dementia as a syndrome can have various symptoms and causes that the criteria do not adequately address. The ICD-10 presents a broad definition of "unspecified dementia" and the DSM-5 only defines "neurocognitive disorders" (i.e., dementia) in the context of the underlying disease. Fulfillment of ICD or DSM criteria paired with clinical judgment leads to a formal diagnosis of dementia (Breitner, 2006), but appropriate treatment relies on identification of the underlying cause. As such, a diagnosis of dementia is typically followed by further investigation of patient history and a clinical work-up using various other criteria that have been developed to identify the specific subtypes (e.g., AD or VaD).

2.3 Alzheimer's Disease (AD)

2.3.1 Overview

AD is the leading form of dementia, accounting for an estimated 60-80% of cases of dementia worldwide (Alzheimer's Association, 2010) and approximately 63% in Canada (Alzheimer Society of

Canada, 2010). AD is characterized by irreversible brain pathology featuring beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs), which contribute to neurodegeneration and cell death (Maccioni, Muñoz, & Barbeito, 2001). As brain tissue damage occurs, clinical symptoms of dementia appear gradually and progressively. First, memory loss and other cognitive deficits appear, followed by loss of functional and communicative abilities and eventual loss of mobility, thereby increasing susceptibility to infection and death (Grand et al., 2011; Thies, Bleiler, & Alzheimer's Association, 2013). In addition, prevalence of depression and depressive symptoms is high among individuals with AD (Burns & Iliffe, 2009). On average, affected individuals experience cognitive decline for several years before death; a systematic review of mortality in dementia and AD reports a median length of survival ranging from 7 to 10 years after onset of AD-related dementia (Todd, Barr, Roberts, & Passmore, 2013).

Models of AD progression suggest that pathology likely develops insidiously over many years before cognitive decline is observed. AD biomarkers may be found in the blood, brain and cerebrospinal fluid twenty years or more before cognitive symptoms appear (Jack et al., 2010; Jack et al., 2013; Thies et al., 2013). As AD pathology advances, cognitive and functional abilities decline gradually such that clinical diagnosis of dementia associated with AD is preceded by two phases. First, preclinical AD indicates the presence of AD biomarkers, suggesting potential brain pathology, with no obvious cognitive symptoms (Sperling et al., 2011). The second phase describes a transitional state between intact cognition and diagnosis of dementia, often termed mild cognitive impairment (MCI; Petersen et al., 2001). MCI is either amnestic, where the primary complaint is memory loss with otherwise mostly intact cognitive function, or non-amnestic, where decline occurs in one or more cognitive domains other than memory. Amnestic MCI has been found to precede AD-type dementia (Petersen et al., 2001; Riley, Snowdon, & Markesbery, 2002; Tedeschi et al., 2008). Approximately 40-60% of individuals who are diagnosed with MCI convert to AD (Tedeschi et al., 2008), a large proportion of which are likely amnestic MCI cases. Furthermore, incidence of AD is much higher in individuals with amnestic MCI (10 to 15% per year) when compared to healthy individuals (1 to 2% per year) (Petersen et al., 2001). Although preclinical AD and MCI are not definitive stages of AD, identification of these two conditions may be advantageous for early administration of therapeutic interventions (Petersen et al., 2001; Rentz et al., 2013).

Therapeutic interventions for AD are limited. They do not change the course of AD pathology, but rather modify cognitive and behavioural symptoms so that the functional decline is delayed. Pharmaceutical treatments include cholinesterase inhibitors, such as rivastigmine, donepezil and galantamine; and a glutamate regulator, memantine. These drugs help to counteract changes in brain

chemistry that are characteristic of AD so that cognitive function is maintained despite some neuronal damage (Bendlin et al., 2010). In most cases, treatment can delay or improve symptoms for approximately 6 to 12 months (Grand et al., 2011); however, cognitive and functional decline are inevitable as the disease progresses and neuronal damage becomes extensive. Efforts are currently directed toward understanding the underlying causes of AD pathology so that effective treatments can be developed to prevent disease progression.

2.3.2 Etiology of Alzheimer's Disease

The two main biomarkers of AD pathology are neuritic Aβ plaques and NFTs. However, the role of each of these factors is unclear. Both Aβ plaques and NFTs have been found in some cognitively intact older adults, suggesting that the presence of Aβ and NFTs alone is not enough to cause cognitive impairment. Furthermore, Aβ and NFTs differ in their association with clinical symptoms and diagnosis of AD. Aβ deposition is highly related to AD pathology, but less so to cognitive decline associated with AD (Jack et al., 2010; Maccioni et al., 2001). Conversely, NFTs are highly associated with cognitive decline in AD, but are not unique to AD pathology; other neurodegenerative diseases, such as frontotemporal dementia, also feature neurofibrillary degeneration (Iqbal, Liu, Gong, Alonso Adel, & Grundke-Iqbal, 2009; Mohandas & Rajmohan, 2009). Despite these inconsistencies, cognitive decline is the result when the density and location of Aβ plaques and NFTs reach some indeterminate threshold (Price et al., 2009). Thus, a combination of accumulated Aβ plaques and NFTs forms the traditionally accepted model of AD neuropathology on which diagnostic criteria are based (see Section 2.3.3).

Substantial progress has been made in the understanding of molecular processes leading to the neuritic plaques and tangles that are characteristic of AD. Extracellular Aβ plaques are by-products of abnormal proteolysis of an axonal transmembrane protein, amyloid precursor protein (APP; Maccioni et al., 2001). Cerebral amyloid angiopathy, which is characterized by deposition of Aβ at the blood-brain barrier, may also contribute to AD pathology (Jeynes & Provias, 2011). Aβ accumulation is believed to trigger changes in signaling pathways likely involving cyclin-dependent protein kinase (Cdk5) and glycogen synthase kinase (Gsk3b) enzymes that lead to production of NFTs (Maccioni et al., 2001). Indeed, current laboratory and neuroimaging techniques indicate that amyloid is typically the first biomarker detected in individuals who eventually develop AD (Jack et al., 2010; Jack et al., 2013) and may appear approximately ten years before neurodegeneration occurs (Villemagne et al., 2013).

Molecular studies have shown that abnormal function of Cdk5 and Gsk3b enzymes leads to deregulated phosphorylation of tau proteins, which are structural support proteins normally associated

with neuronal microtubules. The resulting hyperphosphorylation of tau prevents their integration into microtubules, thereby compromising the structural integrity of the cells, and leading to neurodegeneration and formation of NFTs by the unincorporated tau proteins (Maccioni et al., 2001). However, discoveries of tau-related neurodegeneration in the absence of Aβ (e.g., Knopman et al., 2013) have led some to rethink the validity of the amyloid cascade hypothesis, positing that Aβ deposition and tau-related neurodegeneration may occur independently in the development of AD (see Landau & Frosch, 2014 for discussion). Most recently, findings of Jack and colleagues (2014) support the amyloid cascade by showing that, although Aβ deposition and hippocampal neurodegeneration occur independently, neurodegeneration is accelerated in the presence of Aβ. Regardless of the pathway, what is certain is that the progressive accumulation of Aβ plaques and NFTs leads to irreversible neuronal degeneration and eventual death associated with AD.

As AD progresses, plaques and tangles spread throughout various regions of the brain corresponding to clinical symptoms of dementia (see section 2.2.1). In particular, AD pathology has been highly associated with the neocortex, hippocampus, amygdala and basal nucleus of Meynert (Wenk, 2003). Although Aβ plaque distribution varies between individuals with AD, NFTs follow a relatively predictable pattern of spread throughout the brain. The dispersion of NFTs throughout the brain is described with Braak staging (Braak & Braak, 1991). Braak staging is divided into six progressive phases of NFT involvement beginning in the transentorhinal region of the cortex and moving into the hippocampus, including the entorhinal region, and eventually involving the isocortical region (Braak & Braak, 1991). NFT pathology is highly associated with dementia (Giannakopoulos et al., 2003; SantaCruz et al., 2011). However, some cases with advanced Braak staging but no dementia have also been identified (SantaCruz et al., 2011), demonstrating the complexity of causal factors of AD.

The only known causes of AD are genetic mutations that lead to AD pathology. Autosomal dominant mutations in genes coding for *APP*-processing presenilins (*PS1* and *PS2*), and in the *APP* gene itself, cause accumulation of $A\beta_{1\text{-}42}$, which is an insoluble form of Aβ (Maccioni et al., 2001). These mutations are sufficient to cause AD pathology (Ferrer, 2012). However, such causes account for only 2% of all cases of AD (Bird, 2008). These genetic mutations are more likely to cause early-onset AD, where symptoms appear before the age of 65. Thirteen percent of early-onset cases are attributable to mutations in *PS1*, *PS2* or *APP* genes (Bird, 2008). The epsilon-4 allele of the gene coding for apolipoprotein E (*APOE*) is also associated with AD. However, *APOE*-ε4 is neither necessary nor sufficient for AD pathology (Bird, 2008) so is considered to be a risk factor, and not a cause.

Beyond the aforementioned genetic factors, the cause of non-inherited, "sporadic" AD is not clear. Sporadic AD has been linked to factors such as brain trauma, impaired immune function, abnormal cholesterol and lipid metabolism, atherosclerosis and cardiovascular disease (see section 2.5.2.5), but causal mechanisms remain unclear. AD etiology is likely multi-factorial, making the definition of specific causes problematic, although many risk factors have been identified (see section 2.5.2).

2.3.3 Diagnosis of Alzheimer's Disease

A definite diagnosis of AD requires both clinical symptoms of dementia and neuropathological evidence of the disease. Currently, imaging and laboratory techniques remain imperfect so diagnosis during life relies on patient and caregiver interviews, patient history, neuropsychological assessments and exclusion of other potential conditions. As such, the clinical diagnosis remains presumptive until pathological evidence of the disease can be confirmed at postmortem autopsy. Several sets of criteria have been developed to support AD diagnosis, including clinical criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984); neuropathologic criteria by the National Institute on Aging and the Reagan Institute (NIA-RI; The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997); and both clinical and neuropathologic criteria put forth by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Mirra et al., 1991; Morris et al., 1989). These diagnostic protocols have their own strengths and limitations and vary in their usefulness in clinical and research settings.

AD biomarkers, Aβ plaques and NFT-associated tau proteins can be identified in laboratory specimens and neuroimaging techniques. Abnormally low levels of $A\beta_{42}$ and high levels of tau in cerebrospinal fluid (CSF) samples are found to approximate AD diagnosis as evidenced by correlations with post-mortem brain autopsies and with clinical symptoms (Jack et al., 2010). Furthermore, ante-mortem PET imaging using Pittsburgh compound B (PiB), which binds to $A\beta_{42}$, has been associated with plaque loads in most individuals with confirmed AD pathology (Jack et al., 2010). However, these diagnostic techniques are not consistent: CSF-tau is also found in other diseases and Aβ observed in CSF and PiB-PET imaging does not capture all cases of AD (Jack et al., 2010). Thus, current diagnostic criteria do not rely on these biomarkers, but rather focus on clinical symptoms and neuropathology to form a diagnosis.

In order to establish a definite diagnosis of AD, evidence of both neuropsychological (i.e., dementia) and neuropathological (i.e., Aβ plaques and NFTs) components is required. However, neuropathology cannot be determined in the clinical setting, preventing definitive diagnoses of AD from being made during life. The NINCDS-ADRDA working group has addressed this problem through the development of criteria that classify AD as "possible" or "probable" based on appearance and progression of symptoms (McKhann et al., 1984; McKhann et al., 2011). These criteria are typically used in clinical trials and clinical research. Pathophysiological evidence, such as that obtained from CSF levels and PiB-PET imaging, may be incorporated to increase or decrease the level of certainty of AD for research purposes, but is not recommended for standard clinical diagnoses (Jack et al., 2011; McKhann et al., 2011). The updated NINCDS-ADRDA criteria employ the NIA-RI criteria to establish a definitive diagnosis of AD: a diagnosis is confirmed if the NINCDS-ADRDA criteria for "probable" AD, as well as AD neuropathology according to NIA-RI criteria, are fulfilled (McKhann et al., 2011).

The NIA-RI focuses on determination of postmortem neuropathological evidence for the diagnosis of AD (The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997). The protocol requires identification of both neuritic plaques and NFTs to establish a pathological diagnosis of AD. Neuritic plaques are quantified using CERAD criteria (described below), while NFT spread is classified by Braak staging (see Section 2.3.2). However, a particular weakness of the NIA-RI criteria is that they do not adequately address pathology in which levels of NFTs and Aβ plaques are inconsistent (e.g., CERAD "frequent" and Braak stage 0-II, CERAD "infrequent" and Braak stage V-VI; Nelson, Kukull, & Frosch, 2010).

An updated version of the NIA-RI guidelines also accounts for potential pathology associated with preclinical AD and MCI in an attempt to provide a more complete picture of disease progression throughout the various stages (Hyman et al., 2012). Genetic and biomarker data can be used to support neuropathological findings in a research setting, but do not further define the disease state so are not deemed necessary (Hyman et al., 2012). The identification of co-morbid brain pathology is also recognized in this protocol and should be considered when assessing clinical and pathological correlations of AD (Hyman et al., 2012). As mentioned previously, correlations between clinical neuropsychological criteria (e.g., NINCDS-ADRDA) and post-mortem neuropathology according to the NIA-RI criteria form a definitive diagnosis of AD.

The CERAD protocol incorporates clinical, neuropsychological, neuropathological and behavioural data to provide an all-encompassing diagnosis of AD (Fillenbaum et al., 2008). For clinical determination

of the disease, a battery of tests is recommended to assess cognitive processes such as memory, language, visuospatial ability, concentration and orientation (Morris et al., 1989). CERAD also provides neuropathological criteria for Aβ plaque load so that diagnosis of AD can be confirmed at post-mortem autopsy. A semi-quantitative approach to documentation of the density of neuritic plaques, which are Aβ plaques directly associated with neuronal degeneration, is used (Mirra, 1997). However, NFTs, which are a well-recognized component of AD, are not considered for diagnosis using CERAD criteria. This presents a gap in the ability to fully understand the disease and therefore, CERAD is not typically used for research with a focus on AD neuropathology. Overlapping neurodegenerative disorders such as Parkinson's disease and dementia with Lewy bodies are accounted for in the original set of criteria (Mirra, 1997), but the protocol has not been updated to reflect the most recent understanding of such comorbidities (Fillenbaum et al., 2008). Given that it defines both neuropsychological and neuropathological criteria, the CERAD protocol is widely used for diagnosis of AD in the clinical setting.

2.4 Vascular Dementia (VaD)

2.4.1 Overview

Commonly co-occuring with AD (see Section 2.5.1), vascular dementia (VaD) is a subtype of dementia resulting from vascular damage to brain tissue. VaD lacks a clear definition because of the variability with which damage can occur (Grand et al., 2011). The condition may result from a range of circulatory disorders that lead to vascular complications such as infarcts, hemorrhaging and lesions in various areas of the brain (Grinberg & Heinsen, 2010). Such variation in the location and extent of damage and the resulting symptoms associated with VaD makes classification of the disease challenging.

As with dementia of other subtypes, the major clinical symptoms of VaD include an irreversible decline from previous cognitive and functional ability that may lead to emotional and behavioural disturbance, challenges with ADLs and ultimate loss of independence (Román, 2005). However, characteristics that may distinguish VaD from other forms of dementia include abrupt onset, fluctuation of symptoms, history of stroke and hypertension, possible focal neurological signs and symptoms, stepwise deterioration, complaints of poor physical health, emotional instability and more severe symptoms of depression than are found in AD (Grand et al., 2011; Groves et al., 2000). Symptom presentation is highly dependent on the underlying pathology causing VaD.

Following onset of symptoms of VaD, treatment is limited to symptom management. Cholinergic drug therapies used in AD, such as rivastigmine, donepezil, galantamine, and memantine may also partially delay VaD symptoms, although studies investigating treatment efficacy have been inconsistent (Korczyn, Vakhapova, & Grinberg, 2012). Other treatments, such as anxiolytics, antidepressants and anticonvulsants, have been used to treat non-cognitive symptoms (Korczyn et al., 2012), but none are known to reverse or suspend the degeneration caused by VaD. Among VaD cases, the cause of death is most often cerebrovascular disease and the average length of survival after onset of symptoms is 3.9 years (Fitzpatrick, Kuller, Lopez, Kawas, & Jagust, 2005). Thus, preventative measures to reduce the cardiovascular risk factors that underlie VaD etiology may be the most effective way to reduce the occurrence of the disease, and its influence on the development of AD (Monsuez, Gesquiere-Dando, & Rivera, 2011).

2.4.2 Etiology of Vascular Dementia

VaD is caused by a wide range of cardiovascular abnormalities, and thus has several etiologic factors that affect the presentation of symptoms. Damage to brain tissue occurs as a result of ischemic or hemorrhagic cerebrovascular diseases, or of cardiovascular or circulatory disturbances (Román, 2005). Vessel disorders such as atherosclerosis, small vessel disease and cerebral amyloid angiopathy cause cerebrovascular lesions in the form of white matter lesions, cerebral hemorrhages or brain infarcts (Thal, Grinberg, & Attems, 2012). Cognitive impairment ensues when the extent of damage is sufficient to disrupt normal neuronal function. However, the cognitive and functional symptoms vary based on the size and location of the lesion.

As the name suggests, white matter lesions are characterized by damage to white matter, which is the axon-rich area of the brain. These lesions include demyelination, axon loss, astrogliosis, and microglial activation (Thal et al., 2012). The deterioration of neuronal connections causes psychomotor slowing, memory impairment and neuropsychiatric symptoms, such as depression and apathy (Grand et al., 2011; Thal et al., 2012). VaD associated with white matter lesions progresses subtly as a result of gradual white matter degeneration.

Conversely, a stroke, defined by a disruption of blood supply to the brain resulting in acute tissue damage, can lead to sudden onset of VaD. Strokes can be hemorrhagic or ischemic. Hemorrhagic strokes occur when vessel walls in the brain rupture, allowing blood to invade brain tissue (Thal et al., 2012). Vessel ruptures result when the integrity of vessel walls is compromised. Arterial hypertension associated with small vessel disease is the most common cause of cerebral hemorrhage, followed by cerebral

amyloid angiopathy, which is characterized by deposition of Aβ proteins in cerebral blood vessels (Thal et al., 2012). Bleeding in large or small vessels may cause dementia through displacement of brain tissue and disruption of neuronal function. Symptoms and severity of hemorrhagic stroke are dependent on which, and to what extent, brain regions are affected (Thal et al., 2012).

Ischemic strokes, which are the most common type of stroke, are characterized by brain tissue death due to insufficient blood flow. Areas of brain tissue death, known as infarcts, may lead to severe loss of cognitive function and thus diagnosis of VaD. Cerebral infarcts, the most common cause of VaD, typically result from atherosclerosis and related embolic or thrombotic events. However, when associated with AD pathology (see section 2.3.1), small vessel disease or cerebral amyloid angiopathy can also lead to infarction (Thal et al., 2012). Brain infarcts may also cause cerebral hemorrhage if tissue necrosis is severe enough to allow extravascular leakage of blood (Román, 2002).

Brain infarcts vary in size, shape, location and cognitive influence. Multi-infarct dementia (MID), a subtype of VaD, is the result of multiple infarcts in cortical or subcortical regions of the brain that impair cognition (Grand et al., 2011). Such impairments are experienced across various domains, depending on the location of the infarcts (Grand et al., 2011). Strategic infarct dementia, another subtype of VaD, occurs when a single infarct produces focal damage in a functionally critical region (Román, 2002), leading to impairment in some cognitive domains, while others remain intact (Grand et al., 2011). As a result of the wide variation of etiologic factors contributing to VaD, development of clear neuropathologic criteria has been difficult.

VaD can develop sporadically or from inherited genetic mutations (familial). The majority of cases of familial VaD are due to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), caused by a mutation in the *Notch 3* gene leading to small vessel disease (Grand et al., 2011). Sporadic VaD, associated with vessel disorders and vascular lesions derived from environmental factors, is much more common than familial VaD. Identification of potential underlying causes of VaD, familial or sporadic, are important to form a diagnosis of the disease.

2.4.3 Diagnosis of Vascular Dementia

Diagnostic criteria such as the Hachinski Ischemic Scale (HIS; Hachinski et al., 1975), the DSM-5 (American Psychiatric Association, 2013) and the National Institute of Neurologic Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement et Neurosciences (NINDS-AIREN) criteria (Román et al., 1993) outline the essential components required for clinical diagnosis of VaD. The

HIS, a 13-item instrument, is used to differentiate VaD from other dementia subtypes and focuses on clinical symptoms as opposed to pathological evidence. Conversely the DSM-5 and the NINDS-AIREN criteria, in addition to excluding other causes of dementia, require evidence of vascular lesions through neuroimaging techniques (i.e., CT, MRI; Grand et al., 2011; Román, 2002). The most widely used system for clinical diagnosis, developed by the NINDS-AIREN, also requires that the location of the lesions corresponds to the specific symptoms as a plausible mechanism for VaD to be confirmed (Román, 2002).

Diagnostic criteria for VaD rely on cognitive tests to determine presence of dementia (see section 2.2.3). Wide variations in clinical symptoms of VaD, based on the location of cerebrovascular lesions, require assessment of several cognitive domains. For example, vascular damage in subcortical tissue leads to deficiencies in executive function that can be detected by tests such as the clock drawing test (for review, see Agrell & Dehlin, 1998), rather than the MMSE, which is better suited to assess cortical functions such as memory (Román, 2005). Assessments that focus on specific cognitive domains can be used to map tissue damage, allowing more accurate diagnoses. In addition, Mathias and Burke (2009) found significant differences in results of delayed story recall (memory) and emotional recognition (perception) between patients with AD and VaD, suggesting opportunities for differentiation of the two diseases. This is especially valuable based on the fact that significant overlap of neurodegenerative and vascular pathology has been found, making distinction between VaD and AD difficult.

2.5 Dementia, AD and VaD

2.5.1 Mixed Dementia

Mixed dementia is diagnosed when evidence of both AD and VaD pathology are found concurrently. Mixed dementia differs from “pure” AD and “pure” VaD in that the dementia is caused by a combination of neurodegenerative and vascular pathology and the contribution of each is unclear (Jellinger, 2002; Jellinger, 2007; Nadeau & Black, 2010). Poor understanding has made classification of the disease difficult, and agreement among researchers is low. Mixed dementia is reported to comprise from 0 to 58% of all dementia cases (Jellinger, 2007; Zekry, Hauw, & Gold, 2002), with more recent estimates suggesting the prevalence of mixed pathology to comprise about half of all dementia cases (Schneider, Arvanitakis, Leurgans, & Bennett, 2009). Lack of a clear definition of what constitutes a diagnosis of mixed dementia is a likely explanation for the disagreement in reported prevalence.

Several conflicting models have been used to describe the role of AD and vascular pathologies in mixed dementia. Some view vascular pathology as a confounder, rather than an equal entity, in the relationship between AD pathology and dementia (Román et al., 1993). Others suggest that AD pathology is a result of vascular factors and should be considered a vascular disorder (de la Torre, 2002). Alternatively, others have found no correlation between vascular pathology and AD, and report an additive effect of the two pathologies in causing dementia (Schneider, Wilson, Bienias, Evans, & Bennett, 2004). Indeed, cognitive impairment is more severe in AD patients when cerebrovascular lesions are present, when compared to patients at the same stage of AD pathology in the absence of vascular lesions (Snowdon et al., 1997). Although the two may not be directly linked, co-occurence of AD and VaD pathology is not surprising, given that they share many of the same risk factors.

2.5.2 Common Risk and Protective Factors

2.5.2.1 Demographic Factors

Age is a major risk factor for all-cause dementia, AD and VaD. Susceptibility to neuronal and vascular tissue damage naturally increases with age. As time progresses, Aβ deposition, minor vascular events, lesions and inflammation accumulate to increase risk of dementia. Indeed, the risk of all subtypes of irreversible dementia increases with age (Lopez-Pousa, Vilalta-Franch, Llinas-Regla, Garre-Olmo, & Román, 2004). Only 6 to 7% of cases of AD are diagnosed before age 65 (Gorelick, 2004) and incidence increases exponentially with age. Likewise, the incidence of VaD is ten times greater in adults aged 80 or over as compared to those between 60 and 69 years of age (Leys, Pasquier, & Parnetti, 1998).

In addition to age, sex may be associated with risk of both AD and VaD, although this point is debated. Women have been found to be at greater risk of developing AD than men in some studies (Gao, Hendrie, Hall, & Hui, 1998), but not in others (Corrada, Brookmeyer, Paganini-Hill, Berlau, & Kawas, 2010; Tyas, Manfreda, Strain, & Montgomery, 2001). A pooled analysis of four cohort studies found an age effect: women over the age of 85 were at a greater risk of AD when compared to men in the same age group, but the incidence rates did not differ between sexes for any other age group (Andersen et al., 1999). Sex-related differences in risk may also vary by location: European studies have found that women are at increased risk of AD, while American studies did not find any association (Edland, Rocca, Petersen, Cha, & Kokmen, 2002). Conversely, females may be at lower risk of VaD across all age groups (Ruitenberg, Ott, van Swieten, Hofman, & Breteler, 2001), although sex differences are not always found (Andersen et al., 1999). Since risk due to sex is complicated by other factors, such as age, education,

hormone levels, *APOE*-ε4 status, comorbidities and lifestyle, it is likely not a meaningful risk factor on its own (Bendlin et al., 2010; Chen, Lin, & Chen, 2009).

2.5.2.2 Genetic Factors

A family history of AD was one of the earliest established risk factors for the disease (Graves, 2004). Having a parent with AD may increase an individual's risk up to six-fold (Bendlin et al., 2010). Aside from the autosomal dominant mutations that directly cause AD and VaD (see sections 2.3.2 and 2.4.2), other genetic factors increase the likelihood of these outcomes. In particular, the *APOE* gene, which codes for a transport protein involved in cholesterol regulation, affects the risk of AD: the ε2 allele has a protective effect, but the ε4 allele increases risk by a graded dose effect (Corder et al., 1993). One copy of the ε4 allele increases risk slightly, while ε4 homozygosity is associated with the highest risk of AD (Corder et al., 1993). Approximately 40% of AD cases have at least one *APOE*-ε4 allele compared to 15% of the general population, and cases with the allele typically experience earlier onset of the disease (Bendlin et al., 2010). *APOE*-ε4 has also been identified as a significant risk factor for VaD in some studies (Chuang et al., 2010; Hebert et al., 2000), but not in others (Korczyn et al., 2012). Despite inconsistent evidence, a link between *APOE*-ε4 and risk of VaD is plausible, as *APOE*-ε4 increases the risk of atherosclerotic disease and may play a role in cognitive decline after incidence of stroke, two health conditions that are associated with VaD (Korczyn et al., 2012).

2.5.2.3 *Cognitive Factors*

Cognitively stimulating activities have a protective effect against development of AD and VaD in late adulthood (Ferri et al., 2014). Such findings may be explained by the cognitive reserve theory, which states that a high level of cognitive activity over time enhances the capacity to resist the decline typically associated with brain damage (Stern, 2002; Stern, 2012). According to this theory, cognitive factors such as educational attainment and skills-building contribute to development of efficient synaptic connections and complex neuronal networks that allow the brain to compensate in the event of neurodegeneration (Stern, 2002). The underlying pathology may be present but clinical symptoms do not appear or are reduced or delayed. Indeed, studies have shown inconsistencies between clinical dementia and degree of AD or cerebrovascular neuropathology: in some cases, individuals have maintained relatively intact cognition during life despite discovery of extensive neuropathology at post-mortem autopsy (Davis, Schmitt, Wekstein, & Markesbery, 1999; Price et al., 2009; SantaCruz et al., 2011). Furthermore, the rate of cognitive decline in late life is inversely associated with lifetime cognitive activity, independent of

underlying neuropathology (Wilson et al., 2013). These findings suggest that a high level of cognitive development throughout life protects against the decline of aging and neuropathology.

Other mentally stimulating activities, such as complex occupations, social engagement and leisure activities, are also protective against dementia. High complexity of work involving people and objects significantly reduced the risk of dementia and VaD, but not AD, in the Canadian Study of Health and Aging (Kröger et al., 2008). A study on Swedish twins found that complex work involving interaction with people was associated with lower odds of AD (odds ratio [OR]=0.83, 95% confidence interval [CI]=0.70-0.98) and all-cause dementia (OR=0.86, 95% CI=0.76-0.98) after adjusting for age, sex and education (Andel et al., 2005). Alternatively, high levels of stress that often accompany complex jobs may contribute to AD and dementia risk (Wang, Wahlberg, Karp, Winblad, & Fratiglioni, 2012), thereby obscuring the effect of work complexity on cognitive outcomes.

Leisure activities involving mental or physical stimulation are also thought to be protective against dementia, AD and VaD. Mental activities, such as seeking new experiences, exchanging ideas, travelling, working on odd jobs, and knitting have been associated with decreased odds of dementia or AD (for review, see Fratiglioni & Wang, 2007). A prospective cohort study of non-demented older adults found a significantly reduced risk of dementia with increased participation in cognitive activities, such as reading or writing for pleasure, doing crosswords or playing a musical instrument (Verghese et al., 2003). This association was similar for both AD and VaD, instead of dementia, as the outcome.

The protective benefits of cognitive stimulation against the development of dementia reach into early adulthood. Consistent with cognitive reserve theory, indicators of adolescent cognitive performance, such as mental ability (Whalley et al., 2000) and written language skills (Riley, Snowdon, Desrosiers, & Markesbery, 2005; Snowdon et al., 1996b), have been linked to cognitive function and AD in old age. Indeed, low idea density, a measure of written language skills, in autobiographies written in early adulthood was strongly associated with MCI, dementia, higher Braak stage, and lower brain weight over fifty years later in the Nun Study (Riley et al., 2005). Formal educational attainment is protective against dementia. Low levels of education are associated with an increased risk of all-cause dementia and specifically AD (EClipSE Collaborative Members et al., 2010; Evans et al., 1997; Fratiglioni et al., 1997; Gatz, Prescott, & Pedersen, 2006; Karp et al., 2004; Launer et al., 1999; Ott et al., 1999; Qiu, Backman, Winblad, Aguero-Torres, & Fratiglioni, 2001; Stern et al., 1994). Investigation of the association has been less extensive in individuals with VaD: low levels of education were associated with an increased risk of

post-stroke dementia (Pohjasvaara, Erkinjuntti, Vataja, & Kaste, 1997), but not with VaD in an Italian population (Ravaglia et al., 2005).

2.5.2.4 Psychosocial Factors

Social engagement, in the form of close confidants, sports, and cultural activities at age 30 and 50, was associated with a reduced risk of dementia (Seidler, Bernhardt, Nienhaus, & Frolich, 2003), although data may have been subject to recall and proxy biases based on the case-control nature of the study. Among longitudinal studies, social factors such as marital status, living arrangements, close friendships, and parenthood all have an effect on dementia, with more social connections associated with lower risk of dementia (Fratiglioni & Wang, 2007). A decline in social engagement from mid- to late-life has been associated with dementia (Saczynski et al., 2006), suggesting that individuals who, serving as their own controls for optimal social engagement, had lower engagement in late life were at higher risk of developing dementia. An alternative interpretation of these findings might suggest that social withdrawal is a prodromal sign of dementia (Saczynski et al., 2006).

Findings have suggested that the quality of social interactions may better predict dementia risk: supportive, engaging relationships, as opposed to superficial ones, may offer greater protection. Indeed, emotional support is associated with better cognitive function (Seeman, Lusignolo, Albert, & Berkman, 2001) and is more protective against cognitive decline than is practical support through help with daily tasks (Ellwardt, Aartsen, Deeg, & Steverink, 2013). Social ties and emotional support are also found to protect against post-stroke cognitive decline (Glymour, Weuve, Fay, Glass, & Berkman, 2008), an effect that may be mediated by feelings of loneliness (Ellwardt et al., 2013). Indeed, Holwerda and colleagues (2014) found self-reported loneliness (i.e., perceived social isolation), but not objective social isolation, to increase the risk of dementia. In another study, adjustment for cognitive activity reduced the effect of loneliness in older adulthood on the risk of AD (Wilson et al., 2007). Altogether, these findings suggest that emotionally supportive and mentally stimulating relationships may reduce the risk of dementia, AD and VaD, while loneliness may increase the risk.

A growing body of literature suggests that personality characteristics may affect dementia outcomes. Indeed, high neuroticism, the tendency to experience negative emotions (e.g., anxiety, anger and sadness), was associated with an approximately three-fold increase in AD risk compared to individuals with low neuroticism (Terracciano et al., 2014; for review, see Prina, Pender, Ferri, Mazzotti, & Albanese, 2014). Similarly, stress, anxiety and depression may contribute to the risk of dementia, AD and VaD. A longitudinal study of Swedish women found that self-reported frequent psychological stress

at multiple time points throughout mid- and late-life was associated with an increased risk of dementia and AD (Johansson et al., 2010). Chronic psychological distress has also been identified as a risk factor for AD in the Religious Orders Study (Wilson et al., 2003). High proneness to distress increases the likelihood of developing AD by 2.7 times when compared to those not prone to distress (Rothman & Mattson, 2010). Several studies have suggested that a history of severe or prolonged trauma may increase the risk of cognitive decline and dementia (Johnston, 2000; Sapolsky, 2000). Prisoner of war survivors who have a history of posttraumatic stress disorder show significant deficits in several aspects of cognition including memory, attention and executive function (Golier et al., 2002; Joffe, Brodaty, Luscombe, & Ehrlich, 2003; Sutker, Vasterling, Brailey, & Allain Jr., 1995). However, this association is not found consistently, leading some to suggest that cognitive deficits in prisoners of war may be attributed to depression rather than to stress (Sulway et al., 1996).

Indeed, depression is widely acknowledged as a contributor to cognitive decline (Gatz, Tyas, St. John, & Montgomery, 2005). The population attributable risk due to depression is estimated to be 10.6% of AD cases worldwide (Barnes & Yaffe, 2011). Two meta-analyses found that depression is significantly associated with risk of all-cause dementia, AD and VaD (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Jorm, 2000). Another study found depressive symptoms to be correlated with NFT and Aβ plaque loads in MCI (Lavretsky et al., 2009). However, these findings obscure the fact that depression is the most common cause of reversible dementia (Tripathi & Vibha, 2009), raising the question as to the true directionality of the observed association. Studies reviewed in the aforementioned meta-analyses on depression and dementia (Diniz et al., 2013; Jorm, 2000) were prospective cohort studies, which allowed temporal associations to be made. However, the average follow-up was only five or six years (Diniz et al., 2013), while AD pathology may be seen up to twenty years prior to clinical manifestation (Jack et al., 2010). Along these lines, researchers (Gallagher et al., 2011; Olariu et al., 2001; Ringman et al., 2004) have suggested that depression and anxiety in MCI may be prodromal symptoms of AD rather than risk factors. This argument is supported by the fact that depression, and affective disorders in general, are commonly found as symptoms of dementia. Long-term, prospective studies would be beneficial to clarify this association.

2.5.2.5 *Factors Related to Physical Health*

Several health conditions, particularly cardiovascular and metabolic irregularities, have been identified as risk factors for dementia, AD and VaD. Cerebrovascular disease, atherosclerosis, hypercholesteremia and hypertension are highly associated with VaD (Gorelick, 2004) and are also risk

factors for AD and all-cause dementia (Bendlin et al., 2010; Reitz & Mayeux, 2014). Cerebrovascular diseases, including various types of infarcts and lesions, lead to brain tissue damage that may cause VaD (Reitz & Mayeux, 2014). In a meta-analysis, incidence of post-stroke dementia was 7.4% among individuals who had experienced a single stroke (Pendlebury & Rothwell, 2009). Cerebrovascular disease contributes to development of AD as well (Toledo et al., 2013). Damage to brain tissue may lead to abnormal Aβ deposition, AD-related inflammatory response or inappropriate activation of Cdk5, one of the proteins involved in tau phosphorylation and production of NFTs (Reitz & Mayeux, 2014).

Substantial evidence links blood pressure to risk of AD and VaD (for review, see Qiu, Winblad, & Fratiglioni, 2005). However, the effect of blood pressure on these types of dementia is complex and varies by age and disease. Extreme hypertension (≥160/95) in participants between age 42 and 68 ("midlife") has been significantly associated with risk of developing dementia and AD (Qiu et al., 2005). Approximately 5% of cases of AD worldwide are attributed to midlife hypertension (Barnes & Yaffe, 2011). Conversely, hypotension late in life is associated with increased risk of AD, most likely due to cerebral hypoperfusion leading to neuronal damage (Qiu et al., 2005). Risk of VaD due to hypertension may vary by sex (Hebert et al., 2000), or may be limited to untreated hypertension (Launer et al., 2000) or systolic blood pressure only (Yamada et al., 2003). Taken all together, evidence indicates that blood pressure is an important risk factor for dementia, AD and VaD.

Metabolic syndrome, the co-occurrence of several reversible metabolic disorders (e.g., hypertension, dyslipidemia, glucose intolerance, and obesity), may be a risk factor for VaD (Raffaitin et al., 2009; Yaffe, Weston, Blackwell, & Krueger, 2009), although this association has not been found consistently (Forti et al., 2010). The relationship between metabolic syndrome and cognitive impairment is mediated by high levels of inflammatory proteins interleukin 6 and C-reactive protein (Yaffe et al., 2004), but further research is needed to clarify the association (Reitz & Mayeux, 2014).

The link between metabolic syndrome and dementia, AD and VaD is likely significant since many of the individual components of the syndrome, including dyslipidemia, diabetes mellitus, and body mass index (BMI), have been found to contribute to the risk of dementia and underlying conditions. Dyslipidemia increases the risk of vascular diseases, which are underlying factors in both VaD and AD (Korczyn et al., 2012; Raffaitin et al., 2009). Similarly, diabetes may contribute to development of AD and VaD through vascular associations (e.g., stroke, hypertension and dyslipidemia; for review, see Reitz & Mayeux, 2014). A meta-analysis of eight prospective cohort studies from Canada, USA and Europe estimated the relative risk of all-cause dementia, AD and VaD in individuals with diabetes to be 1.47

(95% CI=1.25-0.73), 1.39 (95% CI=1.16-1.66) and 2.38 (95% CI=1.79-3.18), respectively (Lu, Lin, & Kuo, 2009). Worldwide, 2.4% of cases of AD may be attributed to diabetes mellitus (Barnes & Yaffe, 2011). The effect of BMI on risk of dementia is U-shaped: both underweight and obesity pose an increased risk (Beydoun, Beydoun, & Wang, 2008). Furthermore, midlife overweight and obesity increase the risk of both AD and VaD, independent of stroke, cardiovascular disease and diabetes. This association is graded, such that individuals who are obese in midlife have a greater risk of developing VaD and AD compared to those who are overweight (Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007). Indeed, the population attributable risk of midlife obesity is 2.0% of the global prevalence of AD (Barnes & Yaffe, 2011).

Physical activity has a potential protective effect against dementia and its subtypes. In a systematic review, 11 out of 14 studies reviewed found that physical activity significantly decreased risk of dementia or AD (Fratiglioni & Wang, 2007). A similar protective effect is also found for VaD. A meta-analysis of five studies that investigated the relationship between physical activity and VaD demonstrated an OR of 0.62 (CI=0.42-0.92; Aarsland, Sardahaee, Anderssen, Ballard, & Alzheimer's Society Systematic Review group, 2010). The prevalence of AD worldwide would be reduced by 12.7% if physical activity was universal (Barnes & Yaffe, 2011). The inverse relationships of physical activity with dementia and its subtypes are not surprising given the positive effect that physical activity has on cardiovascular health, a contributing factor to both AD and VaD pathology.

2.5.2.6 Other Factors

Other lifestyle factors that influence the risk of dementia, AD and VaD include smoking cigarettes, alcohol consumption, and diet. Moderate or heavy smoking in mid-life is associated with an increased risk of AD (Tyas et al., 2003) and VaD (Korczyn et al., 2012). Alcohol consumption may affect the risk of all-cause dementia and AD, although the association is not straightforward. Smoking and alcohol use may interact to affect risk (Tyas, Koval, & Pederson, 2000). Moderate consumption of red wine was found to decrease risk of dementia and AD in both French (Larrieu, Letenneur, Helmer, Dartigues, & Barberger-Gateau, 2004) and American (Luchsinger, Tang, Siddiqui, Shea, & Mayeux, 2004) populations. However, other types of alcohol do not seem to have the same effect (Luchsinger et al., 2004). In terms of nutrition, the Mediterranean diet and other diets that contain antioxidant-rich fruits and vegetables as well as sources of polyunsaturated fats, such as fish and seafood, provide several cardiovascular, inflammatory and neuronal benefits and are associated with decreased risk of all

dementias, including AD and VaD (Hebert et al., 2000; Larrieu et al., 2004; Lourida et al., 2013; Reitz, Brayne, & Mayeux, 2011; Scarmeas, Stern, Mayeux, & Luchsinger, 2006).

2.5.2.7 *Risk Across the Lifespan*

Risk factors for dementia, AD and VaD may be cumulative across the lifespan. Furthermore, adverse conditions encountered during growth and development, even as early as at conception, have been associated with cognitive decline in late life. Such findings indicate that chronic dysfunction or acute physiological disruption at critical developmental points across the lifespan may contribute to neuropathology. However, reversal of these risk factors may lower the risk of eventual AD or VaD. For example, treatment of cardiovascular risk factors, such as antihypertensive therapy, has been associated with decreased risk of dementia (Monsuez et al., 2011). Alternatively, other factors such as mentally stimulating hobbies, close social relationships and physical activity, as described previously, have been found to be protective against the effects of neurodegeneration. As such, identification and reversal of lifetime risk factors in addition to interventions focused on enhancement of protective factors across the lifespan may help to delay the onset or slow the progression of disease and thereby decrease the burden of dementia, and, in particular, AD.

2.6 Emotions

Emotions are a driving force in many life events and are the result of conscious or subconscious appraisal of situations. As a result of such appraisal, emotions function to assign contextual value as well as to stimulate mental and physical responses (Dolan, 2002; Farb, Chapman, & Anderson, 2013). Each emotion is comprised of a highly specific set of responses (Farb et al., 2013), but they are commonly grouped together based on positive or negative valence, that is, the attractiveness or aversiveness of a stimulus (Dolan, 2002; Frijda, 1986). Similarly, emotions can be described by the arousal level, or significance, of a stimulus (i.e., high or low) such that highly arousing cues, regardless of valence, are more likely to receive perceptive awareness and as a result, elicit more intense responses (Dolan, 2002). The valence-arousal model categorizes emotions based on hedonic value and bodily activation (Feldman-Barrett, 1998). Emotions within the same valence demonstrate relatively consistent patterns of brain region activity and associated physiologic responses (Anders, Lotze, Erb, Grodd, & Birbaumer, 2004). Thus, this model is useful in describing underlying physiological effects of emotions. Positive and negative emotions differ in direction of attention, behavioural tendencies and autonomic nervous system

activation (Anders et al., 2004). These differences present unique adaptive benefits such that positive and negative emotions are not equal and opposite, but rather are complementary to allow the best response to the situation at hand.

Appropriate response to environmental stimuli relies on three key functions of emotions: sensory gating, defined as the control of perceptions and attention; knowledge integration, which involves the cognitive organization of complex events and determination of stimuli relevance; and embodied expression, or the physical representation of the emotion that is experienced (Farb et al., 2013). These functions, which are highly integrated in daily psychological and physiological function, may be the basis for a potential effect of emotional experience across the lifespan on development of dementia and AD in late life.

Emotional processing relies on the orchestration of cognitive and physical functions. Cognitive appraisal and physical action lead to immediate internalization and communication of, and response to, emotional stimuli while further psychological consideration assigns context to the situation. Meanwhile, processes involving learning and memory formation are engaged for efficient recognition and management in future encounters. Intricate neural pathways spanning several brain regions, including the limbic system and the reticular formation in the brainstem, regulate the emotional response (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Noback, Strominger, Demarest, & Ruggiero, 2005). Emotional processing that occurs within these regions of the brain subsequently triggers physiological responses through stimulation of the ANS. The interplay between each of these key components, including the limbic system, the reticular formation and the ANS, have implications in cognitive, behavioural and physical processes that may contribute to the risk of dementia, AD and VaD.

2.6.1 **Cognitive Effects of Emotions**

2.6.1.1 *The Limbic System*

Brain regions associated with emotions, including the thalamus and parts of the limbic system (e.g., the amygdala and hippocampus) are commonly affected in AD and other forms of dementia, and may present a link between emotions and the risk of dementia. The limbic system, which governs emotions and memory, is comprised of a neural circuit spanning cortical and subcortical areas of the brain (Noback et al., 2005). Bidirectional reciprocal pathways throughout the limbic system guide emotional processes including stimulus appraisal, learning, memory formation and activation of effector systems for appropriate physical response (Noback et al., 2005; Purves, 2001; Cahill & McGaugh, 1998). Notably,

the amygdala is responsible for integrating sensory and cognitive inputs in the processing of emotions, and is most commonly associated with implicit (i.e., unconscious) memory formation involving negative emotions, such as fear conditioning (Phelps & LeDoux, 2005), given the high priority of response to threatening situations associated with negative emotions. However, the amygdala has also been implicated in positive reward conditioning in some individuals (Canli et al., 2002). Furthermore, the amygdala is likely indirectly involved in the regulation of cognitive functions such as attention, perception and explicit memory formation (LeDoux, 2007). These cognitive influences may have implications for the development of dementia and AD. Indeed, atrophy of the amygdala is associated with AD neuropathology; however, it is less clearly associated with the clinical symptoms of the disease (Horinek, Varjassyova & Hort, 2007). Potential mechanisms by which emotion-regulated cognitive functions, such as perception, attention, learning and memory formation, may affect cognitive reserve and the development of dementia and AD, are discussed below.

2.6.1.2 *Perception and Attention*

As discussed, one of the key functions of emotions is sensory gating, which is the control of perception and attentional direction in the presence of an emotional stimulus. Highly arousing stimuli are more likely to induce an emotional response thereby enhancing perception, attention and memory associated with the specific cue (for review, see Dolan, 2002). For example, emotion-inducing images are perceived to be more vivid than neutral images (Todd, Talmi, Schmitz, Susskind, & Anderson, 2012) and negative facial expressions draw attention quicker than neutral faces (Frischen, Eastwood, & Smilek, 2008), suggesting that emotionally salient stimuli receive preferential perceptive and attentive awareness (see review by Vuilleumier, 2005). Furthermore, valence differentially affects attention and perception: negative stimuli are associated with greater direct attention and impairment of peripheral awareness when compared to positive valence stimuli (Fredrickson & Branigan, 2005). This association between valence and attention is likely modulated by the arousal level of the stimulus (Fernandes, Koji, Dixon, & Aquino, 2011). In addition, the pre-existing mood of an individual at the time of emotional stimulation also contributes to attention: positive moods increase peripheral perception, whereas negative moods yield acute attentional focus (see review by Farb et al., 2013). Emotion-directed attention and perception influence exchanges with, and analysis of, environmental stimuli. Such interactions with the surroundings provide the basis for higher cognitive processing including learning, memory, decision-making and problem solving, which may have implications for the development of dementia by contributing to cognitive reserve over the long-term.

2.6.1.3 *Learning and Memory*

After initial sensory gating, a second function of emotions is adaptive knowledge integration, in which motivational relevance is assigned to stimuli in order to facilitate cognitive organization of emotional experiences (Farb et al., 2013). That is, information conveyed in the environment is further appraised for contextual meaning and stored in the memory for future retrieval. Indeed, emotional memories of high personal relevance are most likely to be retained and higher levels of arousal evoke more vivid memories (for review, see Holland & Kensinger, 2010). Emotional valence also affects the way in which events are remembered; memories of positive emotional valence are more likely to include global, "big-picture" characteristics while negative memories tend to feature more specific details (Holland & Kensinger, 2010). Such patterns of memory formation may partially determine the value of the memories in the context of cognitive reserve theory. Global memories that result from positive emotional experiences may have broad application for future reference in a variety of situations, thereby building reserve. On the other hand, negative-emotion memories that are detail-oriented may only apply in highly specific contexts.

2.6.1.4 *Decision-Making and Problem-Solving*

Differences in memory formation and retrieval based on emotional experiences may in turn, affect decision-making and problem solving over the long term. Indeed, negative moods signal that the current environment is problematic and focus is placed on each situation-specific detail in order to make decisions (for review, see Schwarz, 2000). Alternatively, positive mood allows referral to, and manipulation of, pre-existing knowledge (Schwarz, 2000). These patterns of information retrieval based on emotional state play a role in decision-making and problem solving. Positive affect consistently enhances creative problem solving, suggesting that the neuropsychological effect of positive emotions allows for cognitive flexibility and access to a larger number of more innovative thoughts (for review, see Ashby, Isen, & Turken, 1999). In a randomized controlled trial, physicians in whom positive emotions were induced through receipt of a small bag of candy generated correct hypotheses for a diagnosis in significantly less time when compared with control groups who did not receive an emotion-inducing treatment (Estrada, Isen, & Young, 1997). However, the length of time to confirm the diagnosis did not differ between the treatment and control groups, suggesting that individuals with positive emotions took more time to explore various explanations after establishing a hypothesis (Estrada et al., 1997). Similarly, students asked to perform a computational problem-solving task did not differ in the time it took to complete the task, but rather differed in strategies for completion: those with induced negative emotions

tended to take more time to collect all information before attempting a solution when compared to those with induced positive emotions and to controls (Spering, Wagener, & Funke, 2005). While both positive and negative emotions function similarly to obtain relevant information for decision-making and problem solving, differences in retrieval strategies may have wider implications on cognitive development. Negative emotions are associated with retrieval of task-specific details and may limit cognitive development. In contrast, positive emotions allow cognitive flexibility, creativity and exploration that may confer long-term benefits and protect against expression of clinical symptoms in the event of neuropathology.

2.6.1.5 *The Broaden-and-Build Theory*

The differences in development of cognitive resources as a result of positive and negative emotions may be attributed to behavioural tendencies associated with each emotional valence. The broaden-and-build theory (Fredrickson, 1998; Fredrickson, 2001; Fredrickson, 2004) explains this phenomenon in terms of momentary thought-action repertoires, such that positive emotions increase the tendency to play, explore, try new things and interact with people and objects in the environment. Although this broadened mindset presents an increased potential for distractibility that may detract from cognitive efficiency (Dreisbach & Goschke, 2004), persistent positive emotions lead to the discovery of new, creative thoughts and actions. Over time, such exploration likely contributes to the accumulation of enhanced brain functions and the development of a wide array of cognitive resources (for reviews, see Fredrickson, 2001; Fredrickson, 2004). This relationship between positive affect and the development of cognitive functions presents a potential link between emotional well-being across the lifespan and decreased risk of dementia of various subtypes. Over time, broadened thought-action repertoires may contribute to cognitive flexibility and compensatory mechanisms consistent with cognitive reserve theory. As such, positive emotions may be protective against cognitive decline and dementia due to AD and VaD pathology. Alternatively, negative emotions may limit such opportunities for development by narrowing focus and defaulting to specific action tendencies, thus detracting from the development of new skills (Fredrickson, 2001).

2.6.2 **Psychosocial Effects of Emotions**

2.6.2.1 The Reticular Formation

Cognitive processing of an emotion may be achieved in seconds to several minutes depending on quality and perceived urgency of the stimulus. Upon appraisal of environmental stimuli, appropriate

physiological and motor responses are activated via the reticular formation (Purves, 2001). A wide range of functions including sleep and alertness, cardiovascular function, respiration, pain and voluntary motor control are modulated and coordinated by this bundle of nerves in the brainstem, spanning from the thalamus and hypothalamus to the spinal cord (Noback et al., 2005; Purves, 2001). Constant processing of neuronal signals by the reticular formation allows dynamic and precise responses that are based on the quality and novelty of both somatic and cerebral nerve inputs. Such physical responses guide both autonomic nervous system function as well as approach and withdrawal behaviours, which depend on the perceived quality of the stimulus (Lang & Bradley, 2010; Noback et al., 2005). These spontaneous responses provide the basis for interaction with people and objects in the immediate environment (Niedenthal & Brauer, 2012) and thus have implications for social and cognitive experiences that may affect the risk of dementia and AD.

2.6.2.2 *Emotions and Psychosocial Experience*

The associations of positive valence emotions with approach behaviours, and negative emotions with avoidance behaviours, are consistent with the broaden-and-build theory (see section 2.6.1.5). Such tendencies to approach or withdraw affect the way in which individuals pursue social relationships, which may have implications for participation in recreational activities (e.g., Burger & Caldwell, 2000; Watson, Clark, McIntyre, & Hamaker, 1992). Participation in stimulating recreational activities, especially those with physical and social aspects, has been associated with a decreased risk of dementia, AD and VaD (see sections 2.5.2.3 to 2.5.2.5). Thus, behavioural tendencies that present opportunities for social interaction and recreation may contribute to enhanced cognitive function over the long term. Alternatively, withdrawal from social situations as a result of negative emotions limits the benefits gained through such interactions.

In addition to presenting opportunities for stimulating social activities, approach behaviours consistent with positive emotions may enhance development of close relationships and social networks through friendship seeking. Individuals who experience positive moods (i.e., “happy people”) are more likely to exhibit pro-social behaviour including generosity, altruism and charity (Lyubomirsky, King, & Diener, 2005) and demonstrate increased social cooperativeness (Schwarz, 2000), which may lead to stronger friendships. Positive emotions are associated with a greater understanding of others as an extension of self and those who experience positive emotions tend to have greater satisfaction in their relationships (Waugh & Fredrickson, 2006; for meta-analysis, see Lyubomirsky et al., 2005). In turn, close social relationships provide support to cope with negative life events and may be associated with a

decreased risk of dementia and its subtypes. Alternatively, withdrawal from social situations resulting from negative emotions, and subsequent failure to develop close personal relationships, may lead to social isolation, loneliness, and elevated stress levels, all of which may contribute to the development of dementia and AD (Sections 2.5.2.4 & 2.6.4.1).

2.6.3 Physical Effects of Emotions

2.6.3.1 *The Autonomic Nervous System*

The physiological responses of emotions may also affect the risk of dementia, AD and VaD. Emotional processing in the brain leads to stimulation of the autonomic nervous system (ANS). The ANS controls subconscious, involuntary functions, such as respiration, cardiovascular function, digestion, perspiration, pupil dilation and sexual arousal (Purves, 2001). This effector system is regulated by the hypothalamus via the reticular formation and is therefore closely linked to the limbic system and emotional response. The ANS is comprised of two complementary divisions, called the sympathetic and parasympathetic systems, which are alternately employed.

In the absence of intense stimuli, the parasympathetic division maintains homeostasis and energy metabolism (Purves, 2001). Emotional arousal stimulates the sympathetic division to prepare the body for appropriate action by stimulating highly precise physiological processes. Functions such as vascular, bronchial and pupillary dilation; increased heart rate and stroke volume; stimulation of glucose production; and secretion of sweat, hormones and neurotransmitters are variably activated based on the context of the situation (Purves, 2001). Other neuronal pathways within the sympathetic system inhibit functions that are not immediately required during activity (e.g., parasympathetic processes involved in digestion) so that all available energy can be diverted to the task at hand, if warranted (Purves, 2001). Repeated emotional arousal leading to chronic stimulation of the sympathetic ANS may contribute to dysfunction of these processes, leading to negative health outcomes associated with an increased risk of dementia, AD and VaD.

2.6.3.2 *Cardiovascular Effects of Emotions*

Most negative emotions stimulate ANS function, variably leading to accelerated heart rate, vasoconstriction and increased cardiac output. When experienced chronically, such cardiovascular reactivity may contribute to the development of cardiovascular conditions such as hypertension (Jonas, Franks, & Ingram, 1997), atherosclerosis (Stewart, Janicki, Muldoon, Sutton-Tyrrell, & Kamarck, 2007)

and coronary heart disease (Mauss & Gross, 2004). Several negative personality variables, such as impatience, anger, hostility, depression, and anxiety, are significantly associated with negative cardiovascular outcomes such as coronary heart disease, myocardial infarction, angina and cardiac death (for review, see Booth-Kewley & Friedman, 1987; Sirois & Burg, 2003). In addition, a prospective cohort study of older adults showed that depressive symptoms were associated with an increased risk of stroke even after adjusting for various comorbidities and lifestyle factors (Ostir, Markides, Peek, & Goodwin, 2001). Cerebrovascular disease, atherosclerosis and hypertension accelerate the onset of dementia in AD and contribute to VaD pathology (see section 2.5.2.5). Thus, tendency toward negative emotions, which increase cardiovascular reactivity and the risk of adverse cardiovascular events, may also contribute to the development of AD and VaD.

Alternatively, positive emotions serve to overcome the cardiovascular effects of negative emotions. Several studies have demonstrated that positive emotions have an undoing effect. The physiological effects caused by negative emotions return to baseline at a faster rate when positive, as compared to neutral, emotions are induced following a negative event (e.g., Fredrickson & Levenson, 1998; Fredrickson, Mancuso, Branigan, & Tugade, 2000). This phenomenon may explain the protective effects of positive emotions against health outcomes (Cohen & Pressman, 2006) and cardiovascular diseases in particular (Kubzansky, Sparrow, Vokonas, & Kawachi, 2001). Consistent with this idea, positive affect reduces the risk of stroke, which is highly involved in VaD (Ostir et al., 2001). As such, the combination of both positive and negative emotions acting together may affect the development of cardiovascular diseases that are associated with dementia outcomes. Over the long-term, the accumulation of positive and negative emotions and the tendency towards one valence or the other may differentially affect the development of diseases of dementia by increasing or decreasing the risk of underlying cardiovascular diseases.

2.6.4 Emotions, Stress and Emotion Regulation

2.6.4.1 *Stress as a Risk Factor for Dementia, AD and VaD*

Negative emotions, especially those of high arousal experienced over a prolonged period of time, are highly related to psychological stress. The stress response, which involves the release of corticotropin releasing hormone (CRH) and subsequent secretion of the hormone cortisol, is a recognized risk factor for dementia, AD and VaD (see section 2.5.2.4). Studies using animal models provide strong evidence of a molecular link between stress and the development of dementia and particularly AD. Stress leads to the

upregulation of the enzymes involved in the amyloidogenic pathway, causing an accumulation of Aβ plaques (Catania et al., 2009; Dong et al., 2012). In addition, CRH has been shown to affect neurogenesis; its overexpression in genetically modified mice is associated with significantly less dendritic arborization and fewer dendritic spines (Dong et al., 2012). Such findings indicate that stress may reduce the potential for neuroplasticity, thus restricting cognitive development. Chronically high levels of cortisol that are associated with the stress response increase hypertension and general cardiovascular risk (for review, see Whitworth, Williamson, Mangos, & Kelly, 2005). As such, stress may mediate the association of emotions with dementia, AD and VaD. Indeed, a Swedish cohort study with 38 years of follow-up found the association between neuroticism and clinically diagnosed AD was mediated by long-standing distress (Johansson et al., 2014). Alternatively, extraversion (i.e., the tendency to be sociable, assertive, enthusiastic and energetic), which was associated with low distress, did not affect the risk of AD (Johansson et al., 2014).

2.6.4.2 Coping and Emotion Regulation

The ability to cope with adverse situations, negative emotions and stress is important for optimal health and may have implications in the development of dementia and AD. Mature coping strategies such as positive reframing, creative exploration, humour and redirection of focus allow psychological growth even in the face of adversity (see meta-analysis by Lyubomirsky et al., 2005; Tugade, Fredrickson, & Barrett, 2004). Indeed, positive emotions mediate the ability to efficiently regulate negative emotions (Tugade & Fredrickson, 2004). Individuals who experience positive emotions on a daily basis are less reactive to stress and are better able to recover after a stressful event than individuals who do not experience daily positive emotions, an association that is especially true for highly resilient individuals (Ong, Bergeman, Bisconti, & Wallace, 2006). In a laboratory setting, individuals who had a tendency towards positive emotions had lower cortisol levels in response to a stress-inducing treatment and also displayed better cardiovascular recovery afterwards (Bostock, Hamer, Wawrzyniak, Mitchell, & Steptoe, 2011). As such, while negative emotions contribute to stress and long-term poorer health outcomes, positive emotions may confer protective benefits by providing a coping mechanism and by enhancing resilience.

Coping is a function of personality under a broader construct of emotion regulation. Emotion regulation is the dynamic process by which an individual controls, either consciously or unconsciously, which, when and how emotions are experienced and expressed (Gross, 1998). While coping focuses on decreasing negative emotion experiences, the goals of emotional regulation are much wider ranging such

that feelings and behaviours are adjusted to match situational context. Such strategies for reaching these goals include situation selection, situation modification, attentional deployment, cognitive change, and response modulation (Gross, 1998). These strategies require high-level cognitive manipulation involving bidirectional communication between emotion-generating limbic centers and emotion-regulating cortical centers of the brain (Gross, 1998). As such, capacity for emotional regulation may be demonstrative of cognitive ability and may have implications on the risk of dementia and AD. Indeed, similar to patterns found with coping, individuals who demonstrate high neurotic (negative) and low extraverted (positive) personality characteristics have an increased risk of AD over the long-term (Johansson et al., 2014).

2.6.4.3 *Suppression and Expression of Emotions*

Emotion regulation is generally viewed as a desirable ability, given the advantage it presents in controlling emotional responses to achieve specific goals. However, response modulation through suppression, as a strategy of emotion regulation, is thought to be less healthy than other strategies since it focuses on controlling behavioural responses after the emotion has been generated and thus results in unresolved emotions, depletion of cognitive resources and negative feelings about oneself (John & Gross, 2004). As such, suppression of emotions is associated with negative health outcomes. Indeed, active suppression of an emotional experience heightens cardiovascular activation (Gross & Levenson, 1997) and is hypothesized to be associated with the development of cardiovascular diseases (Brosschot & Thayer, 1998; Pennebaker, 1992). Conversely, expression of emotions through verbal or written communication as a coping strategy has been associated with improved health outcomes in people with physical or psychiatric disorders (see meta-analysis by Frisina, Borod, & Lepore, 2004). In the short term, expressive writing of deep personal thoughts and emotions is found to decrease heart rate (Pennebaker, 1997). Improvements in immune function, blood pressure, and lung and liver function have been found following interventions that asked participants to write about traumatic events over several weeks (Baikie & Wilhelm, 2005). Such findings suggest that coping with negative emotions through written or verbal expression may reduce the risk of cardiovascular diseases.

In addition to serving as a regulatory mechanism, emotional expressivity also communicates the emotional state of an individual and thus is useful as a measurement of emotional experience. This is especially true for positive emotions, in which behavioural expression is closely correlated with habitual experience (Gross, John, & Richards, 2000). This same association is present, but weaker, for negative emotions, in which emotional disposition (i.e., high or low expressivity) interacts with experience to predict nonverbal emotional expression (Gross et al., 2000). Indeed, studies have found that emotional

expressivity may have predictive value for long-term health outcomes. Written emotional expressivity has been linked to several aspects of physical and psychological health (Pennebaker, 1997) and longevity (Danner et al., 2001). Similarly, emotional expression in single college yearbook photos was highly predictive of long-term outcomes (Harker & Keltner, 2001). As such, observation of emotional expressivity made at a single time-point may serve as a proxy measure of emotional experience in predicting long-term health outcomes, such as the development of dementia and AD.

2.6.5 Factors Affecting Emotional Expressivity

The benefits of emotional expression through writing are consistent despite individual differences, such as age and sex (Pennebaker, 1997). However, these factors should be considered when measuring expressivity in written work given that expression may vary between individuals. Carstensen and colleagues (2003; 1999) posit that the perception of time, which tends to narrow with age, affects cognitive processing of emotional information so that older adults are more motivated by emotional, rather than knowledge-based, goals. As such, they experience a positivity bias compared to their younger counterparts (Charles, Mather, & Carstensen, 2003; Mather & Carstensen, 2005). Furthermore, men and women show fundamental differences in neural activation in emotion processing (Whittle, Yücel, Yap, & Allen, 2011) and women are more emotionally expressive than men (Kring & Gordon, 1998). Written language skills (i.e., idea density and grammatical complexity) may also affect the ability to communicate emotional experience through writing and have been considered in past investigations using scored autobiographies from the Nun Study (described in detail in section 4.2). Although idea density did not affect the association between positive emotional expressivity and longevity (Danner et al., 2001), correlations between idea density and both positive ($r=0.26$, $p=0.01$) and negative ($r=0.19$, $p=0.07$) emotion words (Snowdon et al., 1996a) suggest that idea density may confound the association between emotional expressivity and AD. Thus, individual differences in characteristics, such as age, sex and written language skills, may influence the association of emotional expressivity with dementia and AD.

2.7 Summary

The psychological, behavioural and physiological aspects of emotions present several possible mechanisms by which cognitive function and brain pathology in late life may be affected. Emotions guide perception and attention and are highly linked with learning, memory formation, decision-making and problem solving. Positive emotions tend to broaden the scope of attention and lead to more global thought

processes, while negative emotions narrow attention and lead to detail-oriented information retrieval. In addition to cognitive development, the behavioural effects of emotions affect the pursuit and development of close social relationships that increase opportunities for recreational activities and provide emotional support in the face of adversity. Emotional support is crucial for coping with negative life events, and thus may alleviate stress. Furthermore, the physiological characteristics of emotions may contribute to the risk of developing health concerns such as hypertension, atherosclerosis and various other cardiovascular diseases. The influence of emotions on these aspects of health and well-being is suggestive of a potential role in the development of dementia and associated neurodegenerative diseases.

The aforementioned influences of emotions may affect the development of dementia, AD and VaD through one of two pathways: by a damaging, neuropathogenic effect or a beneficial, neuroprotective effect. In particular, the experience of negative emotions and the resulting psychological stress may contribute to the neuropathogenesis that is characteristic of AD and VaD by increasing underlying risk factors such as cardiovascular diseases and overexpression of the amyloidogenic pathway. Consistent with these ideas, affective disorders such as depression and posttraumatic stress disorder have been found to increase the risk of dementia and AD. Alternatively, positive affect reduces the cardiovascular effects of negative emotions and provides a source of resilience in stressful situations and thus may counteract the pathogenic effects of negative emotions.

Beyond reversing the effects of negative emotions, positive emotions may have a neuroprotective effect against the development of dementia in the presence of brain pathology by helping to build cognitive resources and resist cognitive decline. Positive emotions also facilitate social networking that may further contribute to cognitive development by increasing the likelihood of mental stimulation through recreational activities. Such plausible mechanisms support the potential association between emotions and the development of dementia and AD. However, previous literature exploring this relationship is limited. Therefore, the objective of the current study is to establish the association of emotional expressivity with dementia and AD. Findings will provide a foundation on which future research can build to further explore the value of emotions in predicting these conditions. These efforts will also inform the development of preventative strategies to help reduce the expected burden of the diseases at both the individual and societal level.

Chapter 3
Study Rationale

3.1 Motivation

3.1.1 Gaps in Current Literature

The current investigation builds upon previous findings from the same study (i.e., from the Nun Study described in section 4.2), which showed that emotional expressivity is predictive of longevity (Danner et al., 2001). In that study, individuals who expressed a high level of positive emotions were likely to live longer than those who expressed a low level of positive emotions. A possible explanation for this finding is that positive emotions are associated with higher quality of life and better health outcomes. Indeed, individuals with a positive mindset tend to have faster recovery times and better psychological well-being, immune function and general health outcomes than people who tend toward negative emotions (for review, see Naseem & Khalid, 2010). Such evidence points to a possible association between emotional expressivity in early adulthood and the development of dementia in late life. However, few studies have explored the relationship between emotions and the risk of dementia or its subtypes. Even fewer have taken a lifespan approach to investigate this relationship. Despite the limited availability of literature, several aspects of emotions experienced across the lifespan present potential mechanisms that may contribute to the risk of dementia and its subtypes. Emotions influence cognition and cardiovascular function, which have been shown to affect the risk of all-cause dementia and underlying pathology. In addition, psychosocial effects of emotions may have implications for cognitive decline and neurodegeneration. Given this evidence, the current study is intended as a novel investigation of the association between emotional expressivity in early adulthood and the development of dementia and the most prevalent subtype, AD, in late adulthood.

Previous investigations of the association of emotional expressivity with dementia and its subtypes are limited and most of the literature has focused only on negative valence emotions. For example, perceived sadness has been associated with both MCI and an increased risk of converting from MCI to dementia when compared to individuals who did not report sadness (Caracciolo, Backman, Monastero, Winblad, & Fratiglioni, 2011). In addition, studies have found that neuroticism, depression, anxiety and loneliness are highly associated with dementia, and in particular, AD and VaD (see section 2.5.2.4). However, these studies have been relatively short-term and may not demonstrate a true causal relationship. Most had only five to eight years of follow-up even though evidence of AD pathology may

be present up to twenty years prior to disease diagnosis (see section 2.3.1). As such, the possibility that anxiety, depression and social withdrawal may be prodromal symptoms of the underlying neuropathology of dementia cannot be ruled out. Nevertheless, the observed effects of depression, anxiety and loneliness suggest a potential role of chronic emotional distress in the risk of dementia and its subtypes.

The potential for novel research in this area is broad given the previous concentration on negative emotions, the relatively short follow-up periods in these studies, and the lack of literature on the effects of positive emotions on dementia. Danner and colleagues (2001) found that positive emotions predicted longevity, suggesting that positivity may confer benefits to general health. These benefits may extend to protecting against dementia and its subtypes because positive emotions broaden attention and perception and contribute to cognitive resources (Fredrickson, 2004). The present study is intended to further the understanding of the long-term effects of emotional expressivity of both positive and negative valence in predicting the development of dementia and AD.

3.1.2 Plausible Mechanisms

Emotional expressivity may affect the risk of dementia and underlying neuropathology through two separate mechanisms. First, emotions are highly involved in cognitive processing and development and may confer neuroprotective benefits by contributing to cognitive reserve. Increased cognitive reserve allows an individual to maintain cognitive function even if neurodegeneration occurs (see section 2.5.2.3). Emotions guide perception and attention: negative emotions, in general, tend to narrow attention and lead to habitual thought-action repertoires whereas positive emotions increase the tendency to explore the environment, try novel experiences and interact with surrounding people and objects. Positive emotions arise from personally enriching experiences and contribute to further personal development through maximization of resources that may lead to enhanced cognitive ability (see section 2.6.1.5). Over the long term, a tendency toward either positive or negative emotions may have beneficial or detrimental effects, respectively, on cognitive development. Positivity, which broadens thoughts and enhances exploratory behaviour, is more likely to build cognitive reserve and protect against cognitive impairment associated with AD and related vascular pathology while negativity may limit such protective effects.

The second mechanism by which emotional expressivity may affect the risk of dementia and its subtypes is through a neuropathogenic effect. In particular, negative emotions may increase the risk of AD pathology because they stimulate cardiovascular activity and are associated with psychological stress. Over the long term, chronic stress and cardiovascular over-stimulation can lead to atherosclerosis, hypertension and cardiovascular disease, which increase the risk of developing neuropathology associated

with AD as well as other subtypes of dementia, such as VaD (see section 2.5.2.5). Thus, in addition to limiting cognitive benefits associated with positive emotions, a tendency toward negative emotions may increase the risk of AD and resulting dementia by contributing to vascular pathology. However, positive and negative emotions interact to regulate cardiovascular function during emotional events. Positive emotions act as a coping mechanism to reverse the effects of negative emotions by efficiently returning cardiovascular function to baseline (see section 2.6.3.2) and may therefore protect against the adverse physiological effects associated with negativity. As such, the combined effects of positive and negative emotions may drive the association of emotional expressivity with dementia and AD.

3.2 Objective

To my knowledge, this is the first study of its kind to investigate the relationship between emotions in early adulthood and the development of dementia and AD in late life. Since this relationship has not previously been explored, the current research project is intended to, first and foremost, establish if an association exists. Data from the Nun Study, described elsewhere (section 4.2), will be used to explore this association. Low prevalence of vascular pathology in this study population prevented the investigation of the effects of emotions on VaD as an outcome, although this association is recommended as a focus for future study.

Various measures of emotions expressed in single autobiographical accounts written in early adulthood by participants of the Nun Study will be compared to late-life outcomes of dementia and AD, diagnosed by cognitive assessments and post-mortem brain pathology. The validity of emotional expressivity in autobiographical documents as an indicator of broader emotional tendencies is supported by previous studies, which have linked written emotional expressivity to several aspects of physical and psychological health (Pennebaker, 1997). The data that will be used in the current investigation have been used previously to show that emotional expressivity affects longevity (Danner et al., 2001). Similarly, emotional expression in single college yearbook photos was highly predictive of long-term outcomes (Harker & Keltner, 2001). Such findings suggest that single, brief observations of emotional expressivity in early adulthood, such as those found in the Nun Study autobiographies, may be indicative of more stable temperament and personality traits and are useful for studying health outcomes in late adulthood.

A secondary purpose of this project is to begin to understand the potential mechanisms by which emotions may affect the development of dementia and AD. All-cause dementia and AD specifically may

be differentially affected by overall expressivity, either emotional valence separately, or the interaction between positive and negative emotions. Analyses accounting for factors including age, education, *APOE*-ε4 status, cerebral infarcts and measures of linguistic ability, have been designed with the intention of investigating different aspects of emotional expressivity and hypotheses have been formed based on previous literature.

First, overall emotional expressivity will be used to assess the effect of emotional expression in contrast to suppression or nondisclosure. Previous literature suggests that suppression of emotions may have long-term negative health effects (see section 2.6.4.3). Furthermore, written expression has been used as a therapeutic tool in helping to cope with emotional adversity. As such, overall emotional expressivity is expected to be associated with a decreased risk of dementia and its subtypes.

Second, positive and negative emotional expressivity, measured individually, will provide insight into the effects of the tendency toward one or the other valence. Positive emotions have been found to increase exploratory behaviours and broaden thought-action repertoires, thereby enhancing cognition and potentially protecting against dementia and AD (see section 2.6.1.5). As such, positive emotions may be associated with a decreased risk of the outcomes of interest. Alternatively, negative emotions have deleterious cardiovascular effects and may increase the risk of dementia and AD by contributing to underlying brain pathology (see section 2.6.3.2). Considering these hypotheses, analyses featuring measures of positive and negative emotional expressivity separately may help to clarify the effects on cognitive and pathological outcomes of dementia and AD.

Finally, the interaction between positive and negative emotions will be tested to determine whether emotions of different valence act together to affect the risk of dementia and AD. Positive emotions have been found to reverse the cardiovascular stimulation caused by negative emotions; thus, the risk of dementia, and more so AD given the significant vascular component, is expected to be highest when negative emotions are high and positive emotions are low (see section 2.6.3.2). Critical analysis of the results of this study will provide insights into the effects of emotional expressivity in early adulthood on development of dementia and AD in late life. However, definitive conclusions regarding the underlying mechanisms cannot be formed as this is beyond the scope of these data.

Chapter 4
Methods

4.1 Literature Search

A systematic review of the literature was conducted in October 2013, and updated in September 2014, to explore the current understanding of the effect of emotions across the lifespan on development of dementia and its two major subtypes, AD and VaD. Since this concept is relatively novel, a broad search of various terms synonymous to, and including, "emotions", "Alzheimer's disease", "dementia" and "vascular dementia" were entered into the Medline database using the PubMed interface as well as into the PsycINFO database of the APA PsycNET. See appendix A for the full search construct. Publications were reviewed for relevance to the proposed topic and were included if they pertained to emotional experience or expression and development of dementia, AD or VaD. Inclusion was limited to English-speaking, peer-reviewed articles. Date of publication was not limited.

The purpose of the search was to review studies that had explored emotions as predictors of neurocognitive disorders. Thus, articles that investigated emotionality following onset of neurocognitive disorders were excluded. Study participants had to be at risk of dementia, AD and VaD at baseline (i.e., incident cases) to be considered for inclusion. Publications that discussed the temporal association between any aspect of emotions or a specific emotion and dementia outcomes were retained. In addition, the current investigation is concerned with non-disordered emotional expressivity so studies including major depression and anxiety disorder were excluded, although they were considered for inclusion in the background literature review. Likewise, studies on stress were also excluded from the core literature (Appendix A, Table 2); although stress is indicative of potential emotional state, it is not an emotion itself.

In all, 2732 publications were identified: 2199 from Medline and 533 from PsycINFO. After duplicates were removed, 2595 remained. A review of titles narrowed the number to 56 publications for full review, and out of these, three were kept for incorporation into the current investigation. Concern for the low number of publications retrieved led to additional manual searches using dementia, AD or VaD terms and specific emotions. Reference lists of related articles were also scanned. Through these supplemental searches, two additional publications were obtained. In all, five publications were identified. The scarcity of literature on the topic supports the novelty and value of the current investigation.

4.2 Data Source: The Nun Study

4.2.1 Background

The Nun Study is a longitudinal study on aging and Alzheimer's disease (Snowdon et al., 1996b; Snowdon et al., 1997). In 1986, the principal investigator, Dr. David Snowdon, began a pilot study on a small group of religious sisters from the congregation of the School Sisters of Notre Dame (SSND) in Mankato, Minnesota, USA. This initial study led to the present Nun Study, which expanded the population to include members of the SSND congregation from seven religious provinces spanning midwestern, southern and eastern regions of the USA (Snowdon et al., 1997).

The Nun Study provides a unique opportunity to investigate factors across the lifespan that contribute to late-life cognitive outcomes. Data, which will be described further in section 4.2.3, have been gathered from three main sources: archival documents from childhood onwards, annual assessments in older adulthood, and brain examinations at post-mortem autopsy.

4.2.2 Population

Members of the SSND were eligible for the study if they were aged 75 or over at the time of recruitment in 1991. Agreement to full participation in all components of data collection, including post-mortem brain donation, was required. Of the 1031 individuals who were eligible, 678 (66%) agreed to participate (Snowdon et al., 1996b) and written consent was obtained. Non-participants were similar to participants in age, country of birth, race and annual mortality rate (Snowdon et al., 1996b).

At the time of recruitment, participants were aged 75 to 102, with a mean age of 83 (Danner et al., 2001; Snowdon et al., 1997). The study population was highly educated, with 85% having obtained a bachelor's degree or higher at the time of the first cognitive assessment (Tyas, Snowdon, Desrosiers, Riley, & Markesbery, 2007). The population is also unique because of the relatively homogeneous lifestyle of its members. That is, participants are similar in factors such as tobacco and alcohol use, marital status, reproductive history, housing, occupation and access to healthcare from adulthood to the end of life.

4.2.3 Data Collection

Data in the Nun Study has three components, including annual cognitive and physical assessments, post-mortem brain autopsies and archival documents of personal history. These components provide valuable resources for study of lifespan factors contributing to health and cognitive function.

Annual cognitive assessments included the MMSE and the CERAD battery of neuropsychological tests (e.g., delayed word recall, verbal fluency, Boston Naming and constructional praxis; see section 2.3.3). Physical function was measured as ability to perform basic and instrumental ADLs (Snowdon et al., 1996b). *APOE* status was determined using DNA obtained from buccal swabs and from brain tissue at the post-mortem autopsy according to standard techniques (Riley et al., 2000; Saunders et al., 1996).

All participants agreed to post-mortem brain donation, which has provided a rich source of neuropathologic data. Brains underwent both gross and microscopic examinations to identify NFTs, Aβ plaques, infarcts, and various other lesions. Braak stage, brain weight and degree of atrophy were also documented (Riley et al., 2002). Neuropathological data collected at brain autopsy allow for a reliable diagnosis of AD and VaD. Evidence of vascular comorbidities, such as cerebral infarcts, was also assessed.

Convent archives, which have been made available to the investigators, provide invaluable data on the participants from childhood and early adulthood. Academic report cards and autobiographies present measures of academic performance, intellectual ability and emotional expressivity. Various other documents offer insights into early-life experiences such as parental education, socioeconomic status, family environment and key life events. A more detailed description of information contained within the archives is provided elsewhere (Patzwald and Wildt, 2004).

4.3 Study Design

4.3.1 Analytic Sample

The sample for the present study was obtained based on availability of archival autobiographies. These autobiographies were written upon formal entry into the religious congregation, as instructed by the Mother Superior of the North American congregation of the SSND beginning in 1930 (Danner et al., 2001). The instructions required that the individuals wrote an autobiographical sketch of key life details that did not exceed two to three hundred words and was written on a single sheet of paper (Danner et al., 2001). This implies that the autobiographies were relatively consistent in length for the purpose of comparison in the current investigation. In order to ensure that the autobiographies were written personally and that English proficiency was consistent, autobiographies were selected for scoring if they had been handwritten and the participant was born and raised in the USA (Danner et al., 2001). The majority of autobiographies that met these criteria were found in two convents in Milwaukee, Wisconsin

and Baltimore, Maryland. In all, 180 autobiographies from these two locations fit the criteria for inclusion and were scored for emotional expressivity and written language skills, as described elsewhere (Danner et al., 2001; Snowdon, 1996b). Participants were eligible for inclusion in the current study if they had a scored autobiography as well as complete data on all other variables of interest.

Cognitive assessments to determine the presence or absence of dementia were available for all 180 individuals. Of these, 164 (91.1%) had full data on all covariates of interest. However, the availability of data on neuropathology greatly limited the number of individuals eligible for inclusion in the sample for the analysis of AD: only 95 (52.8%) of the 180 individuals at baseline had neuropathologic data. Individuals were missing these data because they were still alive or their post-mortem brain autopsy was not available. So as not to limit the number of participants included in the dementia analysis, a subset for the analyses of AD was defined. Of the 164 individuals who were included in the sample for the dementia analysis, 70 individuals had complete neuropathologic data, leaving 94 (52.2% of the original sample) who fulfilled all criteria for inclusion in the subset for the analysis of AD. However, multivariate logistic regression analysis using these initial samples yielded poorly fit models given the high impact, but low prevalence, of low education (see Appendix D). As a result, the samples were subsequently restricted by low education. After restriction, 149 participants were included in the final sample for the dementia analyses, and 85 remained in the final sample for the AD analyses (Figure 1).

4.3.2 Exposure Measures

Measures of emotional expressivity as the exposure of interest were obtained from the handwritten autobiographies, described previously. Emotional content scores were derived from raw counts of words indicating positive or negative emotional experiences in the autobiographies. Two coders counted the emotion words independently and then a third coder verified each word for accuracy. A detailed description of the methods used to score emotional expressivity in the autobiographies is provided elsewhere (Danner et al., 2001). To meet the objective of the current study, emotions were measured as positive or negative in valence rather than as discrete emotions. Emotions of the same valence tend to show similar patterns of brain region activity and associated physiologic processes and thus likely have similar effects on cognitive, social and physical factors that potentially affect dementia outcomes (see Section 2.6).

Measures of overall (i.e., the sum of positive and negative emotions), positive and negative emotional expressivity were included in the analyses. Each measure was categorized as “high” or “low” based on within-convent ranking of the respective raw word count: those that were in the top two

quartiles were categorized as high, while those who were in the bottom two quartiles were categorized as low. A second component of the analysis of dementia further separated the measures of expressivity into three categories, based on tertile rankings of the respective word counts (high, top tertile; moderate, middle tertile; and low, bottom tertile). Word counts were ranked within each convent separately to control for differences in distribution of expressivity and length of the autobiographies between the convents.

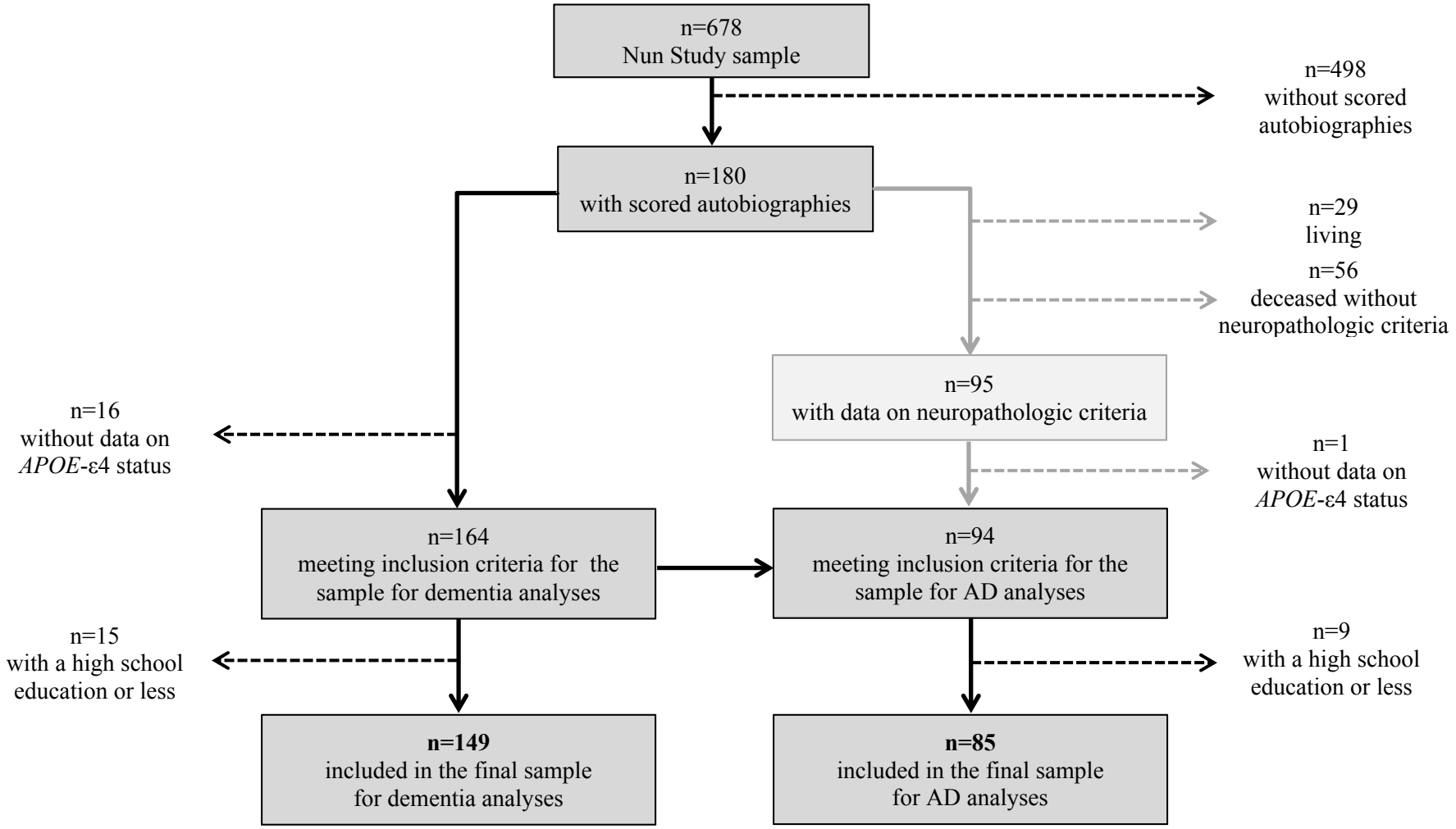

Figure 1. Flow chart illustrating the selection of samples for analyses of dementia and Alzheimer's disease (AD) in association with emotional expressivity. The dashed arrows represent individuals who were excluded. The subset for analyses of AD was defined as individuals included in the dementia analyses who had available neuropathology data. The grey arrows represent an alternative derivation of this subset, based on missing neuropathologic criteria.

4.3.3 Outcome Measures

Two outcomes – dementia and AD – were assessed. VaD was also considered as an outcome given the relationship to AD (Section 2.5.1) and the strong vascular influence of emotions (Section 2.6.3); however, low prevalence of VaD prevented the performance of meaningful analysis. Dementia cases were defined as individuals who fulfilled the cognitive criteria for dementia at the time of the last cognitive assessment. AD cases were those who had dementia at the last cognitive assessment, and who fulfilled AD neuropathologic criteria at the postmortem autopsy. All cases were considered incident regardless of time of diagnosis, given the early age at which exposure data were collected (i.e., in young adulthood). Variables for dementia and AD were both dichotomous, defined as either presence (cases) or absence (non-cases) of the respective condition. For the analysis of AD, several combinations of case and non-case definitions were analyzed to investigate the specific effects of emotional expressivity.

The diagnosis of dementia in the Nun Study has been described previously and was based on normative data from the CERAD battery of functional tests (Riley et al., 2002). Criteria for a dementia diagnosis included impairment in memory and at least one other cognitive domain, impaired performance of ADLs and a decline from a previous level of function (see section 2.2.3). Specifically, neuropsychological tests indicated cognitive impairment if scores were <13 out of a possible 60 points on the Boston Naming test, <11 points (with no ceiling) on Verbal Fluency, <4 out of 10 for Delayed Word Recall, and <8 out of 11 for Constructional Praxis (Riley et al., 2002). These criteria had previously been compiled to derive a variable within the Nun Study dataset indicating if a dementia diagnosis was established at the last cognitive assessment. The referent group for the analysis of dementia was individuals who did not have a diagnosis of dementia at the last cognitive assessment.

The case definition for AD required a diagnosis of dementia at the last cognitive assessment in addition to presence of AD neuropathology at post-mortem autopsy. Two different case definitions were analyzed, based on the fulfillment of neuropathologic criteria according to CERAD or NIA-RI guidelines (see section 2.3.3). The patterns of association of the two case definitions with emotional expressivity were compared. Two different non-case definitions were also analyzed to elucidate the potential effects of the cognitive and neuropathological components of an AD diagnosis. The two non-case definitions were (1) those who did not fit the case definition and who did not have dementia and (2) those who did not fit the case definition and who had neither dementia nor AD pathology. In all, four different samples for the analyses of AD were selected, based on the two case and two non-case definitions (Table 1).

Table 1. Case and non-case definitions: samples for AD analyses

	Case Definition	Non-Case Definition
Analytic Sample		
NIA-RI/D	- Dementia diagnosis - NIA-RI AD neuropathology	- Not fulfilling case definition - No dementia diagnosis
NIA-RI/DN	- Dementia diagnosis - NIA-RI AD neuropathology	- Not fulfilling case definition - No dementia diagnosis - No NIA-RI AD neuropathology
CERAD/D	- Dementia diagnosis - CERAD AD neuropathology	- Not fulfilling case definition - No dementia diagnosis
CERAD/DN	- Dementia diagnosis - CERAD AD neuropathology	- Not fulfilling case definition - No dementia diagnosis - No CERAD AD neuropathology

Abbreviations: AD= Alzheimer's disease; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; D= non-cases without dementia; DN= non-cases without dementia and AD neuropathology; NIA-RI= National Institute on Aging-Reagan Institute

Diagnosis of VaD was based on NINDS-AIREN criteria for MID, a specific form of vascular dementia caused by multiple large infarcts (see section 2.4.2) that was diagnosed by researchers on the Nun Study. As such, the case definition for VaD in the current investigation required a dementia diagnosis at the last cognitive assessment and positive evidence of MID as determined by presence of multiple cerebral infarcts at postmortem autopsy. The sample for VaD analyses included the same 85 individuals who were eligible for inclusion in the sample for AD analyses. Of these, only 1 (1.2%) was defined as a case so further analysis was not performed.

4.3.4 Covariates

Associations between emotional expressivity in early adulthood and development of various dementia outcomes in late life were adjusted for age and highest level of education attained. The influence of cerebral infarcts, *APOE-ε4*, and measures of written language skills including idea density and grammatical complexity in the autobiographies was also evaluated.

Age was measured as a continuous variable. All participants were aged 75 or older based on the age restrictions for participant recruitment. The age variable differed by model according to the case definition. In the dementia models, age was defined as the age at the last cognitive assessment. Age in the

AD models was defined as the age at death, given that diagnoses rely on pathological evidence observed in a post-mortem autopsy.

Education, *APOE*-ε4 and cerebral infarcts were each measured as dichotomous variables. After restriction on low education, which was defined as high school or less, the education variable was divided into two categories: bachelor's degree, or master's degree or higher. Participants were categorized as having at least one *APOE*-ε4 allele or having none. Likewise, individuals were classified as having either presence or absence of any cerebral infarct based on gross neuropathologic assessments that included visual inspection of both the intact brain and 1.5 centimeter-thick coronal sections (Snowdon et al., 1997). Several participants were missing data on cerebral infarcts (n=43); however, the presence of infarcts in the remaining sample (n=106) was determined to have no effect on the results so the sample was not restricted based on the availability of these data and the variable was not included in any further analyses. A full discussion and sensitivity analysis of the subset with complete data on cerebral infarcts are found in appendix B.

In addition to being scored for emotional expressivity, the autobiographies were scored for idea density (Kintsch & Keenan, 1973; Turner & Greene, 1977) and grammatical complexity (Cheung & Kemper, 1992) as measures of written language skills. Idea density was measured as the average number of ideas expressed per ten words. Grammatical complexity was measured according to an established eight-level scale ranging from simple, one-clause sentences to complex, multi-clause sentences. Each score was ranked into quartiles within each convent separately. A detailed description of how these scores were obtained in the Nun Study autobiographies is described elsewhere (Snowdon, 1996b; Snowdon, 2000). For the purpose of the current investigation, the top three quartiles of each variable were collapsed to obtain dichotomous variables classified as levels of "higher" (i.e., those in the upper 3 quartiles) and "low" (i.e., those in the bottom quartile) idea density and grammatical complexity. The idea density and grammatical complexity measures were both collapsed in this way given the significant difference in prevalence of dementia in the lowest quartile compared to the top three quartiles. Among participants with scored autobiographies, 64% of individuals in the lowest quartile of idea density were diagnosed with dementia, compared to 23% in the top three quartiles ($p<0.01$). Likewise, 52% of individuals in the lowest quartile of grammatical complexity were diagnosed with dementia, compared to 28% with dementia in the top three quartiles ($p<0.01$). These dichotomous variables (bottom vs. top 3 quartiles) were used in all analyses.

4.4 Analytic Strategy

4.4.1 Descriptive Analysis

Summary measures (e.g., mean, standard deviation) were used to describe variables that were included in the analyses. Associations between each exposure (i.e., three measures of emotional expressivity), outcome (i.e., dementia or AD), and covariates (i.e., age, education, *APOE*-ε4 status, idea density and grammatical complexity) were tested separately through bivariate analyses. Pearson chi-square or Fisher's exact tests were used to compare categorical variables. Associations where one variable was categorical and the other was continuous were measured using independent samples *t*-tests with Satterthwaite's unequal variance correction, as appropriate.

4.4.2 Multivariate Analysis

Multivariate logistic regression models were used to analyze the association of emotional expressivity with dementia and AD. First-order interactions between the covariates and the exposures were explored. A significant interaction was found between overall emotional expressivity and idea density with dementia as the outcome ($p<0.05$). Thus, further models of the sample for dementia analyses were stratified by idea density. Within the sample for the analyses of AD, none of the first-order interactions between the exposures of interest and the covariates were found to be significant. However, in order to maintain comparability with the dementia analysis, the sample used for the AD analyses was stratified by idea density as well. Sensitivity analyses without stratification were also performed for all models.

After stratification by idea density, backwards elimination was performed to identify variables that significantly influenced the outcomes of interest. This method is preferable to the forward selection method because it is generally associated with a smaller mean squared error (Tyas et al., 2000). Backwards elimination started with the full model and nonsignificant variables were removed individually so only those variables that affected the outcome of interest were retained. Variables were eliminated if they exceeded a significance level of $\alpha=0.15$ for main effects and $\alpha=0.05$ for interaction terms (Tyas et al., 2000). Idea density and *APOE*-ε4 were consistently retained in the models. These results were taken into consideration when constructing subsequent models.

The backwards elimination method was not sufficient to meet the objective of the study (i.e., to investigate the association of emotional expressivity with dementia and AD) because the emotional expressivity variable was rarely retained in the models. As such, crude, adjusted and full models were

generated manually to explore the effect of each covariate on the association between each emotional expressivity exposure and each outcome. All models were adjusted for age, education, *APOE-ε4* status, and grammatical complexity in succession to obtain the most parsimonious model (Table 2).

Table 2. Analytic strategy to investigate the association of emotional expressivity with dementia and AD, stratified by idea density[1]

Variable	Crude	1B	1C	1D	Full	Final[3]
Emotional Expressivity[2]	✓	✓	✓	✓	✓	✓
Age		✓	✓	✓	✓	✓[4]
Education			✓	✓	✓	✓
APOE-ε4 Status				✓	✓	✓
Grammatical Complexity					✓	✓

[1] Analyses were repeated for low and higher idea density subgroups and for dementia and AD outcomes.
[2] Measures of overall, positive and negative emotional expressivity were analyzed separately.
[3] Variables that were significant in the model or affected the point estimate of emotional expressivity were included in the final model.
[4] The grey check marks indicate potential inclusion of covariates in the final model based on their effects in previous models.
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4 = apolipoprotein E ε4 allele

The sample size of the sample for dementia analyses was sufficient to perform further analyses to clarify the association between emotional expressivity and dementia. These analyses included the investigation of the effects of overall, positive, and negative expressivity when divided into tertiles (i.e., low, moderate and high categories), and the interaction between positive and negative emotional expressivity. This interaction was significant among individuals with higher idea density (p=0.036). As such, the sample was subsequently stratified by positive emotional expressivity (as well as by idea density) and models were generated to investigate the association between negative emotional expressivity and dementia within each strata of positive expressivity

Assessment of all final models included the Hosmer-Lemeshow goodness of fit test (LACKFIT command in PROC LOGISTIC) to ensure 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 flagged for further investigation. Diagnostic tests, including C, CBAR and DFBETAS in PROC LOGISTIC, were used to identify influential outliers in all final models. C and CBAR indicate the influence of each observation on the confidence interval of the parameter estimate, and DFBETAS indicates the influence on the parameter estimate itself (SAS Institute Inc.,

2009). C, CBAR and DFBETAS outside of ±1.96 (p=0.05) indicated a significant influence on the parameter estimate. Variance inflation factors (VIF command in PROC REG) were also generated; VIFs of 10 or greater indicate issues with multicollinearity (Belsley, Kuh, & Welsch, 1980). All analyses were carried out using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

4.5 Ethics Approval

All study participants provided written informed consent at the time of participant recruitment in 1990 and again in 2006. Initial ethics approval for all aspects of data collection was obtained through the University of Kentucky. Since then, the study has moved to the University of Minnesota, where ethics approval and confidentiality practices are maintained. Hard copies of data sources, including archival material and clinical and neuropathological records, are kept in locked filing cabinets at the University of Minnesota. Access to these data is restricted. Data are also kept in electronic records by non-identifying participant ID numbers that were used in the current investigation. These electronic records are stored at the University of Waterloo on password-protected computers and are only available to authorized personnel. The Office of Research Ethics at the University of Waterloo has granted ethical clearance for this study (ORE#16551). Investigators have also signed confidentiality agreements pertaining to the ethics of this research.

Chapter 5
Results

The results of the analyses are described below. All univariate and bivariate statistics of the sample for dementia analyses (Section 5.1.1), followed by those of the AD analyses (Section 5.1.2), are described first. Then the results of the main multivariate analyses of both dementia and AD as outcomes using the respective samples are presented together, but separated by low (Section 5.2.1) and higher (Section 5.2.2) idea density strata. Following the main results, the extended analyses of the sample used for dementia analyses (i.e., emotional expressivity categorized by tertiles and the modifying effects of positive expressivity on the association with negative emotional expressivity) are described (Section 5.2.3). Again, the results of the low and higher idea density subgroups are presented separately for each of these extended analyses. The model diagnostics are then reported (Section 5.2.4). Finally, sensitivity analyses of the findings, including investigation of the association between emotional expressivity and dementia using the smaller subset (Section 5.3.1), and reporting of the analyses without stratification by idea density (Section 5.3.2), are presented.

5.1 Descriptive Statistics

5.1.1 Sample Selected for the Dementia Analyses

Of 180 eligible individuals, 164 (91.1%) were initially included in the sample for dementia analyses (see Appendix C for a comparison to those who were excluded). However, given the strong influence of low education on dementia and AD, and the small number of participants with low education (i.e., a high school diploma or less; n=15), controlling potential confounding by education through adjustment in multivariate models was problematic. The multivariate logistic regression models including education as a significant covariate had a poor fit, which prevented meaningful conclusions from being made (Appendix D). As such, restriction was added as a strategy to control confounding. The analytic sample was restricted by education so that only participants with a university degree were included, and the education variable for the multivariate models was defined dichotomously as individuals with a Bachelor's degree, or a Master's degree or higher. After restriction, the new sample for dementia analyses had 149 individuals (82.8% of the original 180 participants). Of those who were included, 47 (31.5%)

were classified as dementia cases, having been diagnosed with dementia at their last cognitive assessment.

Cases (n=47) did not differ from individuals without dementia (n=102) in age or education; however, they did differ in *APOE*-ε4 status ($p<0.01$) and idea density ($p<0.0001$) (Table 3). Emotional expressivity, including raw emotion word counts, was similar between individuals with and without dementia (Table 4). Individuals with dementia expressed a mean of 9.8 (8.5 positive and 1.3 negative) emotion words, whereas individuals without dementia expressed an average of 8.3 (7.1 positive and 1.2 negative) emotion words. However, the variation of expressivity was wide within each group: individuals with dementia ranged from zero to 29 (0-22 positive and 0-7 negative) emotion words and those without dementia ranged from zero to 32 (0-27 positive and 0-9 negative) emotion words. As such, no significant differences in raw emotional expressivity were detected between individuals with and without dementia, nor were significant differences found when emotional expressivity was ranked and assessed as quartiles or as a dichotomous variable. Furthermore, only seven individuals did not express any emotion words. These individuals were not different from the rest of the sample in the distribution of dementia (28.6% vs. 31.7%, $p=0.86$), age, education, *APOE*-ε4 status, idea density or grammatical complexity. Furthermore, the overall patterns of association did not change in any of the models when these individuals were excluded, so they were retained in the sample.

The distribution of dementia was significantly different between the two idea density strata ($p<0.0001$). Of the 29 participants with low idea density, 20 (69.0%) had dementia, whereas only 27 (22.5%) of the 120 individuals with higher idea density had dementia (Table 5). Dementia status did not differ by age, education, *APOE*-ε4 status, or grammatical complexity (Table 5). Again, a wide range of emotional expressivity was found among individuals with and without dementia in both the low and higher idea density subgroups. As such, emotional expressivity, measured as raw counts, quartile rankings or dichotomous variables, did not differ by dementia status in either stratum (Table 6).

Table 3. Participant characteristics by dementia status: sample for dementia analyses (n=149)

	All (n=149)	Dementia[1] No (n=102)	Dementia[1] Yes (n=47)
Characteristic			
Covariates			
Age[2], Mean Years (SD)	88.1 (4.98)	88.2 (5.03)	88.0 (4.91)
Level of Education, %			
Bachelor's Degree	42.3	42.2	42.6
≥ Master's Degree	57.7	57.8	57.4
Presence of *APOE*-ε4, %**	26.2	19.6	40.4
Idea Density, %**			
Low	19.5	8.8	42.6
Q2	24.8	27.4	19.2
Q3	26.8	30.4	19.2
High	26.9	33.3	19.2
Grammatical Complexity, %			
Low	21.5	16.7	31.9
Q2	23.5	25.5	19.2
Q3	28.8	30.4	25.5
High	26.2	27.4	23.4

* $p<0.05$
** $p<0.01$
[1] Based on diagnosis of dementia at the last cognitive assessment
[2] Age at last cognitive assessment
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; Q= quartile; SD= standard deviation

Table 4. Emotional expressivity by dementia status (n=149)

	All (n=149)	Dementia[1] No (n=102)	Dementia[1] Yes (n=47)
Emotional Expressivity			
Raw Word Counts[2], Mean (SD)			
Overall	8.8 (7.39)	8.3 (7.32)	9.8 (7.51)
Positive	7.6 (6.30)	7.1 (6.23)	8.5 (6.41)
Negative	1.2 (1.65)	1.2 (1.63)	1.3 (1.72)
Raw Word Counts[2], Median (Range)			
Overall	7.0 (0-32)	6.0 (0-32)	8.0 (0-29)
Positive	6.0 (0-27)	5.0 (0-27)	7.0 (0-22)
Negative	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %			
Overall			
Low	22.1	23.5	19.2
Q2	24.2	24.5	21.3
Q3	30.2	27.5	36.2
High	23.5	23.5	23.4
Positive			
Low	24.8	25.5	23.4
Q2	24.2	25.5	21.3
Q3	24.8	23.5	27.7
High	26.2	25.5	27.7
Negative			
Low	12.1	10.8	14.9
Q2	41.6	43.1	38.3
Q3	29.5	28.4	31.9
High	16.8	17.6	14.9

[1] Based on diagnosis of dementia at the last cognitive assessment
[2] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparison
Abbreviations: Q= quartile; SD= standard deviation
Note: Emotional expressivity did not significantly differ by dementia status.

Table 5. Participant characteristics by dementia and idea density: sample for dementia analyses (n=149)

	Idea density[1]					
	Low			Higher		
		Dementia[2]			Dementia[2]	
Characteristic	All (n=29)	No (n=9)	Yes (n=20)	All (n=120)	No (n=93)	Yes (n=27)
Covariates						
Age[3], Mean Years (SD)	86.2 (5.29)	87.5 (6.38)	85.6 (4.81)	88.6 (4.81)	88.2 (4.92)	89.7 (4.29)
Level of Education, %						
Bachelor's Degree	51.7	44.4	55.0	40.0	41.9	33.3
≥ Master's Degree	48.3	55.6	45.0	60.0	58.1	66.7
Presence of *APOE*-ε4, %	48.3	33.3	55.5	20.8	18.3	29.6
Grammatical Complexity, %						
Low	37.9	22.2	45.0	17.5	16.1	22.2
Q2	24.1	33.3	20.0	23.3	24.7	18.5
Q3	10.3	0.0	15.0	33.3	33.3	33.3
High	27.6	44.4	20.0	25.8	25.8	25.9

Note: Participant characteristics did not differ by dementia status in either idea density stratum.
[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density
[2] Based on diagnosis of dementia at the last cognitive assessment
[3] Age at last cognitive assessment
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; Q= quartile; SD= standard deviation

Table 6. Emotional expressivity by dementia status and idea density: sample for dementia analyses (n=149)

	Idea density[1]					
	Low			Higher		
		Dementia[2]			Dementia[2]	
	All (n=29)	No (n=9)	Yes (n=20)	All (n=120)	No (n=93)	Yes (n=27)
Emotional Expressivity						
Raw Word Counts[3], Mean (SD)						
Overall	8.3 (7.07)	8.4 (7.91)	8.3 (6.88)	8.9 (7.49)	8.3 (7.31)	11.0 (7.87)
Positive	7.3 (6.21)	7.6 (7.67)	7.2 (5.66)	7.6 (6.35)	7.1 (6.12)	9.5 (6.86)
Negative	1.0 (1.54)	0.9 (0.93)	1.0 (1.76)	1.3 (1.68)	1.2 (1.68)	1.5 (1.70)
Raw Word Counts[3], Median (Range)						
Overall	5.0 (0-25)	5.0 (0-19)	7.0 (0-25)	7.0 (0-32)	6.0 (0-32)	8.0 (0-29)
Positive	5.0 (0-19)	3.0 (0-18)	5.0 (0-19)	6.0 (0-27)	5.0 (0-27)	7.0 (0-22)
Negative	0.0 (0-6)	1.0 (0-2)	1.0 (0-6)	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %						
Overall						
Low	31.0	33.3	30.0	20.0	22.6	11.1
Q2	17.2	0.0	25.0	25.8	28.0	18.5
Q3	31.0	44.4	25.0	30.0	25.8	44.4
High	20.7	22.2	20.0	24.2	23.6	25.9
Positive						
Low	34.5	33.3	35.0	22.5	24.7	14.8
Q2	17.2	22.2	15.0	25.8	25.8	25.9
Q3	24.1	11.1	30.0	25.0	24.7	25.9
High	24.1	33.3	20.0	26.7	24.7	33.3

	Idea density[1]					
	Low			Higher		
		Dementia[2]			Dementia[2]	
	All (n=29)	No (n=9)	Yes (n=20)	All (n=120)	No (n=93)	Yes (n=27)
Quartile Rankings (cont'd), %						
Negative						
Low	17.2	11.1	20.0	10.8	10.8	11.1
Q2	48.3	44.4	50.0	40.0	43.0	29.6
Q3	13.8	11.1	15.0	33.3	30.1	44.4
High	20.7	33.3	15.0	15.8	16.1	14.8

[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density

[2] Based on diagnosis of dementia at the last cognitive assessment

[3] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparison

Abbreviations: Q= quartile; SD= standard deviation

Note: Emotional expressivity did not significantly differ by dementia status in either idea density stratum.

5.1.2 Sample Selected for the AD Analyses

Approximately 57% (n=85) of the 149 individuals from the sample for dementia analyses were included for analysis of AD. Four different analytic samples were created based on case and non-case definitions as described previously (see section 4.3.3). Final sample sizes varied according to these definitions. Twenty-five individuals were defined as cases according to NIA-RI neuropathologic criteria and 24 were cases according to CERAD criteria. Of these individuals, 20 fulfilled both CERAD and NIA-RI neuropathologic criteria while 5 fulfilled only NIA-RI neuropathologic criteria and 4 fulfilled only CERAD criteria. The number and proportion of non-cases depended on the definition used (Table 7). The results obtained in the bivariate and multivariate analyses were similar, regardless of the analytic sample used; as such, the results from the NIA-RI/D sample will be presented and discussed. Results of the bivariate and multivariate analysis using CERAD/D sample for comparison are provided in Appendix F.

Table 7. Sample sizes for the analyses of AD by idea density and case/non-case definitions

	All	Idea Density[1]			
		Low		Higher	
		Non-cases[2]	Cases[3]	Non-cases[2]	Cases[3]
Sample					
NIA-RI/D	79[4]	6	13	48	12
NIA-RI/DN	67	6	13	36	12
CERAD/D	78	6	8	48	16
CERAD/DN	52	4	8	24	16

[1] Low = lowest quartile of idea density; Higher = top three quartiles of idea density
[2] Non-cases do not have AD according to the corresponding criteria (i.e., CERAD or NIA-RI) and are dementia-free (D) or are dementia- and AD neuropathology-free (DN).
[3] Cases have been diagnosed with AD (i.e., clinical dementia at the last cognitive assessment and AD neuropathology at post-mortem autopsy).
[4] Individuals who were eligible for inclusion (n=85) were not necessarily included in the analytic samples, given the non-case definitions excluded individuals according to footnote 2.
Abbreviations: AD= Alzheimer's disease; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; D= non-cases without dementia; DN= non-cases without dementia or neuropathology; NIA-RI= National Institute on Aging – Reagan Institute

In the NIA-RI/D sample, cases did not differ from non-cases on characteristics such as age at death or level of education (Table 8). Similar to the sample used for the analysis of dementia, emotional expressivity varied greatly in individuals both with and without AD, and no significant differences in emotional expressivity were found by AD status either (Table 9). However, diagnosis of AD was significantly associated with *APOE*-ε4 status ($p<0.001$) and idea density

(p<0.0001). Similar to the sample used for the analyses of dementia, the proportion of cases was significantly different between the idea density strata: 13 of 19 (68.4%) individuals with low idea density were diagnosed with AD, whereas 12 of 60 (20.0%) in the high idea density subgroup had an AD diagnosis (p<0.0001; Table 10). Among individuals with low idea density, AD was significantly associated with grammatical complexity (p<0.05; Table 10), but was not associated with emotional expressivity (Table 11) or any other covariates in either idea density stratum.

Table 8. Participant characteristics by AD status: NIA-RI/D analytic sample (n=79)

		AD[1]	
	All (n=79)	No (n=54)	Yes (n=25)
Characteristic			
Covariates			
Age[2], Mean Years (SD)	87.8 (3.83)	87.7 (3.93)	87.9 (3.69)
Level of Education, %			
Bachelor's Degree	49.4	51.8	44.0
≥ Master's Degree	50.6	48.2	56.0
Presence of *APOE*-ε4, %**	27.8	16.7	52.0
Idea Density, %**			
Low	24.0	11.1	52.0
Q2	21.5	27.8	8.0
Q3	24.0	27.8	16.0
High	30.4	33.3	24.0
Grammatical Complexity, %			
Low	24.0	18.5	36.0
Q2	22.8	27.8	12.0
Q3	25.3	24.1	28.0
High	27.8	29.6	24.0

** p<0.01
[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases are individuals who have not been diagnosed with AD and who did not have dementia at their last cognitive assessment
[2] Age at death
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; NIA-RI= National Institute on Aging – Reagan Institute; Q= quartile; SD= standard deviation

Table 9. Emotional expressivity by AD status: NIA-RI/D analytic sample (n=79)

	All (n=79)	AD[1] No (n=54)	AD[1] Yes (n=25)
Emotional Expressivity			
Raw Word Counts[2], Mean (SD)			
Overall	9.5 (8.00)	9.1 (8.01)	10.4 (8.03)
Positive	8.0 (6.72)	7.7 (6.68)	8.8 (6.89)
Negative	1.4 (1.85)	1.4 (1.84)	1.5 (1.92)
Raw Word Counts[2], Median (Range)			
Overall	8.0 (0-32)	6.0 (1-32)	8.0 (0-29)
Positive	6.0 (0-27)	5.0 (1-27)	6.0 (0-22)
Negative	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %			
Overall			
Low	19.0	16.7	24.0
Q2	26.6	29.6	20.0
Q3	29.1	29.6	28.0
High	25.3	24.1	28.0
Positive			
Low	22.8	20.4	28.0
Q2	27.8	31.5	20.0
Q3	22.8	24.1	20.0
High	26.6	24.1	32.0
Negative			
Low	12.7	9.3	20.0
Q2	34.2	35.2	32.0
Q3	34.2	37.0	28.0
High	19.0	18.5	20.0

[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases were individuals who have not been diagnosed with AD or dementia at their last cognitive assessment

[2] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparison

Abbreviations: AD= Alzheimer's disease; NIA-RI= National Institutes on Aging – Reagan Institute; Q= quartile; SD= standard deviation

Note: Emotional expressivity did not significantly differ by AD status.

Table 10. Participant characteristics by AD and idea density: NIA-RI/D analytic sample (n=79)

	Idea density[1]					
	Low			Higher		
		AD[2]			AD[2]	
	All (n=19)	No (n=6)	Yes (n=13)	All (n=60)	No (n=48)	Yes (n=12)
Characteristic						
Covariates						
Age[3], Mean Years (SD)	87.0 (4.32)	86.9 (4.29)	87.0 (4.51)	88.0 (3.67)	87.8 (3.92)	88.8 (2.38)
Level of Education, %						
Bachelor's Degree	47.4	33.3	53.8	50.0	54.2	33.3
≥ Master's Degree	52.6	66.7	46.2	50.0	45.8	66.7
Presence of *APOE*-ε4, %	47.4	16.7	61.5	21.7	16.7	41.7
Grammatical Complexity, %						
Low	31.6	0.0*	46.2	21.7	20.8	25.0
Q2	26.3	50.0	15.4	21.7	25.0	8.3
Q3	15.8	0.0	23.1	28.3	27.1	33.3
High	26.3	50.0	15.4	28.3	27.1	33.3

* $p<0.05$

[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density

[2] Based on diagnosis of AD according to NIA-RI criteria; non-cases are individuals who have not been diagnosed with AD and who did not have dementia at their last cognitive assessment

[3] Age at death

Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; NIA-RI= National Institute on Aging – Reagan Institute; SD= standard deviation

Table 11. Emotional expressivity by AD status and idea density: NIA-RI/D analytic sample (n=79)

	Idea density[1]					
	Low			Higher		
		AD[2]			AD[2]	
	All (n=19)	No (n=6)	Yes (n=13)	All (n=60)	No (n=48)	Yes (n=12)
Emotional Expressivity						
Raw Word Counts[3], Mean (SD)						
Overall	9.3 (6.99)	9.3 (7.17)	9.3 (7.20)	9.5 (3.67)	9.0 (8.18)	11.5 (9.02)
Positive	7.9 (5.96)	8.2 (7.19)	7.8 (5.63)	8.1 (6.99)	7.6 (5.68)	10.0 (4.83)
Negative	1.4 (1.74)	1.2 (0.98)	1.5 (2.02)	1.4 (1.90)	1.4 (1.92)	1.5 (1.88)
Raw Word Counts[3], Median (Range)						
Overall	9.0 (0-25)	8.0 (1-19)	9.0 (0-25)	7.5 (0-32)	6.0 (1-32)	8.0 (0-29)
Positive	5.0 (0-19)	6.5 (1-17)	5.0 (0-19)	6.0 (0-27)	5.0 (1-27)	7.0 (0-22)
Negative	1.0 (0-6)	1.5 (0-2)	1.0 (0-6)	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %						
Overall						
Low	21.0	16.7	23.1	18.3	16.7	25.0
Q2	15.8	0.0	23.1	30.0	33.3	16.7
Q3	36.8	50.0	30.8	26.7	27.1	25.0
High	26.3	33.3	23.1	25.0	22.9	33.3
Positive						
Low	26.3	16.7	30.8	21.7	20.8	25.0
Q2	21.0	33.3	15.4	30.0	31.2	25.0
Q3	26.3	16.7	30.8	21.7	25.0	8.3
High	26.3	33.3	23.1	26.7	22.9	41.7

	Idea density[1]					
	Low			Higher		
		AD[2]			AD[2]	
	All (n=19)	No (n=6)	Yes (n=13)	All (n=60)	No (n=48)	Yes (n=12)
Quartile Rankings (cont'd), %						
Negative						
Low	15.8	16.7	15.4	11.7	8.3	25.0
Q2	36.8	16.7	46.2	33.3	37.5	16.7
Q3	15.8	16.7	5.4	40.0	39.6	41.7
High	31.6	50.0	23.1	15.0	14.6	16.7

[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density

[2] Based on diagnosis of AD according to NIA-RI criteria; non-cases are individuals who have not been diagnosed with AD and who did not have dementia at their last cognitive assessment

[3] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparison

Abbreviations: AD= Alzheimer's disease; NIA-RI= National Institute on Aging – Reagan Institute; Q= quartile; SD= standard deviation

Note: Emotional expressivity did not significantly differ by AD status in either idea density strata.

5.1.3 Sample Selected for the VaD Analyses

The individuals who were eligible for inclusion in the sample for the analyses of AD also fit the criteria for inclusion in the sample for VaD analyses (n=85). Of the participants who had complete emotional expressivity and neuropathological data, only 1 (1.2%) was formally diagnosed with VaD. This individual had low idea density, a Bachelor's degree, at least one *APOE*-ε4 allele and scored below the 50th percentile for all measures of emotional expressivity. Given the low prevalence of cases in the sample, bivariate and regression analysis could not be performed.

5.2 Multivariate Logistic Regression Models

Multivariate logistic regression was performed to test the association of the three emotional expressivity measures (overall, positive and negative) with the presence of dementia and AD in late life, as described in section 4.4.2. For comparability across models, in addition to stratifying by idea density, all final models were adjusted for age and *APOE*-ε4 status. Inclusion of these two covariates with the emotional expressivity variables produced the most parsimonious results in the majority of the models. See Appendix E for the results of all the crude, adjusted and full models.

The direction of association of emotional expressivity with dementia and AD varied across the idea density strata (Table 12). Compared to low expressivity, the odds of high overall and negative emotional expressivity were decreased in individuals with dementia and AD in the low idea density stratum, and increased in the high idea density stratum. In contrast, the odds of high positive emotional expressivity was approximately equal or increased among individuals with dementia or AD in both the high and low idea density subgroups. An interaction between positive and negative emotional expressivity clarified these patterns of association with dementia: negative expressivity was associated with increased odds of dementia only when positive expressivity was low. Otherwise, an inverse association was found between emotional expressivity and dementia.

Table 12. Direction of association of emotional expressivity with dementia and AD, stratified by idea density and adjusted for age at diagnosis and *APOE*-ε4 status

	Dementia			AD[1]		
		Idea Density[2]			Idea Density[2]	
	All[3]	Low	Higher	All[3]	Low	Higher
Emotional Expressivity[4]						
Overall	N/A[5]	↓	↑*	↑	↓	↑
Positive	↑	↑	↑	↑	↑	↑
Negative	↑	↓	↑	↑	↓	↑
Low Positive	↑	↓	↑*			
High Positive	↓	↓	↓			

*p<0.05
[1] AD defined by NIA-RI criteria with non-cases defined as individuals without AD or dementia at the last cognitive assessment.
[2] Low= lowest quartile of idea density; Higher= top three quartiles of idea density
[3] Idea density was included as a covariate in unstratified models
[4] Top two quartiles vs. bottom two quartiles
[5] Not applicable given the significant interaction between overall emotional expressivity and idea density
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; NIA-RI= National Institute on Aging – Reagan Institute

5.2.1 Lower Idea Density Subgroup

Among individuals who displayed low idea density, emotional expressivity was not significantly associated with dementia and AD in any of the models (Table 13). Despite this lack of statistical significance, the results suggest that the odds of overall and negative emotional expressivity may be decreased in individuals with dementia and AD when idea density is low. Conversely, the odds of high positive emotional expressivity were slightly increased in individuals with dementia and AD. However, given the wide confidence intervals, the conclusions that can be drawn from these findings are limited.

Table 13. Association of emotional expressivity with dementia and AD among individuals with low idea density, adjusted for age at diagnosis and *APOE*-ε4 status

	Dementia (n=29)		AD[1] (n=19)	
	OR	**95% CI**	**OR**	**95% CI**
Emotional Expressivity[2]				
Overall	0.44	0.07, 2.30	0.40	0.02, 5.21
Positive	1.37	0.27, 7.54	1.71	0.19, 19.44
Negative	0.63	0.11, 3.56	0.24	0.02, 2.56

[1]AD defined by NIA-RI criteria with non-cases defined as individuals without AD or dementia at the last cognitive assessment; See Appendix F for parameter estimates using alternate sample definitions.
[2] Top two quartiles vs. bottom two quartiles
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein ε4; CI= confidence interval; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio
Note: Full results of all models can be found in Appendix E.

5.2.2 Higher Idea Density Subgroup

Among individuals with higher idea density, odds of high emotional expressivity was increased in individuals with dementia and AD. This pattern was consistent for all measures of emotional expressivity and for both dementia and AD, although the majority of models did not reach significance (Table 14). Overall emotional expressivity was the exception: the association with dementia was significant (OR=2.60, 95% CI=1.04-7.11).

Table 14. Association of emotional expressivity with dementia and AD among individuals with high idea density, adjusted for age at diagnosis and *APOE*-ε4 status

	Dementia (n=120)		AD[1] (n=60)	
	OR	**95% CI**	**OR**	**95% CI**
Emotional Expressivity[2]				
Overall	**2.60**	**1.04, 7.11**	1.68	0.44, 7.14
Positive	1.48	0.61, 3.66	1.14	0.30, 4.34
Negative	1.99	0.81, 5.13	1.67	0.41, 7.91

Bolded values are statistically significant.
[1] AD defined by NIA-RI criteria with non-cases defined as individuals without AD or dementia at the last cognitive assessment; See Appendix F for parameter estimates using alternate sample definitions.
[2] Top two quartiles vs. bottom two quartiles
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein ε4 allele; CI= confidence interval; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio
Note: Full results of all models can be found in Appendix E.

5.2.3 Further Investigation using the Sample for Dementia Analyses

Given the larger sample size, the sample for dementia analysis was subjected to further analyses that could not be performed on the samples selected for the analyses of AD. These analyses included ranking emotional expressivity measures in three categories (as opposed to two), and testing the interaction between positive and negative emotions. The analyses were intended to further clarify the association between emotional expressivity in early adulthood and dementia in late life.

5.2.3.1 Emotional Expressivity Categorized by Tertiles

5.2.3.1.1 Low Idea Density

Categorization of emotional expressivity into three categories (high, moderate and low) presented further information on the association between expressivity and dementia. Again, overall and negative emotional expressivity were generally protective (i.e., OR<1) against dementia among individuals with low idea density (Table 15). Positive emotional expressivity differed from the previous analysis in that the odds of moderate positive expressivity, compared to low expressivity, was increased among individuals with dementia (OR=2.00, 95% CI=0.23-22.20), whereas the odds of high, compared to low, positive expressivity was decreased, although not significantly so, in individuals with dementia (OR=0.74, 95% CI=0.10-5.29).

Table 15. Association between emotional expressivity tertiles and dementia adjusted for age at diagnosis and *APOE*-ε4 status, stratified by idea density (n=149)

	Idea Density[1]			
	Low (n=29)		Higher (n=120)	
	OR	**95% CI**	**OR**	**95% CI**
Emotional Expressivity[2]				
Overall[3]				
Moderate vs. Low	0.85	0.08, 10.05	1.70	0.54, 5.59
High vs. Low	0.59	0.08, 3.89	1.74	0.59, 5.46
Positive				
Moderate vs. Low	2.00	0.23, 22.20	1.48	0.47, 5.24
High vs. Low	0.74	0.10, 5.29	1.98	0.62, 7.06
Negative				
Moderate vs. Low	0.56	0.04, 14.72	**3.59**	**1.13, 11.89**
High vs. Low	0.57	0.10, 3.42	1.34	0.46, 3.97

Bolded values are statistically significant.
[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density
[2] Top two quartiles vs. bottom two quartiles
[3] Model adjusted for education, in addition to age and *APOE*-ε4 status.
Abbreviations: *APOE*-ε4= apolipoprotein ε4 allele; CI= confidence interval; OR= odds ratio

5.2.3.1.2 Higher Idea Density

Among individuals with high idea density, all measures of emotional expressivity were consistently associated with increased odds of dementia (Table 15). The only significant association was found between moderate negative expressivity and dementia (OR=3.59, 95% CI=1.13-11.89). High negative emotional expressivity had a weaker (non-significant) association than moderate expressivity, when compared to low expressivity.

All models were adjusted for age and *APOE*-ε4 status. However, the model of overall emotional expressivity and dementia had a poor fit (Hosmer-Lemeshow Goodness of Fit test, p=0.02) when adjusted for these two variables. As such, this model was adjusted for age, *APOE*-ε4 and education, which improved the fit. Neither moderate nor high overall expressivity was significantly associated with dementia.

5.2.3.2 The Association Between Negative Emotional Expressivity and Dementia, Modified by Positive Expressivity

A significant interaction was found between positive and negative emotional expressivity among individuals with higher idea density (p=0.04). Thus, a fourth model was generated to test the association between negative emotional expressivity and dementia when stratified by both idea density and positive emotions. Among individuals with higher idea density, the odds of negative emotions was significantly increased in individuals with dementia only when positive emotions were low (OR=8.17, 95% CI=1.66-58.96; Table 16).

Table 16. Association between negative emotional expressivity and dementia stratified by idea density and positive emotional expressivity (n=149)

		Unadjusted		Adjusted for Age		Adjusted for Age and *APOE*-ε4	
		OR[1]	**95% CI**	**OR[1]**	**95% CI**	**OR[1]**	**95% CI**
Idea Density[2]	*Positive Emotional Expressivity*[3]						
Low	Low (n=15)	0.17	0.01, 2.34	0.12	0.003, 2.13	0.15	0.003, 3.55
	High (n=14)	1.00	0.09, 11.32	0.77	0.04, 10.94	0.68	0.03, 10.64
High	Low (n=58)	**4.58**	**1.18, 20.05**	**5.62**	**1.34, 29.02**	**8.17**	**1.66, 58.96**
	High (n=62)	0.69	0.21, 2.24	0.70	0.22, 2.28	0.76	0.23, 2.57

Bolded values are statistically significant.
[1] Top two quartiles vs. bottom two quartiles of negative emotional expressivity
[2] Low= lowest quartile; Higher= top three quartiles
[3] Low= bottom two quartiles; High= top two quartiles
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; OR= odds ratio

5.2.4 Model Diagnostics

Diagnostic plots were generated for all final models of dementia and AD. In general, the plots were satisfactory and no issues with multicollinearity were detected. For all analyses using the sample for dementia analyses, one individual was repeatedly identified as an outlier compared to the rest of the sample. The participant had low idea density and low emotional expressivity, but was not diagnosed with dementia. She was 100.9 years old at her last cognitive assessment, did not have any *APOE*-ε4 alleles, was highly educated (Master's degree or higher) and had high grammatical complexity.

The displacement of the parameter and confidence intervals caused by this individual was not statistically significant, as determined by C, CBAR and DFBETAS diagnostic tests. The participant had a notable (non-significant) influence on the age parameter estimate but not on the estimate for overall emotional expressivity. Furthermore, the influence of this individual on the model was also tested by manual removal of the participant from the analytic sample. Neither the significance of the parameter estimates, nor the direction of associations between emotional expressivity and dementia, were changed when this individual was removed from the analysis, compared to when she was left in the sample. Eliminating this individual did not affect the results of the bivariate analyses: cases did not differ from non-cases on any of the variables of interest. Given this individual only influenced the age parameter estimate and not the main exposure of interest, and that inclusion of the individual did not affect the statistical significance of any of the analyses, this individual was retained in the sample. However, her influence on the results leads to further discussion (see Section 6.1.1).

5.3 Sensitivity Analysis

5.3.1 Dementia Analyses using the Subset Selected for the Analyses of AD

In order to make a comparison between the association of emotional expressivity with dementia to that with AD, a sensitivity analysis of emotional expressivity and dementia was performed on the subset that was restricted based on the availability of neuropathologic data (n=85). The association between emotional expressivity and dementia was analyzed using the smaller subset to test how the results compared to those of the full sample for dementia analyses, and to the AD models. The sensitivity analysis was generally consistent when compared to the full sample. That is, the odds of overall and negative emotional expressivity was decreased among those with dementia while the odds of positive emotions was slightly increased in the low idea density stratum. Furthermore, the odds of high emotional expressivity, regardless of valence (i.e., overall, positive or negative), was increased in individuals with

dementia within the high idea density strata. However, the results of the sensitivity analysis using the smaller subset deviated from the full sample in that the association between overall expressivity and dementia was no longer significant (OR=2.27, 95% CI=0.72-7.94). See Appendix G for further results of the sensitivity analysis of the association between emotional expressivity and dementia using the subset selected for the AD analyses.

5.3.2 Analysis of Models Not Stratified by Idea Density

The interaction between emotional expressivity and idea density was only significant in the model for overall emotional expressivity and dementia, and not in the models for positive or negative emotional expressivity with dementia, nor in any of the models for AD. For comparability, all models were stratified by idea density; however, a small number of participants had low idea density, so the parameter estimates had very wide confidence intervals. Thus, a sensitivity analysis was performed to investigate the association of emotional expressivity with dementia and AD without stratification. Instead, the models were adjusted for idea density, in addition to age at diagnosis and *APOE*-ε4 status. None of the associations of emotional expressivity with dementia and AD were significant (Table 17). The odds of high emotional expressivity was consistently increased in dementia and AD cases. The exception was when the analysis was stratified by positive emotional expressivity: the odds of negative emotional expressivity was decreased among cases when positive emotional expressivity was high.

Table 17. Sensitivity analysis of the association of emotional expressivity with dementia and AD without stratification by idea density

	Dementia (n=149)		AD[1] (n=79)	
	OR	**95% CI**	**OR**	**95% CI**
Emotional Expressivity[2]				
Overall	N/A[3]		1.19	0.37, 4.00
Positive	1.47	0.68, 3.24	1.24	0.40, 3.88
Negative	1.49	0.68, 3.35	1.02	0.32, 3.42
Low Positive	3.36	0.91, 14.07	2.62	0.43, 23.32
High Positive	0.77	0.27, 2.23	0.49	0.08, 2.69

[1] AD defined by NIA-RI criteria with non-cases defined as individuals without AD or dementia at the last cognitive assessment; See Appendix F for parameter estimates using alternate sample definitions.
[2] Top two quartiles vs. bottom two quartiles
[3] Not applicable given the significant interaction between overall emotional expressivity and idea density
Abbreviations: AD= Alzheimer's disease; CI= confidence interval; NIA-RI= National Institute on Aging–Reagan Institute; OR= odds ratio

Chapter 6
Discussion

6.1 Summary of Findings

The results support an association between emotional expressivity in early adulthood and dementia in late life, modified by idea density in the written autobiographies. Significant associations were seen among individuals with higher idea density only (Tables 14 and 15). In this subgroup, odds of both high overall and moderate negative emotional expressivity were significantly greater in individuals with dementia. The increased odds of dementia associated with negative emotions was further clarified by an interaction between positive and negative emotions. This finding indicated that the odds of negative emotions was significantly higher in individuals with dementia when positive emotional expressivity was low (Table 16).

Most of the associations of emotional expressivity with dementia and AD were inverted across idea density strata: the odds of emotional expressivity was increased in individuals with dementia in the higher idea density subgroup, and decreased in the low idea density subgroup (Table 12). This suggests that the association varies based on written language skills, a previously identified risk factor for dementia and AD (Riley et al., 2005; Snowdon et al., 1996b). In all, the findings indicate that emotional expressivity in early adulthood is predictive of dementia in late life, as expected; however, the relationship is not straightforward.

Emotional expressivity was not significantly associated with AD, regardless of emotional valence or sample selection criteria. A sensitivity analysis was performed to determine whether the association of emotional expressivity with dementia was consistent between the full analytic sample (n=149) and the subset retained for the analysis of AD (n=85). In the smaller sample, the association between emotional expressivity and dementia was no longer significant, suggesting that the sample size may have been insufficient to detect meaningful effects. This may have been true for the non-significant associations with AD as well. Indeed, the directions of association of emotional expressivity with both dementia and AD in the sub-sample were consistent with the results of the full sample used for the dementia analyses, despite the lack of significance. These similarities suggest that emotional expressivity may affect the risk of AD in the same way that it affects all-cause dementia; however, distinctions that may exist could not be identified given the non-significant results. Further studies are needed to clarify the association.

Four main findings are highlighted in this investigation. First, the results were supported by cognitive reserve theory. Second, overall emotional expressivity was associated with increased odds of

dementia among individuals with higher idea density. Third, negative emotional expressivity increased the odds of dementia, an effect that was modified by positive emotional expressivity. Fourth, the effect of emotional expressivity on dementia and AD was modified by idea density, a measure of written language skills that is a known risk factor for dementia and AD. These four key points form the conclusions of this investigation and direct future studies. As such, the discussion will focus on these four findings.

6.1.1 Emotional Expressivity, Dementia and the Theory of Cognitive Reserve

The association between emotional expressivity and dementia was only found among individuals with high idea density. This finding is consistent with the theory of cognitive reserve (Section 2.5.2.3). As found in previous studies, low idea density is likely indicative of a reduced ability to cope with neuropathological deterioration, thus signifying an increased risk of dementia compared to individuals with higher idea density (Riley et al., 2005; Snowdon et al., 1996b). As such, individuals who have a low level of cognitive resources likely begin to experience cognitive decline earlier when compared to individuals with a higher level of cognitive reserve (Figure 2). The findings of the current investigation indicate that overall emotional expressivity, and especially an imbalance of high negative and low positive expressivity, may be associated with an earlier decline in cognitive function among individuals with high idea density, as illustrated by the dashed line in Figure 2.

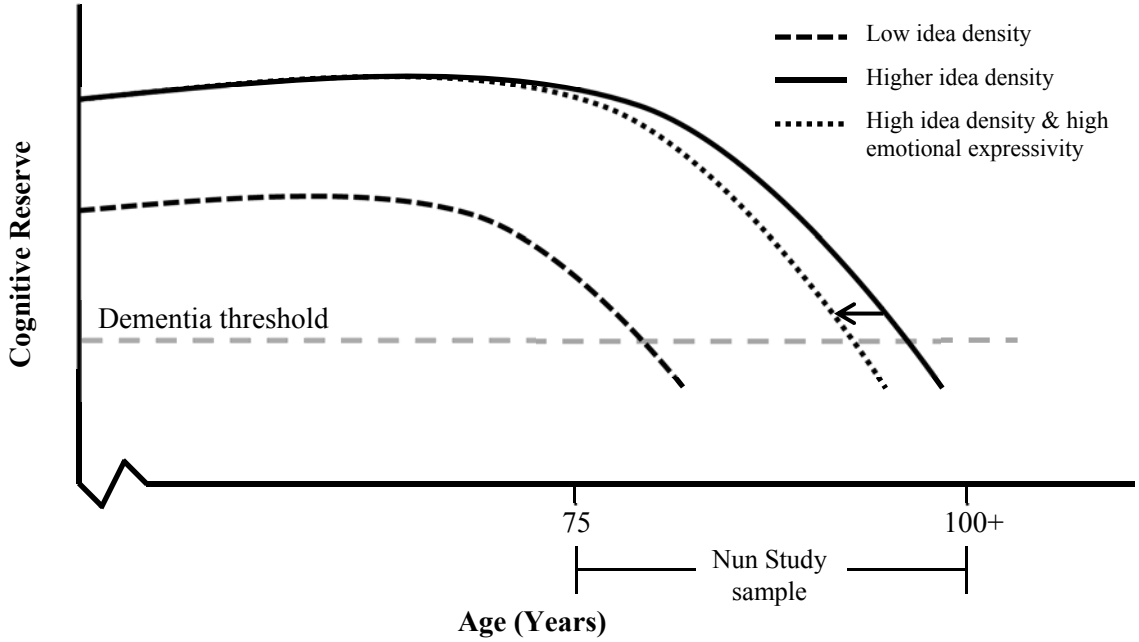

Figure 2. The effect of emotional expressivity on the risk of dementia according to the cognitive reserve theory. The theoretical trajectory of cognitive reserve indicates earlier onset of decline in individuals with low idea density (dashed line) compared to individuals with higher idea density (solid line). The dotted line represents the effects of overall emotional expressivity (or similarly, negative expressivity when positive expressivity is low) among individuals with higher idea density. High emotional expressivity may be associated with earlier, or steeper, decline among individuals with high idea density. The effect of emotional expressivity among individuals with low idea density was unclear, possibly because of the relatively old age of the Nun Study sample (75-100+ years) and the earlier onset of symptoms within this group.

6.1.2 Overall Emotional Expressivity and the Risk of Dementia

Contrary to what was expected, overall emotional expressivity increased the odds of dementia. This increased odds was only found in low-risk individuals (i.e., individuals with higher idea density). Emotional writing has previously been shown to be therapeutic; expressive writing interventions have led to improvements in both short- (e.g., decreased heart rate) and long-term (e.g., lower blood pressure) health outcomes when participants were encouraged to disclose their emotions (see Section 2.6.4.3). This suggests that written expression of emotions may help to reduce the risk of cardiovascular issues over the long-term. However, the opposite was found in the current investigation: individuals who were highly expressive had higher odds of dementia than those who demonstrated low expressivity. Furthermore, a sensitivity analysis showed that individuals who did not express any emotion words did not differ in

proportion of dementia diagnoses from the rest of the study sample, and excluding them did not change the overall results of the logistic regression analysis. As such, the absence of emotion words in the autobiographies may not have indicated emotional suppression as anticipated.

The measure of overall emotional expressivity in the current investigation is likely not a representative measure of individual tendencies to express or suppress emotions, which may explain the inconsistency with existing literature. The previous studies included direct instructions for participants to either expressively write about their emotions (Baikie & Wilhelm, 2005; Pennebaker, 1997), or to suppress their emotions while watching emotionally charged film clips (Gross & Levenson, 1997). In contrast, participants in the Nun Study were not directed on the emotional content to be included in their autobiographies. As such, the emotional expressivity in the autobiographies is likely not a measure of the dichotomy between emotional expression and suppression. Rather, the combination of writing style and emotional expressivity better reflects the natural expressive tendencies of the participants and is thus more indicative of cognitive processing and personality than of emotional disclosure.

A single outlier in the sample for dementia analyses illustrates how the emotional expressivity measure does not indicate the tendency to suppress or express emotions. The individual did not express any emotion words and was in the low idea density subgroup, but had high grammatical complexity. This combination of non-expressive, multi-clause sentences suggests that, rather than suppressing emotions, the individual had written with high complexity but lacking detailed content, emotional or otherwise. As such, the low emotional expressivity score does not necessarily suggest that she was suppressing her emotions. Although this is just one anecdotal example, it suggests that a low overall emotional expressivity score does not represent emotional suppression. Instead, another aspect of emotionality is captured by the variable, as suggested by the significant association between overall emotional expressivity and dementia. Further studies are necessary to clarify the meaning of the overall emotional expressivity measure.

Although the meaning of the emotional expressivity measure is not yet well-understood, the findings support an effect of emotional expressivity on the development of dementia. Potential reasons for this effect are hypothesized. As discussed previously, emotions affect perceptive awareness and the way in which the environment is experienced (Section 2.6.1). Positive emotions function to broaden perception and exploration of the surroundings and thus, provide an apparent advantage in learning and development; however, a drawback could be an increase in distractibility, as described by Dreisbach and Goschke (2004), which may reduce efficient processing of new information for future use. This is consistent with the current findings that high overall emotional expressivity, potentially driven by the

high proportion of positive emotions, may distract from tasks at hand and thus may detract from focus and opportunities for cognitive development.

Another explanation for the increased risk may be that the emotional expressivity in the autobiographies reflects more stable personality traits, such as neuroticism or extraversion, which are known to contribute to the risk of dementia and AD (Prina, Pender, Ferri, Mazzotti, & Albanese, 2014). Indeed, positive emotional expressivity measured in college yearbook photos was associated with personality traits across thirty years of follow-up, with some of these associations becoming stronger with age (Harker & Keltner, 2001). These findings support the possibility that emotional expressivity across the lifespan, as an indicator of more stable personality traits, may affect the development of dementia. Furthermore, the current finding that emotional expressivity is associated with the development of dementia may be based on competency in emotional regulation as a function of personality (Section 2.6.4.2). As discussed in the following section, the odds of high negative emotional expressivity was increased among individuals with dementia only when positive emotions were low. This imbalance of high negative and low positive expressivity may be indicative of poor emotional regulation that may contribute to an increased risk of dementia. However, these explanations are speculative and further investigation is required to clarify the meaning of the association.

6.1.3 Negative Expressivity and the Modifying Effects of Positive Expressivity

The association between negative emotional expressivity and dementia was complex. Negative emotions were expected to increase the risk of dementia given their effects on the cardiovascular system (Section 2.6.3.2) and the stress response (Section 2.6.4.1). The results partially supported this hypothesis, but the association was complicated by the expression of positive emotions. Intuitively, negative emotional expressivity may be expected to follow a dose-response relationship based on the reasoning that greater negativity may indicate more pronounced elevations in cardiovascular and stress responses. However, the results did not support this theory; individuals with moderate, but not high, negative emotional expressivity had significantly higher odds of dementia compared to the low emotional expressivity reference group. (As with overall emotional expressivity, this association was only found in the higher idea density subgroup).

This deviation from an expected dose-response relationship may be partially explained by the fact that a large proportion of individuals with high negative emotional expressivity also had high positive expressivity. Previous studies have found that positive emotions reverse the acute effects of negative emotions (Fredrickson & Levenson, 1998; Fredrickson, Mancuso, Branigan, & Tugade, 2000), and

reduce the risk of stroke in individuals with depression (Ostir, Markides, Peek, & Goodwin, 2001). Indeed, positive emotional expressivity modified the effects of negative emotional expressivity: high negativity was only significantly associated with dementia when positive emotions were low. These findings support the hypothesis that the effects of positive and negative emotional expressivity are not independent, but rather interact to contribute to health outcomes. This is consistent with a previous study in which a combination of high neurotic and low extroverted personality traits was associated with an increased risk of AD an average of 29 years later (Johansson et al., 2014). Such findings suggest that an imbalance of negative emotional tendencies may contribute to an increased risk of dementia and AD, and that the ability to cope with such negative emotions may reduce the risk (see Section 2.6.4.2). However, given the small sample size (n=58) and wide confidence interval (OR=8.17, 95% CI=1.66-58.96), the findings from the current investigation are not definitive and conclusions should be drawn with reservations. Nonetheless, the expected interaction between positive and negative emotions is supported by the current results, and should be the focus of future research.

6.1.4 The Modifying Effect of Idea Density

The direction of association of emotional expressivity with dementia and AD differed across the idea density strata; emotional expressivity was associated with increased odds of dementia and AD (OR>1.00) among individuals with higher idea density, and with decreased odds (OR<1.00) among those with low idea density (Table 12). This modifying effect found in the current investigation may be explained by the differing risk among individuals with high and low idea density, according to the cognitive reserve theory (Figure 2). That is, given the relatively advanced age (i.e., 75 years and older at baseline) of the current study population, the effects of emotional expressivity may be masked among individuals with low idea density because of the earlier onset of symptoms in this high-risk group.

As described previously, the significant association found between emotional expressivity and dementia among individuals with higher idea density (Table 14) suggests that emotional expressivity, and particularly an imbalance of high negative expressivity, may detract from the cognitive advantage associated with superior written language skills. This same pattern of association was not found among individuals with low idea density. Rather, the odds ratio indicated decreased odds of high (compared to low) emotional expressivity with dementia, although none of the estimates were statistically significant (Table 13).

This opposite, but non-significant, effect found in the low idea density subgroup has three possible explanations. First, emotional expressivity truly may not affect the development of dementia among high-

risk individuals. Second, the point estimate may be accurate in that emotional expressivity is protective in this subgroup, but the small sample size and lack of survivors limited the statistical power so that the association did not reach significance. Third, emotional expressivity may have the same effect in individuals with low idea density as in those with high idea density but the effect could not be detected given the relatively old age of the study population. In all, the modifying effect of idea density indicates that the association of emotional expressivity with dementia and AD is not straightforward and is affected by other cognitive factors. Exploration of the association in a more diverse population, including individuals younger than 75 years, is recommended to gain further insight into the association.

6.2 Strengths and Limitations

6.2.1 Limitations

Limitations of the data and design used in the current investigation should be acknowledged. A major limitation lies in the exposure data; that is, the positive and negative word counts obtained from archived autobiographies. Emotional expressivity was obtained from a single time point and the implications of the measures are unclear, leading to questions of the meaning of the results.

Furthermore, the situation in which the autobiographies were written may have affected the emotions that were expressed. For example, individuals may have been less likely to express negative emotions given that they were just entering the community and their superior would be reading what they had written. Indeed, the autobiographies contained significantly fewer negative emotion words, and the variability of negative expressivity was lower in comparison to positive emotion words (Table 4, 6, 9 and 11). This limitation was addressed by collapsing the expressivity variables into ordinal categories to reflect relative expressivity. The data would be further strengthened by inclusion of other variables, such as emotional scores from a second autobiography written at a later time, or depression diagnoses to validate the measure. Regardless, the significant association found in this investigation and by others (Danner et al., 2001) suggests that emotional content does have predictive value and future studies should build upon these findings to clarify the effects of emotions across the lifespan on late-life cognitive outcomes.

The conclusions drawn from the investigation were also limited by sample size, based on the availability of handwritten autobiographies. Of the original sample of 678 participants, 180 U.S.-born individuals had written their autobiographies by hand and were thus eligible for inclusion in the analysis.

The sample was further limited by missing data on the covariates of interest. Only 52% of individuals with a handwritten biography also had full data on neuropathologic data so the AD and VaD analyses were especially limited. Indeed, Table 12 demonstrates that the pattern of association between emotional expressivity and AD in the smaller analytic sample (n=79) was similar to that of emotional expressivity and dementia in the larger sample (n=149). However, none of the associations of emotional expressivity with AD reached significance, suggesting that the subset was too small to detect any meaningful differences that may exist. This was supported by the sensitivity analysis of emotional expressivity with dementia using the smaller subset, which did not reach significance either, suggesting that the sample size did not allow adequate statistical power. Furthermore, the analysis of VaD could not be performed given the low number of cases. As such, future studies should focus on obtaining more robust samples for the analysis of AD and VaD.

Another limitation was the lack of data on comorbidities and health indicators. Information on health concerns, such as diabetes, cardiovascular diseases and depression, as well as measures such as blood pressure and heart rate, would have provided further insight into the mechanisms by which emotions may affect the development of dementia, AD and VaD. Inclusion of cerebral infarcts as a covariate in the analysis compensated for this limitation to some extent but further physical, and particularly vascular, indicators would help to confirm the conclusions.

In addition, the generalizability of results is limited because of the characteristics of the study population. Participants in the study were highly educated women from a religious community and as a result had a relatively homogeneous lifestyle. Thus, they are not representative of the wider population in demographic characteristics or in potential confounders (e.g., socioeconomic status, tobacco/alcohol use). While these factors limit the applicability of the findings to the general population, the absence of such confounding factors allows for clearer etiologic conclusions to be made.

Inclusion criteria required participants to be older than age 75 at the beginning of data collection. This may present survival bias because more severe, early-onset cases of the diseases of interest are not represented. As a result, the effects of emotions on dementia and AD may be underestimated or undetected. In addition, defining cases of dementia based on the last cognitive assessment limits potential analysis of the age at onset because onset of clinical symptoms is unspecified.

6.2.2 Strengths

The homogeneity of the study population, which was mentioned as a limitation above, is also a key strength of the Nun Study data. Although the participants are not representative of the wider population,

their relatively uniform and conservative lifestyle free from many factors that contribute to disease risk naturally controls for many potential confounders. Furthermore, the etiology of dementia and AD likely does not differ in the Nun Study population compared to the wider population, so the results are an accurate reflection of the association without the noise of potential confounding lifestyle factors. As a result, stronger conclusions can be made regarding the contribution of emotional expressivity to the risk of dementia.

Another strength of the study is the post-mortem brain autopsies, which provided neuropathological data for a definite diagnosis of AD and VaD. These data provided a strong measure of the outcome. The brain autopsy data also allowed analysis of cerebral infarcts as a potential confounding factor in the association of emotional expressivity with dementia and AD. Such detailed information on the condition of the brain at death also presents many opportunities for future studies to further evaluate the effects of emotional expressivity on neuropathologically defined conditions.

Existing literature on the long-term effect of emotional experience on dementia and its subtypes is limited, raising the question of temporality (see Section 2.5.2.4). For example, many of the studies of the effects of depression, anxiety and loneliness on the development of AD had only five to eight years of follow-up. With such short follow-up periods, the possibility that depression and other affective disorders are a prodromal symptom of the disease cannot be ruled out given that evidence of AD neuropathology has been identified approximately twenty years prior to the appearance of clinical symptoms. The current investigation uses longitudinal data with over half a century of follow-up, which is substantially longer than any previous study. Such a long follow-up period allows temporal associations to be made with greater confidence.

A major strength of the current investigation is the ability to control for written language skills using measurements from the same document as the emotional expressivity measures. This provides a unique opportunity to directly control for the effect of written language skills on emotional expressivity without relying on a proxy measure from another source. Indeed, the results indicate that idea density, as a measure of written language skills, is a key modifying factor in the association between emotional expressivity and the development of dementia. Without consideration of this unique variable, the main association of interest would not have been uncovered.

6.3 Implications

The current investigation advances the understanding of emotional expressivity as a predictor of dementia. The findings are consistent with previous studies that suggest an integral role of emotions in affecting long-term health outcomes such as longevity (Danner et al., 2001), heart disease (Mauss & Gross, 2004), and mental health (Charles, Piazza, Mogle, Sliwinski, & Almeida, 2013). The results also support the positivity effect in older adults (Carstensen et al., 2003) by indicating that a balance of positive and negative emotions is advantageous across the lifespan and not only in late adulthood. Indeed, overall emotions, and a tendency toward negative emotional expressivity in particular, predicted the development of dementia over half a century later.

Given the known effects of emotional experience on cognitive, psychosocial and physiological functions, the predictive nature of emotional expressivity on the risk of dementia is not surprising. The findings of the current investigation establish that an association across the lifespan may exist, but the underlying mechanisms are unclear. Establishing the relationship of emotions with these conditions is important because, although several lifestyle factors have been found to reduce the risk, AD and many other forms of dementia are irreversible. As such, the development of prevention strategies is key. Identification of further risk-reducing factors, such as the ability to regulate emotions and to cope with negative emotions, may help to lessen the burden of disease by providing opportunities for intervention. For example, increased focus on emotional coping skills in elementary education may be warranted. Awareness of the importance of emotions in affecting the development of dementia may also encourage the integration of emotional support into existing dementia interventions. Most importantly, the current findings support the theory that emotions in early adulthood contribute to the late-life development of dementia, and thus motivate further research to identify the underlying mechanisms of the association.

6.4 Future Directions

Given that this specific association between emotional expressivity in early adulthood and dementia in late life has not previously been explored, these novel findings provide a platform on which to base future studies. Further investigations are necessary to expand the understanding of the association. In particular, four key objectives are recommended for future studies to advance the current investigation. These recommended objectives are to: 1) replicate the study using other sample populations and measures of emotional experience to support the current findings; 2) develop an understanding of the emotional expressivity measure and what it reflects; 3) elucidate potential mechanisms by which emotions may

affect late-life development of dementia; and 4) expand the study population to clarify the association with AD and VaD.

6.4.1 Replicate the Study

The novelty of this study calls for further investigation of the relationship between emotions and dementia. In order to establish the association, findings should be reproduced using a variety of study samples and measures of emotional experience. Consistency in future results would serve to support the findings of the current investigation that emotional expressivity has predictive value across the lifespan.

Future investigations should replicate the current study using a more diverse, representative sample including men and women from the general population. In particular, assessment of the association of emotional expressivity with dementia and AD in men, in comparison to the current study of women, may help to clarify the mechanism underlying the association, given the recognized differences in emotional expressivity between genders. Also, different measures of emotional expressivity are recommended to broaden the understanding of the effects on cognitive decline and neurodegeneration. Beyond written autobiographies, potential sources for measuring emotional expressivity include yearbook photographs, videos and self or proxy reports. Primary sources (e.g., photographs, videos, autobiographies) are preferable for an accurate measure of emotional expressivity and are ideal for use in a prospective or retrospective cohort study design. However, recruitment and follow-up of a representative population of individuals with available yearbook photographs or autobiographies presents several logistic challenges. Alternatively, sample selection and data collection for a case-control study using self or proxy reports of emotional expressivity is more straightforward, but the exposure data are less reliable, especially given that dementia cases face cognitive challenges and may not be able to give an accurate estimation of emotional experience in a self-report. Selection of suitable proxies may also be difficult. In addition, conclusions of temporality are limited in case-control studies. These difficulties in designing a study to investigate the lifespan effect of emotions on dementia and related outcomes attest to the high value of the current investigation and the Nun Study in general.

6.4.2 Validate the Emotional Expressivity Measure

The results of the current investigation indicate a significant association between emotional expressivity in autobiographies written in early adulthood and development of dementia in late life. However, the meaning of this association is unclear because the implications of the emotional expressivity measure are not well understood. Further clarification of the association is required to

understand the association on broader terms. For example, a second measure of emotional tendencies or personality at the time that the autobiographies were written would provide stronger evidence of how emotions, as part of a greater personality profile, may affect long-term cognitive outcomes. Furthermore, measurement of emotional expressivity later in life (e.g., from a second autobiography) would allow for the assessment of the stability of emotional expressivity over time to strengthen the argument that emotional expressivity across the lifespan influences the development of dementia. Further clarification of the meaning of the emotional expressivity measure would contribute to the understanding of the current association.

6.4.3 Clarify Mechanisms Underlying the Association Between Emotional Expressivity and Dementia

Emotional expressivity was predictive of the development of dementia over half a century later, but the mechanism underlying this association is not clear. In the current investigation, presence of cerebral infarcts was included in the initial analysis but did not affect the association between emotional expressivity and development of dementia or its subtypes, suggesting that the mechanism may not be based on cerebrovascular pathology resulting from high emotionality and stress (see Appendix B). However, these conclusions are not definitive and further studies including the effects of various vascular lesions on the main association of interest are required to understand the underlying mechanism as it may relate to the physiological effects of emotions.

Investigation of the association of emotional expressivity with time to onset of dementia, disease trajectory and discrepancies between cognitive decline and neurodegeneration would help to identify potential cognitive effects of emotional expressivity, as well as consistencies with the cognitive reserve theory. The effect of stress on the association between emotional expressivity and the development of dementia, AD and VaD could also be investigated. For example, future analysis could incorporate a measure of the experience of stress. Identification of the contribution of stress in the association between emotional expressivity and dementia would enhance understanding of the effects of emotions on long-term outcomes and could guide strategies to reduce the risk of disease.

6.4.4 Expand the Analysis of AD and VaD

The data available for analysis of the effects of emotional expressivity on the subtypes of dementia, AD and VaD, was limited in the current investigation and thus, is suggested as a focus for future research. Given the non-significant but similar results to the sample for dementia analyses, an association may exist

between emotional expressivity and AD; however, this could not be concluded due to non-significant results, likely because of the small sample size. As such, further investigation using a larger sample is warranted to confirm this suspected association between emotional expressivity and AD.

The analysis could not be performed between emotional expressivity and VaD because of a very low number of cases. This is likely due to the nature of the lifestyle of the religious sisters in the study, which is relatively free of vascular risk factors. As such, a different study population with a higher prevalence of vascular risk factors and VaD is recommended for investigation of the association. Clarification of the effects of emotions on vascular outcomes, including VaD, may help in understanding the association of emotional expressivity with dementia by either confirming a vascular effect, or suggesting an alternative (e.g., cognitive) mechanism underlying the association, as suggested in Section 3.1.2. Again, the difficulty in obtaining a robust sample with all necessary measures available poses a challenge.

6.5 Conclusion

As a novel study of the association of emotions in early adulthood with dementia, AD and VaD in late life, the aim of this research project was to establish whether the association exists. Consistent with related studies, the results support the potential contribution of emotional expressivity in early adulthood to long-term health outcomes, and in particular, the development of dementia, and possibly AD. Given limitations in the dataset, the effects of VaD could not be assessed and so conclusions on this association could not be made. The finding that emotional expressivity is associated with the development of dementia, modified by written language skills, lays the foundation for further research on the effect of emotional experience on dementia and underlying neurodegenerative diseases, as well as on other aspects of health across the lifespan.

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Appendix A. Literature Search Construct and Article Summaries

Table 1. Search terms and construct[1] of literature search concerning emotions as predictors of dementia, AD and VaD.

Emotional expressivity	AD	VaD	Dementia
Medline			
Expressed emotion [MeSH] OR positive emotion [tiab] OR positive emotions [tiab] OR emotions [MeSH] OR negative emotion [tiab] OR negative emotions [tiab]	Alzheimer Disease [MeSH] OR Alzheimer's disease [tiab] OR Alzheimer disease [tiab] OR Alzheimer [tiab] OR Alzheimer's [tiab]	Dementia, Vascular [MeSH] OR Vascular dementia [tiab] OR dementia, multi-infarct [mesh] OR multi-infarct dementia [tiab] OR multiinfarct dementia [tiab] OR multi infarct dementia [tiab]	Dementia [MeSH] OR dementia [tiab]
PsycINFO			
Index Terms: {Affective Valence} OR {Emotional Content} OR {Emotional Responses} OR {Emotional States} OR {Emotionality (Personality)} *OR* **Title**: Emotional expressivity OR emotional expression OR emotion *OR* **Any Field**: Emotional expressivity OR emotional expression OR emotion	**Index Terms**: {Alzheimer's Disease} *OR* **Title**: Alzheimer *OR* **Abstract**: Alzheimer	**Index Terms**: {Vascular Dementia} *OR* **Title**: vascular dementia *OR* **Abstract**: vascular dementia *OR* **Title**: multi-infarct dementia *OR* **Abstract**: multi-infarct dementia *OR* **Title**: multi infarct dementia *OR* **Abstract**: multi infarct dementia	**Index Terms**: {Dementia} *OR* **Title**: dementia *OR* **Abstract**: dementia

[1]Construct: (emotional expressivity) AND [(AD) OR (VaD) OR (dementia)]
Abbreviations: AD= Alzheimer's disease; MeSH= Medical Subject Headings; tiab= title/abstract; VaD= vascular dementia

Table 2. Summary of articles obtained from the literature search.

Author	Year	Analytic sample	N	Independent variable	Dependent variable	Findings
Caracciolo *et al*.	2010	Cognitively intact, community-dwelling, elderly (75+), from Stockholm, Sweden	764	Low mood (perceived sadness on Comprehensive Psychopathological Rating Scale interview, 0-6)	MCI/CIND, clinical dementia	All-MCI: HR=2.6 (95% CI=1.8-3.7) with low mood at baseline; Conversion from amnestic MCI to dementia: HR=5.3 (95% CI=1.2-23.3)
Ellwardt *et al*.	2013	Representative cohort of cognitively intact Dutch men and women mean age (63±6.65)	488	Emotional support; self-reported loneliness as a mediating factor	Cognitive function	Emotional support was associated with less loneliness (β_{int}=-0.35, p<0.001); Less loneliness was associated with better cognitive function (β_{int}=-0.35, p<0.001) suggesting a mediating effect
Holwerda *et al*.	2014	Non-demented, community-dwelling older adults (65+) from the Netherlands	2173	Social isolation; feelings of loneliness	Dementia	Feelings of loneliness: OR=1.64 (95% CI=1.05-2.56); no significant association found for measures of social isolation
Lavretsky *et al*.	2009	Non-demented, middle aged (66.1±12.4), community-dwelling adults from USA	43	Depressive and anxiety symptoms (not diagnoses); stratified for MCI	Brain mapping of Aβ plaques and NFTs through neuroimaging	Correlation between depressive scores and medial temporal lobe Aβ /NFTs was significantly different (80%) between MCI/no MCI groups
Wilson *et al*.	2007	Non-demented older adults (80.7±7.1) from diverse settings in the Chicago area	857	Loneliness and social isolation	Incident AD	Loneliness: RR=1.45 (95% CI=1.01-2.09) controlled for social activity and network size; Social activity: RR=0.52 (95% CI=0.34-0.79)

Abbreviations: Aβ = beta-amyloid; CI= confidence interval; CIND= cognitive impairment, no dementia; HR= hazard ratio; IQ= intelligence quotient; MCI= mild cognitive impairment; NFTs= neurofibrillary tangles; OR= odds ratio; RR= relative risk

Appendix B. Cerebral Infarct Sensitivity Analysis

Emotions influence the development of cardiovascular disorders, such as atherosclerosis and hypertension (see section 2.6.3.2). Given that vascular diseases increase the risk of dementia, AD and VaD outcomes, emotional expressivity could potentially influence these outcomes through vascular involvement. As such, presence of cerebral infarcts, as an indicator of vascular assaults to brain tissue, was expected to mediate the effect of emotions on dementia and AD and was thus included in the analyses. However, in selecting the analytic sample, we found that the sample for dementia analyses was limited by missing infarct data: 43 (28.8%) of 149 who were otherwise eligible for inclusion did not have data on this covariate because they were still alive (n=27) or their post-mortem autopsy had not been processed (n=16). In an effort to maintain a robust sample size, those who did not have infarct data were retained for the main analysis; however, a sensitivity analysis excluding these individuals was also performed.

Individuals who did not have cerebral infarct data were significantly different than the rest of the sample for dementia analyses on several measures. Those with missing infarct data were older at their last cognitive assessment (mean=91.8 years, SD=4.59, vs. mean=86.6, SD=4.32; $p<0.01$), and a greater proportion had a master's degree or higher (76.7% vs. 50.0%; $p<0.01$) and better written language skills ($p<0.01$ for both idea density and grammatical complexity). They did not differ in the proportion that had dementia, at least one *APOE*-ε4 allele or in their expressivity of emotional words. Given that the majority of the excluded individuals were alive, the significant difference in age, education and written language skills may be due to survivor bias. The notion that they may have a lower prevalence of cerebral infarcts as well cannot be ruled out. The descriptive statistics of the subset with complete data on cerebral infarcts is found in below (Section B.1).

The sensitivity analysis revealed that the presence of infarcts did not significantly affect the association between emotional expressivity and dementia; adjusting for cerebral infarcts did not greatly change the parameter estimate of the association between emotional expressivity and dementia (i.e., <10%), nor was the pattern of association different in the infarct subset compared to the main analytic sample (Table B5). The full results of the logistic regression analysis for the infarct subset are also found below (see tables in Section B.2). Notably, the association between overall emotional expressivity and dementia among individuals with high idea density was not significant in the final model, adjusted for age and *APOE*-ε4, in this subset (OR=2.68, 95% CI=0.89-8.96). However, the association was significant in the full model adjusted for all variables and most of the models bordered on significance with very wide confidence intervals

(Table 9). These findings suggested that the subset was too small to provide a robust analysis, and that cerebral infarcts did not mediate the association in this sample as expected. As such, available data on cerebral infarcts were not required for inclusion in the main analysis.

Table B1. Participant characteristics by dementia status: analytic sample with cerebral infarcts data (n=106)

		Dementia[1]	
	All (n=106)	No (n=68)	Yes (n=38)
Characteristic			
Covariates			
Age[2], Mean Years (SD)	86.6 (4.32)	86.5 (4.30)	86.8 (4.41)
Level of Education, %			
Bachelor's Degree	50.0	51.5	47.4
≥ Master's Degree	50.0	48.5	52.6
Presence of *APOE*-ε4, %*	29.2	22.1	42.1
Presence of 1+ Cerebral Infarct, %	31.1	25.0	42.1
Idea Density, %**			
Low	25.5	11.8	50.0
Q2	20.8	25.0	13.2
Q3	25.5	30.9	15.8
High	28.3	32.4	21.0
Grammatical Complexity, %			
Low	29.2	23.5	39.5
Q2	21.7	25.0	15.8
Q3	22.6	25.0	18.4
High	26.4	26.5	26.3

* $p<0.05$
** $p<0.01$
[1] Based on diagnosis of dementia at the last cognitive assessment
[2] Age at last cognitive assessment
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; Q= quartile; SD= standard deviation

Table B2. Emotional expressivity by dementia status: analytic sample with cerebral infarcts data (n=106)

	All (n=106)	Dementia[1] No (n=68)	Dementia[1] Yes (n=38)
Emotional Expressivity			
Raw Word Counts[2], Mean (SD)			
Overall	8.7 (7.74)	8.2 (7.72)	9.7 (7.79)
Positive	7.5 (6.59)	7.0 (6.49)	8.5 (6.76)
Negative	1.2 (1.68)	1.2 (1.70)	1.2 (1.68)
Raw Word Counts[2], Median (Range)			
Overall	6.0 (0-32)	5.0 (0-32)	8.0 (0-29)
Positive	5.0 (0-27)	4.0 (0-27)	6.0 (0-22)
Negative	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %			
Overall			
Low	23.6	25.5	23.7
Q2	24.5	27.9	18.4
Q3	28.3	26.5	31.6
High	23.6	22.1	26.3
Positive			
Low	26.4	26.5	26.3
Q2	25.5	27.9	21.0
Q3	21.7	22.1	21.0
High	26.4	23.5	31.6
Negative			
Low	12.3	10.3	15.8
Q2	40.6	41.2	39.5
Q3	33.0	33.8	31.6
High	14.2	14.7	13.2

[1] Based on diagnosis of dementia at the last cognitive assessment
[2] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparison
Abbreviations: Q= quartile; SD= standard deviation
Note: Emotional expressivity did not significantly differ by dementia status.

Table B3. Participant characteristics by dementia and idea density: analytic sample with cerebral infarcts data (n=106)

Characteristic	Idea density[1]					
	Low			Higher		
		Dementia[2]			Dementia[2]	
	All (n=27)	No (n=8)	Yes (n=19)	All (n=79)	No (n=60)	Yes (n=19)
Covariates						
Age[3], Mean Years (SD)	85.4 (4.44)	85.8 (4.16)	85.3 (4.65)	87.0 (4.23)	86.6 (4.35)	88.3 (3.69)
Level of Education, %						
Bachelor's Degree	55.6	50.0	57.9	48.1	51.7	36.8
≥ Master's Degree	44.4	50.0	42.1	51.9	48.3	63.2
Presence of *APOE*-ε4, %	51.8	37.5	57.9	21.5	20.0	26.3
Presence of 1+ Cerebral Infarct, %	40.7	25.0	47.4	27.8	25.0	36.8
Grammatical Complexity, %						
Low	40.7	25.0	47.4	25.3	23.3	31.6
Q2	25.9	37.5	21.0	20.2	23.3	10.5
Q3	11.1	0.0	15.8	26.6	28.3	21.0
High	22.2	37.5	15.8	27.8	25.0	36.8

Note: Participant characteristics did not differ by dementia status in either idea density stratum.
[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density
[2] Based on diagnosis of dementia at the last cognitive assessment
[3] Age at last cognitive assessment
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; Q= quartile; SD= standard deviation

Table B4. Emotional expressivity by dementia status and idea density: analytic sample with cerebral infarcts data (n=106)

	Idea density[1]					
	Low			Higher		
		Dementia[2]			Dementia[2]	
	All (n=27)	No (n=8)	Yes (n=19)	All (n=79)	No (n=60)	Yes (n=19)
Emotional Expressivity						
Raw Word Counts[3], Mean (SD)						
Overall	8.6 (7.13)	9.5 (7.75)	8.2 (7.04)	8.8 (7.98)	8.0 (7.76)	11.2 (8.38)
Positive	7.5 (6.24)	8.5 (7.62)	7.0 (5.75)	7.6 (6.74)	6.8 (6.37)	9.9 (7.52)
Negative	1.1 (1.57)	1.0 (0.92)	1.1 (1.79)	1.2 (1.73)	1.2 (1.78)	1.3 (1.60)
Raw Word Counts[3], Median (Range)						
Overall	5.0 (0-25)	8.0 (1-19)	5.0 (0-25)	6.0 (0-32)	5.0(0-32)	8.0 (0-29)
Positive	5.0 (0-19)	6.5 (1-18)	5.0 (0-19)	5.0 (0-27)	4.5 (0-27)	7.0 (0-22)
Negative	0.0 (0-6)	1.0 (0-2)	0.0 (0-6)	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %						
Overall						
Low	29.6	25.0	31.6	21.5	23.3	15.8
Q2	14.8	0.0	21.0	27.8	31.7	15.8
Q3	33.3	50.0	26.3	26.6	23.3	36.8
High	22.2	25.0	21.0	24.0	21.7	31.6
Positive						
Low	33.3	25.0	36.8	24.0	26.7	15.8
Q2	18.5	25.0	15.8	27.8	28.3	26.3
Q3	22.2	12.5	26.3	21.5	23.3	15.8
High	25.9	37.5	21.0	26.6	21.7	42.1

	Idea density[1]					
	Low			Higher		
		Dementia[2]			Dementia[2]	
	All (n=27)	No (n=8)	Yes (n=19)	All (n=79)	No (n=60)	Yes (n=19)
Negative						
Low	14.8	12.5	15.8	11.4	10.0	15.8
Q2	48.2	37.5	52.6	38.0	41.7	26.3
Q3	14.8	12.5	15.8	39.2	36.7	47.4
High	22.2	37.5	15.8	11.4	11.7	10.5

[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density
[2] Based on diagnosis of dementia at the last cognitive assessment
[3] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparison
Abbreviations: Q= quartile; SD= standard deviation
Note: Emotional expressivity did not significantly differ by dementia status in either idea density strata.

B.2 Multivariate Logistic Regression Sensitivity Analysis Using the Cerebral Infarcts Subset

Table B5. Sensitivity analysis of the effect of cerebral infarcts on the association between emotional expressivity and dementia, OR (95% CI)

		Infarcts Subset[1] (n=106)			Main Analytic Sample (n=149)
		Crude	Adjusted[2]	Final[3]	Final[3]
Idea Density[4]	*Emotional Expressivity*[5]				
Low	Overall	0.30 (0.04-1.70)	0.33 (0.04-1.97)	0.34 (0.04-2.20)	0.44 (0.07-2.30)
	Positive	0.90 (0.17-4.86)	0.94 (0.17-5.28)	1.00 (0.18-5.69)	1.37 (0.27-7.54)
	Negative	0.46 (0.08-2.55)	0.45 (0.07-2.58)	0.51 (0.07-3.46)	0.63 (0.11-3.56)
Higher	Overall	2.65 (0.92-8.41)	2.55 (0.87-8.13)	2.68 (0.89-8.96)	**2.60** (1.04-7.11)
	Positive	1.68 (0.60-4.91)	1.72 (0.61-5.10)	1.67 (0.58-4.96)	1.48 (0.61-3.66)
	Negative	1.47 (0.52-4.29)	1.44 (0.51-4.23)	1.52 (0.50-4.84)	1.99 (0.81-5.13)

Bolded values are statistically significant.
[1] Subset selected from main analytic sample based on availability of cerebral infarct data
[2] Adjusted for presence of cerebral infarcts
[3] Adjusted for age at last cognitive assessment and *APOE*-ε4
[4] Low= lowest quartile of idea density; Higher= top three quartile of idea density
[5] Top two quartiles vs. bottom two quartiles
Abbreviations: CI= confidence interval; OR= odds ratio

B.2.1 Full Models of Infarct Sensitivity Analysis: Low Idea Density

Table B6. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *dementia* among individuals with *low idea density*, using the analytic sample with cerebral infarcts data, OR (95% CI), n=27

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Infarcts	1E	Grammatical Complexity	Full	Final
Variable											
High Overall EE	0.30 (0.04-1.70)	0.30 (0.04-1.77)	0.28 (0.03-1.63)	0.28 (0.03-1.74)	0.34 (0.04-2.10)	0.34 (0.04-2.25)	0.33 (0.04-1.97)	0.37 (0.04-2.49)	0.33 (0.04-1.97)	0.36 (0.04-2.43)	0.34 (0.04-2.20)
Age		1.01 (0.82-1.24)		1.00 (0.81-1.23)		0.99 (0.80-1.23)		1.00 (0.79-1.25)		1.02 (0.80-1.30)	1.00 (0.82-1.24)
Education (Master's vs. Bachelor's)			0.63 (0.10-3.60)	0.62 (0.10-3.66)		0.60 (0.09-3.59)		0.75 (0.11-4.96)		0.75 (0.11-5.06)	
APOE-ε4 Status					1.81 (0.31-11.66)	1.88 (0.31-12.77)		2.00 (0.32-14.09)		1.63 (0.22-12.68)	1.81 (0.30-11.68)
Cerebral Infarcts							2.36 (0.39-19.75)	2.33 (0.34-21.53)		2.10 (0.28-20.02)	
Grammatical Complexity									0.42 (0.05-2.59)	0.52 (0.05-4.08)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)

Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table B7. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *dementia* among individuals with *low idea density*, using the analytic sample with cerebral infarcts data, OR (95% CI), n=27

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Infarcts	1E[2]	Grammatical Complexity	Full[2]	Final
Variable											
High Positive EE	0.90 (0.17-4.86)	0.92 (0.17-5.09)	0.91 (0.17-4.95)	0.95 (0.17-5.40)	0.98 (0.18-5.61)	1.08 (0.19-6.72)	0.94 (0.17-5.28)	1.00 (0.17-6.17)	0.94 (0.17-5.28)	0.97 (0.16-5.99)	1.00 (0.18-5.69)
Age		0.98 (0.80-1.18)		0.96 (0.79-1.18)		0.96 (0.78-1.18)		0.96 (0.77-1.19)		0.98 (0.78-1.25)	0.98 (0.80-1.19)
Education (Master's vs. Bachelor's)			0.73 (0.13-3.95)	0.68 (0.12-3.84)		0.58 (0.08-3.53)		0.77 (0.10-5.21)		0.80 (0.11-5.42)	
APOE-ε4 Status					2.29 (0.43-14.13)	2.48 (0.45-16.62)		2.40 (0.42-16.31)		2.03 (0.32-14.90)	2.28 (0.42-14.05)
Cerebral Infarcts							2.69 (0.47-21.76)	2.53 (0.39-23.08)		2.32 (0.34-21.62)	
Grammatical Complexity									0.37 (0.05-2.11)	0.55 (0.05-4.19)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Hosmer-Lemeshow Goodness of Fit test, $p<0.01$
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table B8. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *low idea density*, using the analytic sample with cerebral infarcts data, OR (95% CI), n=27

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Infarcts	1E	Grammatical Complexity	Full[2]	Final
Variable											
High Negative EE	0.46 (0.08-2.55)	0.45 (0.07-2.87)	0.45 (0.08-2.49)	0.45 (0.06-2.91)	0.52 (0.09-3.02)	0.50 (0.07-3.44)	0.45 (0.07-2.58)	0.46 (0.05-3.62)	0.52 (0.09-3.03)	0.46 (0.06-3.53)	0.51 (0.07-3.46)
Age		1.01 (0.81-1.25)		1.00 (0.80-1.24)		0.99 (0.79-1.23)		1.01 (0.79-1.29)		1.02 (0.80-1.33)	1.00 (0.81-1.24)
Education (Master's vs. Bachelor's)			0.68 (0.12-3.78)	0.68 (0.11-3.91)		0.58 (0.09-3.52)		0.76 (0.10-5.20)		0.77 (0.10-5.27)	
APOE-ε4 Status					2.07 (0.37-12.93)	2.27 (0.40-15.21)		2.19 (0.36-15.48)		1.84 (0.26-14.09)	2.07 (0.37-12.93)
Cerebral Infarcts							2.76 (0.47-22.95)	2.64 (0.40-25.08)		2.38 (0.34-23.25)	
Grammatical Complexity									0.41 (0.05-2.41)	0.54 (0.05-4.17)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Hosmer-Lemeshow Goodness of Fit test, $p<0.01$
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

B.2.2 Full Models of Infarct Sensitivity Analysis: High Idea Density

Table B9. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *dementia* among individuals with *high idea density*, using the analytic sample with cerebral infarcts data, OR (95% CI), n=79

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Infarcts	1E	Grammatical Complexity	Full	Final
Variable											
High Overall EE	2.65 (0.92-8.41)	2.46 (0.84-7.89)	2.89 (0.98-9.41)	2.80 (0.93-9.40)	2.92 (0.98-9.66)	3.05 (0.98-10.61)	2.55 (0.87-8.13)	2.95 (0.94-10.32)	2.76 (0.95-8.89)	**3.28** (1.03-11.88)	2.68 (0.89-8.96)
Age		1.10 (0.96-1.27)		1.11 (0.97-1.31)		1.11 (0.96-1.31)		1.11 (0.96-1.30)		1.13 (0.97-1.34)	1.09 (0.95-1.27)
Education (Master's vs. Bachelor's)			2.07 (0.71-6.51)	2.34 (0.77-7.77)		2.34 (0.77-7.86)		2.26 (0.73-7.66)		2.40 (0.76-8.35)	
APOE-ε4 Status					1.81 (0.48-6.40)	1.70 (0.44-6.17)		1.73 (0.45-6.34)		1.96 (0.49-7.54)	1.72 (0.45-6.18)
Cerebral Infarcts							1.60 (0.50-4.89)	1.47 (0.44-4.68)		1.48 (0.44-4.77)	
Grammatical Complexity									0.69 (0.19-2.02)	0.47 (0.13-1.69)	

Bolded values are statistically significant.

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)

Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table B10. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *dementia* among individuals with *high idea density*, using the analytic sample with cerebral infarcts data, OR (95% CI), n=79

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Infarcts	1E	Grammatical Complexity	Full	Final
Variable											
High Positive EE	1.68 (0.60-4.91)	1.66 (0.58-4.92)	1.87 (0.65-5.65)	1.91 (0.65-5.96)	1.69 (0.60-4.96)	1.94 (0.66-6.08)	1.72 (0.61-5.10)	1.96 (0.66-6.17)	1.76 (0.62-5.23)	2.16 (0.71-7.05)	1.67 (0.58-4.96)
Age		1.11 (0.97-1.28)		1.12 (0.98-1.31)		1.12 (0.98-1.31)		1.12 (0.98-1.31)		1.13 (0.98-1.34)	1.10 (0.97-1.28)
Education (Master's vs. Bachelor's)			2.02 (0.70-6.27)	2.24 (0.75-7.28)		2.24 (0.75-7.34)		2.14 (0.70-7.09)		2.30 (0.74-7.83)	
APOE-ε4 Status					1.45 (0.40-4.71)	1.39 (0.38-4.66)		1.43 (0.38-4.86)		1.58 (0.42-5.60)	1.41 (0.38-4.67)
Cerebral Infarcts							1.80 (0.58-5.44)	1.66 (0.51-5.22)		1.68 (0.51-5.37)	
Grammatical Complexity									0.62 (0.20-2.05)	0.50 (0.14-1.77)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)

Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table B11. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *high idea density*, using the analytic sample with cerebral infarcts data, OR (95% CI), n=27

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Infarcts	1E	Grammatical Complexity	Full	Final
Variable											
High Negative EE	1.47 (0.52-4.29)	1.35 (0.47-4.00)	1.57 (0.55-4.66)	1.51 (0.52-4.63)	1.69 (0.57-5.38)	1.76 (0.56-5.99)	1.44 (0.51-4.23)	1.73 (0.55-5.94)	1.48 (0.52-4.33)	1.82 (0.57-6.37)	1.52 (0.50-4.84)
Age		1.10 (0.97-1.27)		1.12 (0.97-1.30)		1.11 (0.97-1.30)		1.11 (0.97-1.30)		1.12 (0.97-1.32)	1.10 (0.96-1.27)
Education (Master's vs. Bachelor's)			1.92 (0.67-5.86)	2.12 (0.72-6.83)		2.18 (0.72-7.20)		2.09 (0.68-7.01)		2.24 (0.72-7.85)	
APOE-ε4 Status					1.73 (0.46-6.19)	1.67 (0.43-6.20)		1.70 (0.43-6.39)		1.87 (0.47-7.21)	1.60 (0.42-5.80)
Cerebral Infarcts							1.72 (0.55-5.15)	1.60 (0.49-4.96)		1.59 (0.49-4.98)	
Grammatical Complexity									0.66 (0.21-2.16)	0.54 (0.16-1.89)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Appendix C. Assessment of Non-Response

Various subsets of the total Nun Study population were identified based on "non-response" (i.e., missing data or ineligibility because of restriction). The descriptive statistics of these subsets were compared to assess generalizability of the final analytic sample and to identify potential sources of bias. In total, 678 individuals were included in the Nun Study population; however, emotions data from scored autobiographies was only available for 180 individuals, which made up the baseline population of individuals who were eligible for inclusion in the analysis (Figure 1). As such, individuals who did (n=180) and did not have emotions data (n=498) were compared (Table C1).

Of the 180 individuals who had data on emotions, 164 had complete data on all covariates of interest and were therefore included in the initial sample for the analyses of dementia. Non-response analysis was performed on those who were included in the initial sample (n=164) compared to those who were not included from the baseline sample population (n=16; Table C2).

The multivariate regression analysis of the initial sample for dementia analyses yielded models with poor fit because of the large influence of low education and the relatively low number of individuals with low education. As a result, the sample was further restricted on low education, so that 149 individuals remained in the final analytic sample. Individuals who were included in the final sample (n=149) were compared to those who were excluded from the baseline sample population (n=31; Table C3) and to those who were excluded from the initial sample selected for the analysis of dementia (n=15; Table C4).

Of the 149 individuals who were retained in the final sample for dementia analyses, 85 had complete neuropathologic data and were therefore included in the final sample for AD analyses. The descriptive statistics of the individuals included in this sample (n=85) were compared to those of individuals who were excluded from the baseline sample population (n=95; Table C5) and to those of individuals who were excluded from the final sample used for the analyses of dementia (n=64; Table C6).

Table C1. Descriptive statistics of sample who had emotions data compared to those without emotions data

		Total	Emotions Data	No Emotions Data
Age at Last Cognitive Assessment, Years**	n	678	180	498
	Mean (SD)	89.5 (5.71)	87.5 (5.26)	90.2 (5.70)
Age at Death, Years**	n	606	151	455
	Mean (SD)	90.4 (5.37)	87.9 (4.46)	91.2 (5.39)
Dementia**	n	678	180	498
	%	43.8	33.3	47.6
Education**	n	678	180	498
≤High School	%	15.5	8.9	17.9
Bachelor's Degree		39.8	38.3	40.4
Master's Degree		44.7	52.8	41.8
Presence of At Least One *APOE*-ε4 Allele	n	619	164	455
	%	22.8	26.8	21.3
Presence of At Least One Cerebral Infarct	n	521	122	399
	%	35.1	32.0	36.1

** $p<0.01$

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

Note: Individuals who had emotions data and were therefore eligible for inclusion in the sample were compared to those who did not have emotions data; significant differences in descriptive statistics of the two subsets are indicated with asterisks.

Table C2. Descriptive statistics of initial sample for dementia analyses compared to those with emotions data who were excluded because of missing data on one or more covariates of interest

		Total	Initial Dementia Subset	Excluded[1]
Age at Last Cognitive Assessment, Years**	n	180	164	16
	Mean (SD)	87.5 (5.26)	88.0 (4.95)	81.7 (4.93)
Age at Death, Years	n	151	137	14
	Mean (SD)	87.9 (4.46)	88.0 (4.46)	86.37 (4.33)
Dementia*	n	180	164	16
	%	33.3	36.0	6.2
Education	n	180	164	16
≤High School	%	8.9	9.2	6.2
Bachelor's Degree		38.3	38.4	37.4
Master's Degree		52.8	52.4	56.9
Presence of At Least One *APOE*-ε4 allele	n	164	164	0
	%	26.8	26.8	0.0
Presence of At Least One Cerebral Infarct[2]	n	122	120	2
	%	32.0	31.7	50.0

* $p<0.05$
** $p<0.01$
[1] n=16 excluded due to missing data on *APOE*-ε4 status
Abbreviations: *APOE*-ε4= apolipoprotein ε4; SD= standard deviation
Note: Individuals who had all covariates of interest and who were therefore included in the initial sample for dementia analyses were compared to those who were excluded from the baseline sample; significant differences in descriptive statistics of the two subsets are indicated with asterisks.

Table C3. Descriptive statistics of the final sample for dementia analyses compared to those from the baseline sample who were excluded because of missing data or who were restricted on education

		Total	Final Dementia Subset	Excluded[1]
Age at Last Cognitive Assessment, Years **	n	180	149	31
	Mean (SD)	87.5 (5.26)	88.1 (4.98)	84.5 (5.62)
Age at Death, Years	n	151	122	29
	Mean (SD)	87.9 (4.46)	88.0 (4.44)	87.2 (4.58)
Dementia	n	180	149	31
	%	33.3	31.5	41.9
Education**	n	180	149	31
≤High School	%	8.9	0.0	51.6
Bachelor's Degree		38.3	42.3	19.4
Master's Degree		52.8	57.7	20.0
Presence of At Least One *APOE*-ε4 allele	n	164	149	15
	%	26.8	26.2	33.3
Presence of At Least One Cerebral Infarct	n	122	106	16
	%	32.0	31.1	37.5

**p<0.01

[1]n=16 excluded due to missing data on *APOE*-ε4 status; n=15 restricted due to low education

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

Note: Individuals from the final sample for dementia analyses were compared to those individuals from the eligible baseline sample who were excluded because of missing data on one or more covariates of interest or who were restricted on low education; significant differences in descriptive statistics of the two subsets are indicated with asterisks.

Table C4. Descriptive statistics of final sample for dementia analyses compared to those from the initial sample who were restricted on low education

		Total	Final Dementia Subset	Restricted on Education
Age at Last Cognitive Assessment, Years	n	164	149	15
	Mean (SD)	88.0 (4.95)	88.1 (4.98)	87.4 (4.84)
Age at Death, Years	n	137	122	15
	Mean (SD)	88.0 (4.46)	88.0 (4.44)	88.0 (4.82)
Dementia**	n	164	149	15
	%	36.0	31.5	80.0
Education**	n	164	149	15
≤High School	%	9.2	0.0	100.0
Bachelor's Degree		38.4	42.3	0.0
Master's Degree		52.4	57.7	0.0
Presence of At Least One *APOE*-ε4 allele	n	164	149	15
	%	26.8	26.2	33.3
Presence of At Least One Cerebral Infarct	n	120	106	14
	%	31.7	31.1	35.7

**p<0.01

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

Note: Individuals from the final sample for dementia analyses were compared to those individuals from the initial sample who were restricted on low education; significant differences in descriptive statistics of the two subsets are indicated with asterisks.

Table C5. Descriptive statistics of the final sample for AD analyses compared to those from the baseline sample who were excluded because of missing data or who were restricted on education

		Total	AD Subset	Excluded[1]
Age at Last Cognitive Assessment, Years	n	180	85	95
	Mean (SD)	87.5 (5.26)	87.8 (3.91)	87.2 (6.23)
Age at Death, Years	n	151	85	66
	Mean (SD)	87.9 (4.46)	88.5 (3.74)	87.0 (5.16)
Dementia	n	180	85	95
	%	33.3	36.5	30.5
Education**	n	180	85	95
≤High School	%	8.9	0.0	16.8
Bachelor's Degree		38.3	49.4	28.4
Master's Degree		52.8	50.6	54.7
Presence of At Least One *APOE*-ε4 allele	n	164	85	79
	%	26.8	25.9	27.8
Presence of At Least One Cerebral Infarct	n	122	85	37
	%	32.0	28.2	40.5

**p<0.01

[1]n=16 excluded due to missing data on *APOE*-ε4 status; n=70 excluded due to missing neuropathology data; n=9 restricted due to low education

Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein ε4; SD= standard deviation

Note: Individuals from the final sample for AD analyses were compared to those individuals from the eligible baseline sample who were excluded because of missing data on any covariates of interest or on neuropathology, or who were restricted on low education; significant differences in descriptive statistics of the two subsets are indicated with asterisks.

Table C6. Descriptive statistics of the final Sample for AD analyses compared to those from the final sample for dementia analyses who were missing neuropathology data

		Total	AD Subset	Excluded[1]
Age at Last Cognitive	n	149	85	64
Assessment, Years	Mean (SD)	88.1 (4.98)	87.8 (3.91)	88.5 (6.12)
Age at Death, Years	n	122	85	37
	Mean (SD)	88.0 (4.44)	88.5 (3.74)	86.9 (5.64)
Dementia	n	149	85	64
	%	31.5	36.5	25.0
Education*	n	149	85	64
≤High School	%	0.00	0.00	0.00
Bachelor's Degree		42.3	49.4	32.8
Master's Degree		57.7	50.6	67.2
Presence of At Least One	n	149	85	64
APOE-ε4 allele	%	26.2	25.9	26.6
Presence of At Least One	n	106	85	21
Cerebral Infarct	%	31.1	28.2	42.9

*$p<0.05$

[1]n= 64 excluded due to missing neuropathology data

Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein ε4; SD= standard deviation

Note: Individuals from the final sample for the AD analyses were compared to those individuals from the final sample for dementia analyses who were excluded because of missing data on neuropathology; significant differences in descriptive statistics of the two subsets are indicated with asterisks.

Appendix D. Analysis of the Association Between Emotional Expressivity and Dementia Without Restriction by Education

Initially, 164 individuals were included in the analysis of the association between emotional expressivity and dementia. These individuals were eligible for inclusion because they had complete data on all variables of interest, including emotional expressivity and scores of written language skills in autobiographies written by hand in early adulthood; cognitive assessments to determine presence of dementia in late adulthood; and data on age, education and *APOE*-ε4 status. Of those who were included, 59 (36.0%) were diagnosed with dementia. Individuals with dementia did not differ from those without dementia (n=105) in age or emotional expressivity; however, they had significantly lower levels of education ($p<0.001$) and written language skills (i.e., idea density, $p<0.0001$; grammatical complexity, $p<0.01$), and were more likely to have at least one *APOE*-ε4 allele ($p<0.01$).

Distribution of cases and non-cases was significantly different between the two idea density strata ($p<0.0001$). Of those with low idea density, 28 (75.7%) had dementia. These individuals did not differ from those who did not have dementia in age, education, or *APOE*-ε4 status. Among those with higher idea density, 31 (24.4%) had dementia. In this subgroup, cases had lower education ($p<0.05$), higher overall emotional expressivity ($p<0.05$), and were more likely to have moderate (vs. low) negative expressivity ($p<0.05$) than individuals without dementia.

Multivariate logistic regression analysis of the association between emotional expressivity (overall, positive and negative) and dementia, stratified by idea density, was performed on this sample. Age and *APOE*-ε4 status influenced the parameter estimates of emotional expressivity in many of the models so their inclusion in the final models was necessary. Furthermore, although it did not change the emotional expressivity parameter estimates, education was statistically significant in many of the models so it also had to be included in the final models. However, when all three covariates (i.e., age, education and *APOE*-ε4 status) were included in the final models with emotional expressivity, several of the models did not converge or had a poor fit, in particular among individuals with low idea density (Tables D1-D6).

The poor fit was likely due to the large influence that low education has on the risk of dementia, and the low prevalence of individuals with a high school diploma or less in the Nun Study population. As such, individuals with less than a university education (n=15) were restricted from the sample for the final analysis; 3 individuals without dementia and 12 with dementia were removed based on this restriction criterion. Restriction resolved all of the differences between individuals with and without dementia after stratification by idea density (Section 5.1.1). Furthermore, this method controlled for the confounding effects of low education to allow for a more interpretable estimation of the association of emotional

expressivity with dementia and AD. Indeed, restricting by education yielded better-fit models. However, a drawback of this restriction was that the generalizability of the results was further limited.

Table D1. Multivariate logistic regression analyses of the association between *overall emotional expressivity* and dementia among individuals with *low idea density* before restriction on education (n=37), OR (95% CI)

	Crude[1]	1B	1C	1D[2]	Full[2]
Variable					
High Overall EE	0.38 (0.07-1.73)	0.39 (0.07-1.82)	0.41 (0.07-2.06)	0.44 (0.07-2.30)	0.44 (0.07-2.34)
Age		0.96 (0.82-1.13)	0.93 (0.79-1.09)	0.94 (0.80-1.10)	0.96 (0.80-1.14)
Education (>High School)			**<0.001** (<0.001-0.66)	**<0.001** (<0.001-0.61)	**<0.001** (<0.001-0.95)
APOE-ε4 Status[3]				2.04 (0.38-12.43)	1.70 (0.28-11.16)
Grammatical Complexity					0.52 (0.06-3.82)

Bolded values are significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Model did not converge: quasi-complete separation of data points detected.
[3] Presence of at least *APOE*-ε4 allele
Abbreviations: *APOE*-ε4= apolipoprotein E ε4; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table D2. Multivariate logistic regression analyses of the association between *positive emotional expressivity* and dementia among individuals with *low idea density* before restriction on education (n=37), OR (95% CI)

	Crude[1]	1B	1C[2]	1D	Full
Variable					
High Positive EE	0.94 (0.20-4.50)	0.98 (0.21-4.81)	1.29 (0.26-6.79)	1.37 (0.27-7.54)	1.37 (0.26-7.61)
Age		0.95 (0.82-1.11)	0.93 (0.79-1.09)	0.95 (0.80-1.11)	0.96 (0.81-1.14)
Education (>High school)			**<0.001** (<0.001-0.61)	**<0.001** (<0.001-0.55)	**<0.001** (<0.001-0.89)
APOE-ε4 status[3]				2.30 (0.44-14.01)	1.90 (0.33-12.49)
Grammatical Complexity					0.51 (0.05-3.67)

Bolded values are significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Model did not converge: quasi-complete separation of data points detected.
[3] Presence of at least *APOE*-ε4 allele
Abbreviations: *APOE*-ε4= apolipoprotein E ε4; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table D3. Multivariate logistic regression analyses of the association between *negative emotional expressivity* and dementia among individuals with *low idea density* before restriction on education (n=37), OR (95% CI)

	Crude[1]	1B	1C[2]	1D[2]	Full[2]
Variable					
High Negative EE	0.69 (0.15-3.36)	0.78 (0.16-3.99)	0.60 (0.11-3.31)	0.63 (0.11-3.56)	0.63 (0.11-3.59)
Age		0.96 (0.82-1.12)	0.94 (0.80-1.10)	0.95 (0.81-1.12)	0.97 (0.81-1.15)
Education (>High school)			**<0.001** (<0.001-0.58)	**<0.001** (<0.001-0.55)	**<0.001** (<0.001-0.86)
APOE-ε4 status[3]				2.17 (0.42-13.05)	1.79 (0.30-11.66)
Grammatical Complexity					0.51 (0.06-3.73)

Bolded values are significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Model did not converge: quasi-complete separation of data points detected.
[3] Presence of at least *APOE*-ε4 allele
Abbreviations: *APOE*-ε4= apolipoprotein E ε4; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table D4. Multivariate logistic regression analyses of the association between *overall emotional expressivity* and dementia among individuals with *high idea density* before restriction on education (n=127), OR (95% CI)

	Crude[1]	1B	1C[2]	1D	Full
Variable					
High Overall EE	**2.55** (1.09-6.36)	**2.47** (1.05-6.22)	**2.51** (1.05-6.47)	**2.79** (1.14-7.39)	**2.90** (1.18-7.78)
Age		1.08 (0.98-1.19)	1.09 (0.99-1.20)	1.09 (1.00-1.21)	1.11 (1.00-1.23)
Education (>High school)			**0.18** (0.03-0.91)	**0.18** (0.03-0.92)	0.20 (0.03-1.06)
APOE-ε4 status[3]				2.19 (0.78-6.04)	2.40 (0.84-6.78)
Grammatical Complexity					0.55 (0.18-1.78)

Bolded values are significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Model did not converge: quasi-complete separation of data points detected.
[3] Presence of at least *APOE*-ε4 allele
Abbreviations: *APOE*-ε4= apolipoprotein E ε4; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table D5. Multivariate logistic regression analyses of the association between *positive emotional expressivity* and dementia among individuals with *high idea density* before restriction on education (n=127), OR (95% CI)

	Crude[1]	1B[2]	1C[2]	1D	Full[2]
Variable					
High Positive EE	1.72 (0.76-4.02)	1.65 (0.72-3.88)	1.75 (0.75-4.22)	1.80 (0.77-4.40)	1.90 (0.80-4.70)
Age		1.08 (0.99-1.18)	1.09 (0.99-1.20)	1.09 (1.00-1.21)	1.10 (1.00-1.23)
Education (>High school)			**0.17** (0.03-0.86)	**0.17** (0.03-0.88)	**0.19** (0.03-0.99)
APOE-ε4 status[3]				1.91 (0.70-5.04)	2.07 (0.75-5.60)
Grammatical Complexity					0.57 (0.19-1.80)

Bolded values are significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Model did not converge: quasi-complete separation of data points detected.
[3] Presence of at least *APOE*-ε4 allele
Abbreviations: *APOE*-ε4= apolipoprotein E ε4; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table D6. Multivariate logistic regression analyses of the association between *negative emotional expressivity* and dementia among individuals with *high idea density* before restriction on education (n=127), OR (95% CI)

	Crude[1]	1B	1C	1D	Full
Variable					
High Negative EE	1.79 (0.79-4.19)	1.84 (0.80-4.36)	1.71 (0.74-4.13)	1.97 (0.82-4.94)	1.99 (0.83-4.99)
Age		1.08 (0.99-1.19)	1.10 (1.00-1.21)	1.10 (1.00-1.22)	**1.11** (1.01-1.23)
Education (>High school)			0.20 (0.03-1.00)	0.21 (0.04-1.08)	0.23 (0.40-1.21)
APOE-ε4 status[2]				2.16 (0.78-5.91)	2.32 (0.82-6.48)
Grammatical Complexity					0.62 (0.21-1.93)

Bolded values are significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Presence of at least *APOE*-ε4 allele
Abbreviations: *APOE*-ε4= apolipoprotein E ε4; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Appendix E. All Multivariate Logistic Regression Models

As described in the methods (Section 4.4.2), the association of emotional expressivity with dementia and AD was assessed through multivariate logistic regression analysis. Tables presented in the following sections provide the complete results, including all crude, adjusted, full and final models, beginning with the main analysis of the association of emotional expressivity with both dementia and AD, stratified by idea density (Section E.1). Models were generated for each emotional expressivity measure (i.e., overall, positive, negative) with each outcome (i.e., dementia, AD), and adjusted for each covariate (i.e., age, education, *APOE*-ε4, grammatical complexity) separately and in succession as outlined in the analytic strategy (Table 2).

Analysis using emotional expressivity tertiles was performed to further investigate the association with dementia, also stratified by idea density (Section E.2). In addition, a significant interaction was found between positive and negative emotional expressivity in association with dementia among individuals with high idea density. As such, models of the association between negative emotional expressivity and dementia, stratified both by idea density and by positive emotional expressivity, were generated (Section E.3).

E.1 Main Analysis of Emotional Expressivity with Dementia and AD

E.1.1 Main Analysis: Low Idea Density

Table E1. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *dementia* among individuals with *low idea density*, OR (95% CI), n=29

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Overall EE	0.41 (0.07-2.02)	0.41 (0.07-2.06)	0.36 (0.06-1.86)	0.36 (0.06-1.90)	0.46 (0.08-2.37	0.40 (0.06-2.15)	0.43 (0.07-2.22)	0.39 (0.06-2.18)	0.44 (0.07-2.30)
Age		0.93 (0.79-1.09)		0.94 (0.79-1.09)		0.94 (0.80-1.10)		0.96 (0.80-1.14)	0.94 (0.80-1.10)
Education (Master's vs. Bachelor's Degree)			0.54 (0.09-2.78)	0.54 (0.09-2.84)		0.54 (0.09-2.89)		0.55 (0.09-2.98)	
APOE-ε4 Status					2.19 (0.42-13.15)	2.04 (0.37-12.73)		1.70 (0.28-11.49)	2.04 (0.38-12.43)
Grammatical Complexity							0.37 (0.05-2.06)	0.52 (0.06-3.96)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E2. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *AD*[1] among individuals with *low idea density*, OR (95% CI), n=19

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity[3]	Full[3]	Final
Variable									
High Overall EE	0.23 (0.01-2.02)	0.22 (0.01-2.02)	0.20 (0.01-1.87)	0.22 (0.01-2.09)	0.40 (0.02-5.11)	0.45 (0.02-7.06)	0.27 (0.01-3.07)	0.21 (0.004-4.01)	0.40 (0.02-5.21)
Age		1.03 (0.79-1.33)		0.97 (0.71-1.29)		0.84 (0.51-1.20)		0.92 (0.50-1.61)	0.98 (0.74-1.30)
Education (Master's vs. Bachelor's Degree)			0.36 (0.03-2.80)	0.32 (0.02-3.15)		0.11 (0.001-2.08)		0.10 (0.001-2.22)	
APOE-ε4 Status					6.22 (0.63-145.93)	16.00 (0.89->999.9)		8.70 (0.47->999.9)	6.37 (0.62-152.88)
Grammatical Complexity							**<0.001** (<0.001-0.64)	**<0.001** (<0.001-0.62)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

Table E3. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *dementia* among individuals with *low idea density*, OR (95% CI), n=29

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Positive EE	1.25 (0.26-6.41)	1.29 (0.26-6.79)	1.27 (0.26-6.60)	1.33 (0.26-7.23)	1.39 (0.28-7.64)	1.48 (0.28-8.74)	1.32 (0.26-7.13)	1.46 (0.27-8.56)	1.37 (0.27-7.54)
Age		0.93 (0.79-1.09)		0.93 (0.79-1.09)		0.95 (0.80-1.10)		0.96 (0.80-1.14)	0.95 (0.80-1.11)
Education (Master's vs. Bachelor's Degree)			0.65 (0.12-3.18)	0.64 (0.12-3.20)		0.59 (0.10-3.07)		0.61 (0.10-3.24)	
APOE-ε4 Status					2.54 (0.51-15.28)	2.42 (0.46-15.45)		2.00 (0.34-13.93)	2.30 (0.44-14.01)
Grammatical Complexity							0.34 (0.04-1.87)	0.53 (0.06-3.91)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)

Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E4. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *AD*[1] among individuals with *low idea density*, OR (95% CI), n=19

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity[3]	Full[3]	Final
Variable									
High Positive EE	1.17 (0.16-8.59)	1.17 (0.16-8.71)	1.35 (0.18-11.16)	1.56 (0.19-15.22)	1.74 (0.19-19.24)	5.20 (0.36-217.98)	1.33 (0.14-12.95)	2.52 (0.15-113.93)	1.71 (0.19-19.44)
Age		0.99 (0.77-1.25)		0.92 (0.68-1.20)		0.77 (0.46-1.12)		0.90 (0.50-1.59)	0.98 (0.74-1.28)
Education (Master's vs. Bachelor's Degree)			0.41 (0.04-2.98)	0.28 (0.02-2.89)		0.03 (<0.001-1.23)		0.08 (<0.001-2.35)	
APOE-ε4 Status					8.98 (0.98-216.49)	**38.61** (1.82->999.9)		11.05 (0.54->999.9)	8.95 (0.98-214.98)
Grammatical Complexity							**<0.001** (<0.001-0.55)	<0.001 (<0.001-1.27)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

Table E5. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *low idea density*, OR (95% CI), n=29

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D[2]	Grammatical Complexity	Full	Final
Variable									
High Negative EE	0.54 (0.10-2.82)	0.60 (0.11-3.31)	0.50 (0.09-2.67)	0.55 (0.10-3.12)	0.58 (0.11-3.20)	0.56 (0.09-3.27)	0.59 (0.11-3.23)	0.56 (0.09-3.29)	0.63 (0.11-3.56)
Age		0.94 (0.80-1.10)		0.94 (0.80-1.10)		0.96 (0.81-1.12)		0.97 (0.82-1.15)	0.95 (0.81-1.12)
Education (Master's vs. Bachelor's Degree)			0.60 (0.11-2.99)	0.60 (0.11-3.06)		0.56 (0.09-2.96)		0.57 (0.09-3.08)	
APOE-ε4 Status					2.32 (0.46-13.75)	2.28 (0.43-14.31)		1.88 (0.31-12.86)	2.17 (0.42-13.05)
Grammatical Complexity							0.37 (0.05-2.04)	0.52 (0.06-3.88)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Hosmer-Lemeshow goodness of fit test, $p<0.05$
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E6. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *AD*[1] among individuals with *low idea density*, OR (95% CI), n=19

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D[3]	Grammatical Complexity[3]	Full[3]	Final
Variable									
High Negative EE	0.31 (0.03-2.24)	0.28 (0.02-2.23)	0.24 (0.02-1.91)	0.25 (0.02-2.19)	0.27 (0.02-2.41)	<0.001 (<0.001-1.19)	0.20 (0.02-1.90)	**<0.001** (<0.001-0.17)	0.24 (0.02-2.56)
Age		1.04 (0.80-1.37)		0.98 (0.72-1.32)		0.90 (0.54-1.22)		1.88 (0.68-9.29)	1.04 (0.77-1.37)
Education (Master's vs. Bachelor's Degree)			0.31 (0.03-2.52)	0.29 (0.02-2.94)		**<0.001 (<0.001-0.84)**		**<0.001** (<0.001-0.33)	
APOE-ε4 Status					8.74 (0.93-214.56)	**>999.9** (2.43->999.9)		>999.9 (0.48>999.9)	8.85 (0.92-225.83)
Grammatical Complexity							**<0.001** (<0.001-0.46)	**<0.001** (<0.001-0.12)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

E.1.2 Main Analysis: High Idea Density

Table E7. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *dementia* among individuals with *high idea density*, OR (95% CI), n=120

	Crude[1]	1B	Education	1C	*APOE-ε4*	1D	Grammatical Complexity	Full	Final
Variable									
High Overall EE	2.43 (0.99-6.39)	2.34 (0.95-6.20)	2.38 (0.97-6.30)	2.31 (0.94-6.13)	**2.67** (1.07-7.22)	**2.58** (1.02-7.06)	**2.50** (1.02-6.64)	**2.76** (1.08-7.74)	**2.60** (1.04-7.11)
Age		1.07 (0.97-1.18)		1.06 (0.97-1.18)		1.07 (0.97-1.19)		1.09 (0.98-1.22)	1.07 (0.97-1.19)
Education (Master's vs. Bachelor's Degree)			1.38 (0.56-3.55)	1.33 (0.54-3.45)		1.28 (0.51-3.36)		1.34 (0.53-3.58)	
APOE-ε4 Status					2.29 (0.77-6.06)	2.26 (0.78-6.35)		2.49 (0.85-7.22)	2.30 (0.80-6.45)
Grammatical Complexity							0.62 (0.21-1.94)	0.44 (0.14-1.47)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E8. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *AD*[1] among individuals with *high idea density*, OR (95% CI), n=60

	Crude[2]	1B	Education	1C	*APOE-ε4*	1D[3]	Grammatical Complexity	Full	Final
Variable									
High Overall EE	1.40 (0.39-5.32)	1.36 (0.38-5.19)	1.55 (0.42-6.09)	1.57 (0.42-6.32)	1.75 (0.46-7.40)	1.97 (0.50-8.89)	1.42 (0.40-5.42)	2.11 (0.52-9.74)	1.68 (0.44-7.14)
Age		1.08 (0.90-1.35)		1.11 (0.90-1.42)		1.09 (0.87-1.41)		1.12 (0.88-1.48)	1.06 (0.86-1.33)
Education (Master's vs. Bachelor's Degree)			2.84 (0.68-10.52)	2.68 (0.71-12.01)		2.84 (0.71-13.82)		3.21 (0.77-16.82)	
APOE-ε4 Status					4.00 (0.95-17.27)	3.88 (0.88-17.68)		4.18 (0.93-20.05)	3.75 (0.88-16.48)
Grammatical Complexity							0.77 (0.18-3.96)	0.48 (0.08-2.87)	

[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

Table E9. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *dementia* among individuals with *high idea density*, OR (95% CI), n=120

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Positive EE	1.49 (0.63-3.62)	1.42 (0.56-3.50)	1.49 (0.63-3.65)	1.43 (0.60-3.52)	1.53 (0.64-3.76)	1.49 (0.62-3.71)	1.53 (0.64-3.77)	1.58 (0.65-4.00)	1.48 (0.61-3.66)
Age		1.07 (0.97-1.18)		1.07 (0.97-1.18)		1.07 (0.97-1.18)		1.08 (0.98-1.21)	1.07 (0.98-1.19)
Education (Master's vs. Bachelor's Degree)			1.45 (0.60-3.72)	1.39 (0.57-3.57)		1.35 (0.55-3.50)		1.42 (0.57-3.74)	
APOE-ε4 Status					1.93 (0.70-5.10)	1.98 (0.70-5.32)		2.14 (0.75-5.89)	2.01 (0.72-5.40)
Grammatical Complexity							0.64 (0.23-1.99)	0.48 (0.15-1.55)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)

Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E10. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *AD*[1] among individuals with *high idea density*, OR (95% CI), n=60

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Positive EE	1.09 (0.30-3.94)	1.12 (0.31-4.12)	1.19 (0.32-4.45)	1.28 (0.34-5.01)	1.13 (0.30-4.27)	1.36 (0.34-5.59)	1.09 (0.30-3.97)	1.43 (0.36-6.08)	1.14 (0.30-4.34)
Age		1.08 (0.90-1.35)		1.11 (0.90-1.42)		1.10 (0.88-1.42)		1.12 (0.89-1.48)	1.06 (0.87-1.34)
Education (Master's vs. Bachelor's Degree)			2.41 (0.66-10.12)	2.60 (0.69-11.48)		2.69 (0.68-12.84)		3.01 (0.73-15.38)	
APOE-ε4 Status					3.59 (0.88-14.45)	3.42 (0.81-14.41)		3.65 (0.85-16.02)	3.38 (0.82-13.76)
Grammatical Complexity							0.79 (0.19-4.04)	0.52 (0.10-2.96)	

[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

Table E11. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *high idea density*, OR (95% CI), n=120

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D[2]	Grammatical Complexity	Full[2]	Final
Variable									
High Negative EE	1.69 (0.72-4.12)	1.72 (0.72-4.24)	1.68 (0.71-4.11)	1.73 (0.72-4.28)	1.94 (0.80-4.95)	2.01 (0.82-5.22)	1.68 (0.71-4.10)	2.03 (0.82-5.32)	1.99 (0.81-5.13)
Age		1.07 (0.98-1.19)		1.07 (0.98-1.19)		1.08 (0.98-1.20)		1.09 (0.99-1.22)	1.08 (0.98-1.20)
Education (Master's vs. Bachelor's Degree)			1.44 (0.59-3.68)	1.39 (0.57-3.59)		1.36 (0.55-3.56)		1.45 (0.58-3.86)	
APOE -ε4 Status					2.21 (0.78-6.11)	2.28 (0.79-6.46)		2.45 (0.84-7.06)	2.31 (0.80-6.53)
Grammatical Complexity							0.68 (0.24-2.12)	0.50 (0.16-1.63)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Hosmer-Lemeshow goodness of fit test, $p<0.05$
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E12. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *AD*[1] among individuals with *high idea density*, OR (95% CI), n=60

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Negative EE	1.18 (0.33-4.50)	1.13 (0.31-4.34)	1.30 (0.36-5.10)	1.31 (0.35-5.29)	1.78 (0.45-8.27)	2.30 (0.52-13.22)	1.19 (0.33-4.52)	1.49 (0.55-14.77)	1.67 (0.41-7.91)
Age		1.08 (0.90-1.34)		1.10 (0.90-1.41)		1.09 (0.86-1.42)		1.12 (0.87-1.50)	1.05 (0.85-1.33)
Education (Master's vs. Bachelor's Degree)			2.43 (0.66-10.24)	2.62 (0.69-11.65)		3.17 (0.75-17.49)		3.75 (0.83-24.28)	
APOE-ε4 Status					4.35 (0.98-20.63)	4.74 (0.98-25.85)		**5.16** (1.05-28.98)	4.04 (0.90-19.68)
Grammatical Complexity							0.79 (0.19-4.04)	0.47 (0.08-2.81)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to NIA-RI criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

E.2 Analysis of the Association of Emotional Expressivity Tertiles with Dementia

E.2.1 Analysis with Emotional Expressivity Tertiles: Low Idea Density

Table E13. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity tertiles* and *dementia* among individuals with *low idea density*, OR (95% CI), n=29

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
Overall EE									
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	0.67 (0.08-6.59)	0.70 (0.08-7.14)	0.63 (0.07-6.36)	0.68 (0.07-7.00)	0.81 (0.09-8.66)	0.85 (0.08-10.05)	0.71 (0.08-7.36)	0.86 (0.08-10.75)	0.84 (0.09-9.24)
High	0.58 (0.09-3.51)	0.62 (0.09-3.87)	0.51 (0.07-3.22)	0.55 (0.08-3.58)	0.64 (0.09-4.06)	0.59 (0.08-3.89)	0.60 (0.09-3.77)	0.57 (0.08-3.78)	0.65 (0.09-4.17)
Age		0.94 (0.80-1.10)		0.94 (0.80-1.10)		0.95 (0.80-1.11)		0.96 (0.81-1.14)	0.95 (0.80-1.11)
Education (Master's vs. Bachelor's Degree)			0.58 (0.10-2.95)	0.59 (0.10-3.04)		0.57 (0.10-3.02)		0.58 (0.10-3.14)	
APOE-ε4 status					2.36 (0.46-14.17)	2.26 (0.42-14.48)		1.88 (0.30-12.94)	2.20 (0.42-13.44)
Grammatical Complexity							0.36 (0.04-1.94)	0.51 (0.05-3.70)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E14. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity tertiles* and *dementia* among individuals with *low idea density*, OR (95% CI), n=29

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
Positive EE									
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	1.50 (0.19-14.24)	1.80 (0.22-18.39)	1.27 (0.13-13.74)	1.57 (0.16-18.02)	1.76 (0.21-17.98)	1.77 (0.18-21.17)	2.10 (0.24-22.35)	2.16 (0.20-28.33)	2.00 (0.23-22.20)
High	0.64 (0.09-4.10)	0.66 (0.09-4.48)	0.60 (0.08-3.95)	0.63 (0.08-4.35)	0.76 (0.10-5.31)	0.71 (0.09-5.13)	0.70 (0.09-4.94)	0.71 (0.09-5.41)	0.74 (0.10-5.29)
Age		0.92 (0.78-1.08)		0.93 (0.78-1.08)		0.94 (0.78-1.10)		0.95 (0.79-1.13)	0.93 (0.78-1.09)
Education (Master's vs. Bachelor's)			0.71 (0.12-3.98)	0.74 (0.12-4.28)		0.72 (0.12-4.14)		0.79 (0.13-4.84)	
APOE-ε4 status					2.47 (0.48-15.18)	2.29 (0.42-14.58)		1.85 (0.31-12.51)	2.26 (0.42-14.03)
Grammatical Complexity							0.29 (0.03-1.69)	0.43 (0.04-3.23)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E15. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity tertiles* and *dementia* among individuals with *low idea density*, OR (95% CI), n=29

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
Negative EE									
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	0.67 (0.05-16.61)	0.65 (0.05-16.33)	0.58 (0.04-14.89)	0.57 (0.04-14.88)	0.56 (0.04-14.62)	0.49 (0.02-13.91)	0.47 (0.03-12.66)	0.42 (0.02-12.87)	0.56 (0.04-14.72)
High	0.50 (0.09-2.78)	0.56 (0.09-3.25)	0.45 (0.07-2.59)	0.50 (0.08-3.02)	0.53 (0.09-3.08)	0.50 (0.08-3.09)	0.52 (0.09-3.04)	0.49 (0.07-3.06)	0.57 (0.10-3.42)
Age		0.94 (0.80-1.10)		0.94 (0.80-1.10)		0.96 (0.81-1.12)		0.97 (0.82-1.15)	0.95 (0.80-1.12)
Education (Master's vs. Bachelor's Degree)			0.57 (0.10-2.91)	0.57 (0.10-2.98)		0.53 (0.09-2.87)		0.55 (0.09-3.02)	
APOE-ε4 status					2.42 (0.47-14.77)	2.37 (0.44-15.21)		1.90 (0.31-13.36)	2.26 (0.42-14.00)
Grammatical Complexity							0.33 (0.04-1.93)	0.48 (0.05-3.72)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

E.2.2 Analysis with Emotional Expressivity Tertiles: High Idea Density

Table E16. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity tertiles* and *dementia* among individuals with *high idea density*, OR (95% CI), n=120

	Crude[1]	1B[1]	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final[2]
Variable									
Overall EE									
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	1.46 (0.48-4.57)	1.47 (0.48-4.64)	1.51 (0.50-4.73)	1.52 (0.50-4.84)	1.58 (0.52-5.02)	1.70 (0.54-5.59)	1.40 (0.46-4.14)	1.60 (0.50-5.35)	1.62 (0.52-5.26)
High	1.67 (0.58-5.06)	1.64 (0.56-5.00)	1.68 (0.58-5.10)	1.65 (0.57-5.06)	1.73 (0.60-5.31)	1.74 (0.59-5.46)	1.65 (0.57-5.00)	1.72 (0.58-5.42)	1.72 (0.58-5.34)
Age		1.07 (0.98-1.19)		1.07 (0.97-1.18)		1.08 (0.98-1.19)		1.09 (0.98-1.21)	1.08 (0.98-1.19)
Education (Master's vs. Bachelor's Degree)			1.46 (0.60-3.75)	1.41 (0.57-3.64)		1.38 (0.56-3.62)		1.44 (0.58-3.82)	
APOE-ε4 status					1.96 (0.70-5.23)	2.04 (0.72-5.57)		2.17 (0.76-6.01)	2.07 (0.73-5.62)
Grammatical Complexity							0.69 (0.24-2.16)	0.52 (0.17-1.71)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Hosmer-Lemeshow goodness of fit test, $p<0.05$
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E17. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity tertiles* and *dementia* among individuals with *high idea density*, OR (95% CI), n=120

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
Positive EE									
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	1.66 (0.54-5.79)	1.56 (0.50-5.47)	1.68 (0.54-5.86)	1.58 (0.50-5.54)	1.59 (0.51-5.56)	1.51 (0.48-5.35)	1.63 (0.52-5.67)	1.44 (0.45-5.12)	1.48 (0.47-5.24)
High	2.20 (0.70-7.75)	2.07 (0.65-7.36)	2.20 (0.70-7.77)	2.08 (0.65-7.39)	2.11 (0.67-7.46)	2.00 (0.62-7.15)	2.20 (0.70-7.78)	1.97 (0.61-7.08)	1.98 (0.62-7.06)
Age		1.07 (0.97-1.18)		1.06 (0.97-1.18)		1.07 (0.97-1.18)		1.08 (0.98-1.20)	1.07 (0.97-1.19)
Education (Master's vs. Bachelor's Degree)			1.45 (0.60-3.72)	1.39 (0.56-3.58)		1.35 (0.54-3.51)		1.41 (0.56-3.71)	
APOE-ε4 status					1.80 (0.65-4.76)	1.84 (0.66-4.96)		1.98 (0.69-5.41)	1.88 (0.67-5.06)
Grammatical Complexity							0.67 (0.24-2.09)	0.51 (0.17-1.67)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E18. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity tertiles* and *dementia* among individuals with *high idea density*, OR (95% CI), n=120

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
Negative EE									
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	3.00 (0.99-9.23)	2.97 (0.97-9.25)	**3.40** (1.10-10.91)	**3.34** (1.06-10.86)	**3.58** (1.14-11.70)	**4.06** (1.24-14.14)	2.90 (0.95-9.00)	**3.93** (1.18-13.87)	**3.59** (1.13-11.89)
High	1.14 (0.40-3.20)	1.15 (0.40-3.27)	1.12 (0.40-3.18)	1.14 (0.40-3.27)	1.30 (0.45-3.81)	1.35 (0.46-4.05)	1.12 (0.40-3.17)	1.35 (0.46-4.06)	1.34 (0.46-3.97)
Age		1.07 (0.97-1.18)		1.06 (0.97-1.18)		1.07 (0.97-1.19)		1.08 (0.98-1.20)	1.07 (0.98-1.19)
Education (Master's vs. Bachelor's Degree)			1.77 (0.70-4.79)	1.68 (0.66-4.59)		1.66 (0.64-4.57)		1.76 (0.67-5.00)	
APOE-ε4 status					2.29 (0.79-6.46)	2.37 (0.81-6.83)		2.50 (0.84-7.35)	2.40 (0.82-6.88)
Grammatical Complexity							0.76 (0.26-2.42)	0.56 (0.18-1.88)	

Bolded values are statistically significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

E.3 Analysis of the Association Between Negative Emotional Expressivity and Dementia, Stratified by Idea Density and Positive Emotional Expressivity

Table E19. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *low idea density* and *low positive emotional expressivity*, OR (95% CI), n=15

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D[2]	Grammatical Complexity	Full[2]	Final
Variable									
High Negative EE	0.17 (0.01-2.34)	0.12 (0.003-2.13)	0.17 (0.01-2.48)	0.12 (0.003-2.18)	0.19 (0.005-3.70)	0.15 (0.003-3.31)	0.15 (0.004-2.48)	0.15 (0.003-3.29)	0.15 (0.003-3.55)
Age		0.85 (0.65-1.04)		0.85 (0.62-1.05)		0.90 (0.65-1.15)		0.90 (0.60-1.17)	0.91 (0.68-1.14)
Education (Master's vs. Bachelor's Degree)			1.26 (0.11-14.90)	0.89 (0.05-12.89)		0.53 (0.02-9.41)		0.51 (0.01-9.36)	
APOE-ε4 Status					8.68 (0.74-254.38)	6.56 (0.31-389.07)		7.09 (0.27-655.90)	5.19 (0.28-175.62)
Grammatical Complexity							0.23 (0.01-2.75)	1.24 (0.02-73.35)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Hosmer-Lemeshow goodness of fit test, $p<0.05$
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E20. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *low idea density* and *high positive emotional expressivity*, OR (95% CI), n=14

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Negative EE	1.00 (0.09-11.32)	0.77 (0.04-10.94)	0.80 (0.06-10.12)	0.44 (0.02-7.71)	1.00 (0.09-11.44)	0.32 (0.002-11.53)	0.10 (0.09-13.42)	0.10 (<0.001-12.11)	0.68 (0.03-10.64)
Age		1.07 (0.81-1.46)		1.14 (0.85-1.58)		1.33 (0.90-3.03)		2.60 (1.05-37.47)	1.09 (0.81-1.56)
Education (Master's vs. Bachelor's Degree)			0.21 (0.01-2.46)	0.15 (0.004-2.00)		0.04 (<0.001-1.17)		**<0.001** (<0.001-0.38)	
APOE-ε4 Status					0.68 (0.06-7.55)	0.09 (<0.001-2.96)		**<0.001** (<0.001-0.62)	0.56 (0.03-6.85)
Grammatical Complexity							0.49 (0.02-5.84)	0.01 (<0.001-1.41)	

Bolded values are statistically significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E21. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *high idea density* and *low positive emotional expressivity*, OR (95% CI), n=58

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Negative EE	**4.58** (1.18-20.05)	**5.62** (1.34-29.02)	**4.73** (1.21-21.18)	**6.90** (1.51-43.45)	**5.80** (1.37-30.90)	**10.34** (1.86-97.16)	**4.49** (1.16-19.73)	**11.23** (1.93-114.65)	**8.17** (1.66-58.96)
Age		1.17 (0.99-1.45)		1.19 (1.00-1.49)		**1.21** (1.01-1.54)		**1.24** (1.03-1.60)	1.19 (1.00-1.49)
Education (Master's vs. Bachelor's Degree)			2.12 (0.50-11.32)	2.71 (0.59-16.40)		2.61 (0.53-16.74)		3.45 (0.63-27.30)	
APOE-ε4 Status					2.49 (0.42-14.88)	2.80 (0.42-19.78)		3.08 (0.45-24.09)	3.01 (0.47-20.58)
Grammatical Complexity							0.70 (0.15-3.96)	0.37 (0.06-2.48)	

Bolded values are statistically significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table E22. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *high idea density* and *high positive emotional expressivity*, OR (95% CI), n=62

	Crude[1]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Negative EE	0.69 (0.21-2.24)	0.70 (0.22-2.28)	0.68 (0.21-2.22)	0.69 (0.21-2.26)	0.75 (0.23-2.55)	0.76 (0.23-2.57)	0.68 (0.21-2.22)	0.75 (0.23-2.57)	0.76 (0.23-2.58)
Age		1.02 (0.90-1.18)		1.02 (0.90-1.17)		1.03 (0.90-1.19)		1.05 (0.91-1.22)	1.04 (0.91-1.19)
Education (Master's vs. Bachelor's Degree)			1.20 (0.38-4.07)	1.17 (0.36-4.01)		1.27 (0.38-4.94)		1.28 (0.38-4.54)	
APOE-ε4 Status					2.43 (0.61-9.32)	2.62 (0.64-10.43)		2.85 (0.68-11.84)	2.55 (0.63-9.97)
Grammatical Complexity							0.64 (0.14-3.36)	0.49 (0.10-2.81)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Appendix F. Full Analysis of Alzheimer's Disease Using Alternative Samples

Four samples were selected for the analyses of AD based on NIA-RI and CERAD diagnostic criteria, and on two different non-case definitions (i.e., D= individuals who were dementia-free; DN= individuals who were both dementia- and AD neuropathology-free). Analyses were repeated for each of the samples to identify potential differences; however, the results were very similar for all samples so only those of the NIA-RI/D sample, as the most robust sample, were presented in the main document. The full results, including descriptive statistics (Section F.1.1) and all multivariate logistic regression models (Section F.1.2) of the CERAD/D sample are presented here, as supplementary information. The NIA-RI/DN and CERAD/DN samples did not contribute any further insight into the association between emotional expressivity and AD, so full models are not presented. Instead, the parameter estimates of all analyses, stratified by idea density are presented in Section F.2 for comparison. A summary of the sensitivity analysis without stratification by idea density is also presented for all three of the alternative samples (Section F.3).

F.1 Analysis Using the CERAD/D Sample

F.1.1 Descriptive Statistics

Table F1. Participant characteristics by AD status: CERAD analytic sample (n=78)

Characteristic	All (n=78)	AD[1] No (n=54)	AD[1] Yes (n=24)
Covariates			
Age[2], Mean Years (SD)	88.7 (3.48)	88.4 (3.73)	89.4 (2.81)
Level of Education, %			
Bachelor's Degree	48.7	51.8	41.7
≥ Master's Degree	51.3	48.2	58.3
Presence of *APOE*-ε4, %**	26.9	16.7	50.0
Idea Density, %			
Low	18.0	11.1	33.3
Q2	23.1	27.8	12.5
Q3	26.9	27.8	25.0
High	32.0	33.3	29.2
Grammatical Complexity, %			
Low	24.4	18.5	37.5
Q2	23.1	27.8	12.5
Q3	23.1	24.1	20.8
High	29.5	29.6	29.2

** $p<0.01$

[1] Based on diagnosis of AD according to CERAD criteria; non-cases are individuals who have not been diagnosed with AD and who did not have dementia at their last cognitive assessment

[2] Age at death

Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; Q= quartile; SD= standard deviation

Table F2. Emotional expressivity by AD status: CERAD analytic sample (n=78)

	All (n=78)	AD[1] No (n=54)	AD[1] Yes (n=24)
Emotional Expressivity			
Raw Word Counts[2], Mean (SD)			
Overall	9.4 (8.01)	9.1 (8.01)	10.1 (8.12)
Positive	8.0 (6.73)	7.7 (6.68)	8.8 (6.95)
Negative	1.4 (1.83)	1.4 (1.84)	1.4 (1.86)
Raw Word Counts[2], Median (Range)			
Overall	6.5 (0-29)	6.0 (1-32)	8.0 (0-29)
Positive	6.0 (0-27)	5.0 (1-27)	6.0 (0-22)
Negative	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %			
Overall			
Low	18.0	16.7	20.8
Q2	26.9	29.6	20.8
Q3	29.5	29.6	29.2
High	25.6	24.1	29.2
Positive			
Low	20.5	20.4	20.8
Q2	30.8	31.5	29.2
Q3	20.5	24.1	12.5
High	28.2	24.1	37.5
Negative			
Low	12.8	9.3	20.8
Q2	33.3	35.2	29.2
Q3	35.9	37.0	33.3
High	18.0	18.5	16.7

[1] Based on diagnosis of AD according to CERAD criteria; non-cases were individuals who have not been diagnosed with AD or dementia at their last cognitive assessment
[2] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparison
Abbreviations: AD= Alzheimer's disease; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; Q= quartile; SD= standard deviation
Note: Emotional expressivity did not significantly differ by AD status.

Table F3. Participant characteristics by AD and idea density: CERAD analytic sample (n=78)

	Idea density[1]					
	Low			Higher		
		AD[2]			AD[2]	
Characteristic	All (n=14)	No (n=6)	Yes (n=8)	All (n=64)	No (n=48)	Yes (n=16)
Covariates						
Age[3], Mean Years (SD)	88.4 (3.24)	87.8 (4.07)	88.8 (2.70)	88.8 (3.55)	88.5 (3.72)	89.7 (2.90)
Level of Education, %						
Bachelor's Degree	50.0	33.3	62.5	48.4	54.2	31.2
≥ Master's Degree	50.0	66.7	37.5	51.6	45.8	68.8
Presence of *APOE*-ε4, %	57.1	16.7*	87.5	20.3	16.7	31.2
Grammatical Complexity, %						
Low	21.4	0.0	37.5	25.0	20.8	37.5
Q2	35.7	50.0	25.0	20.3	25.0	6.2
Q3	7.1	0.0	12.5	26.6	27.1	25.0
High	35.7	50.0	25.0	28.1	27.1	31.2

* $p<0.05$

[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density

[2] Based on diagnosis of AD according to CERAD criteria; non-cases are individuals who have not been diagnosed with AD and who did not have dementia at their last cognitive assessment

[3] Age at death

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

Table F4. Emotional expressivity by AD status and idea density: CERAD analytic sample (n=78)

	Idea density[1]					
	Low			Higher		
		AD[2]			AD[2]	
	All (n=14)	No (n=6)	Yes (n=8)	All (n=64)	No (n=48)	Yes (n=16)
Emotional Expressivity						
Raw Word Counts[3], Mean (SD)						
Overall	9.4 (7.16)	9.3 (7.17)	7.65 (2.70)	9.4 (8.23)	9.0 (8.18)	10.5 (8.56)
Positive	8.0 (6.06)	8.2 (7.19)	7.9 (5.59)	8.0 (6.92)	7.6 (6.69)	9.2 (7.67)
Negative	1.4 (1.78)	1.2 (0.98)	1.5 (2.27)	1.4 (1.86)	1.4 (1.92)	1.3 (1.70)
Raw Word Counts[3], Median (Range)						
Overall	7.0 (1-25)	8.0 (1-19)	7.0 (2-25)	6.5 (0-32)	6.0 (1-32)	8.0 (0-29)
Positive	6.5 (1-19)	6.5 (1-17)	6.5 (2-19)	6.0 (0-27)	5.0 (1-27)	6.0 (0-22)
Negative	1.0 (0-6)	1.5 (0-2)	0.5 (0-6)	1.0 (0-9)	1.0 (0-9)	1.0 (0-7)
Quartile Rankings, %						
Overall						
Low	21.4	16.7	25.0	17.2	16.7	18.8
Q2	14.3	0.0	25.0	29.7	33.3	18.8
Q3	28.6	50.0	12.5	29.7	27.1	37.5
High	35.7	33.3	37.5	23.4	22.9	25.0
Positive						
Low	21.4	16.7	25.0	20.3	20.8	18.8
Q2	28.6	33.3	25.0	31.2	31.2	31.2
Q3	14.3	16.7	12.5	21.9	25.0	12.5
High	35.7	33.3	37.5	26.6	22.9	37.5

	Idea density[1]					
	Low			Higher		
		AD[2]			AD[2]	
	All (n=14)	No (n=6)	Yes (n=8)	All (n=64)	No (n=48)	Yes (n=16)
Negative						
Low	21.4	16.7	25.0	10.9	8.3	18.8
Q2	28.6	16.7	37.5	34.4	37.5	25.0
Q3	14.3	16.7	12.5	40.6	39.6	43.8
High	35.7	50.0	25.0	14.1	14.6	12.5

[1] Low= lowest quartile of idea density; Higher= top three quartiles of idea density

[2] Based on diagnosis of AD according to CERAD criteria; non-cases are individuals who have not been diagnosed with AD and who did not have dementia at their last cognitive assessment

[3] Autobiographies were required to be no more than one page in length, providing an approximate standard length for comparisonAbbreviations: AD= Alzheimer's disease; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; Q= quartile; SD= standard deviation

Note: Emotional expressivity did not significantly differ by AD status in either idea density strata.

F.1.2 Multivariate Logistic Regression Models

F.1.2.1 Main Analysis: Low Idea Density

Table F5. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *AD*[1] among individuals with *low idea density*, OR (95% CI), n=14

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D[3]	Grammatical Complexity[3]	Full[3]	Final
Variable									
High Overall EE	0.20 (0.01-2.08)	0.12 (0.003-1.59)	0.11 (0.003-1.56)	0.05 (<0.001-1.19)	0.38 (0.01-13.69)	0.01 (<0.001->999.9)	0.30 (0.01-4.53)	<0.001 (<0.001->999.9)	0.46 (0.01-21.81)
Age		1.24 (0.84-2.13)		1.27 (0.78-2.85)		0.46 (<0.001-4.31)		0.48 (<0.001-4.42)	0.94 (0.50-1.77)
Education (Master's vs. Bachelor's)			0.17 (0.01-1.92)	0.16 (0.001-2.21)		**<0.001** (<0.001-0.60)		<0.001 (<0.001-0.24)	
APOE-ε4 Status					**28.91** (1.96->999.9)	**>999.0** (5.46->999.9)		**>999.9** (2.52->999.9)	**35.65** (1.60->999.9)
Grammatical Complexity							<0.001 (<0.001-1.52)	<0.001 (<0.001-2.68)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to CERAD criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table F6. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *AD*[1] among individuals with *low idea density*, OR (95% CI), n=14

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D[3]	Grammatical Complexity[3]	Full[3]	Final
Variable									
High Positive EE	1.00 (0.11-8.76)	0.94 (0.10-8.40)	1.20 (0.12-13.25)	1.15 (0.11-13.12)	1.00 (0.03-29.59)	>999.9 (<0.001->999.9)	1.50 (0.13-19.11)	>999.9 (0.83->999.9)	1.05 (0.03-32.74)
Age		1.10 (0.78-1.62)		1.04 (0.71-1.55)		**0.004** (<0.001-0.79)		**0.005** (<0.001-0.68)	0.89 (0.49-1.52)
Education (Master's vs. Bachelor's)			0.29 (0.02-2.57)	0.32 (0.02-3.16)		**<0.001** (<0.001-0.02)		**<0.001** (<0.001-0.005)	
APOE-ε4 Status					**35.00** (2.57->999.9)	**>999.9** (286.38->999.9)		**>999.9** (326.39->999.9)	**47.62** (2.67->999.9)
Grammatical Complexity							**<0.001** (<0.001-0.91)	<0.001 (<0.001->999.9)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to CERAD criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table F7. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *AD*[1] among individuals with *low idea density*, OR (95% CI), n=14

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D[3]	Grammatical Complexity[3]	Full[3]	Final
Variable									
High Negative EE	0.30 (0.03-2.58)	**0.02** (<0.001-0.86)	0.19 (0.01-2.06)	**0.001** (<0.001-0.50)	0.49 (0.02-14.72)	0.01 (<0.001->999.9)	0.33 (0.02-3.72)	<0.001 (<0.001->999.9)	0.64 (0.001-92.66)
Age		1.73 (0.97-4.17)		2.27 (0.99-13.20)		0.46 (0.001-4.30)		0.48 (0.002-4.42)	0.95 (0.39-2.67)
Education (Master's vs. Bachelor's)			0.19 (0.01-2.06)	0.07 (<0.001-2.07)		**<0.001** (<0.001-0.55)		**<0.001** (<0.001-0.21)	
APOE-ε4 Status					**30.91** (2.16->999.9)	**>999.9** (4.05->999.9)		**>999.9** (2.08->999.9)	37.23 (0.81->999.9)
Grammatical Complexity							<0.001 (<0.001-1.12)	<0.001 (<0.001-2.68)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to CERAD criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

F.1.2.2 Main Analysis: High Idea Density

Table F8. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *AD*[1] among individuals with *high idea density*, OR (95% CI), n=64

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Overall EE	1.67 (0.53-5.58)	1.66 (0.52-5.63)	1.88 (0.58-6.59)	2.04 (0.61-7.63)	1.94 (0.60-6.92)	2.39 (0.68-9.48)	1.74 (0.55-5.98)	3.09 (0.82-14.09)	1.88 (0.58-6.76)
Age		1.11 (0.94-1.35)		1.15 (0.95-1.44)		1.15 (0.94-1.44)		1.20 (0.96-1.56)	1.10 (0.92-1.35)
Education (Master's vs. Bachelor's)			2.81 (0.86-10.32)	3.25 (0.95-13.08)		3.45 (0.98-14.59)		**4.69** (1.20-23.11)	
APOE-ε4 Status					2.62 (0.66-10.17)	2.60 (0.62-10.90)		3.60 (0.78-17.97)	2.42 (0.60-5.60)
Grammatical Complexity							0.42 (0.12-1.51	**0.23** (0.05-0.99)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to CERAD criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table F9. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *AD*[1] among individuals with *high idea density*, OR (95% CI), n=64

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Positive EE	1.09 (0.35-3.42)	1.13 (0.35-3.61)	1.23 (0.38-4.05)	1.36 (0.41-4.71)	1.11 (0.35-3.54)	1.41 (0.42-4.99)	1.14 (0.36-3.66)	1.72 (0.48-6.75)	1.14 (0.35-3.69)
Age		1.11 (0.94-1.35)		1.14 (0.95-1.43)		1.14 (0.94-1.43)		1.17 (0.95-1.51)	1.10 (0.93-1.35)
Education (Master's vs. Bachelor's)			2.67 (0.83-9.72)	2.99 (0.89-11.63)		3.09 (0.90-12.44)		**4.10** (1.08-19.31)	
APOE-ε4 Status					2.28 (0.59-8.36)	2.20 (0.55-8.52)		2.84 (0.66-12.43)	2.13 (0.54-7.88)
Grammatical Complexity							0.44 (0.13-1.54)	0.27 (0.06-1.09)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to CERAD criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table F10. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *AD*[1] among individuals with *high idea density*, OR (95% CI), n=64

	Crude[2]	1B	Education	1C	*APOE*-ε4	1D	Grammatical Complexity	Full	Final
Variable									
High Negative EE	1.09 (0.35-3.50)	1.06 (0.33-3.45)	1.24 (0.39-4.16)	1.32 (0.40-4.70)	1.34 (0.41-4.72)	1.76 (0.48-7.37)	1.08 (0.34-3.51)	2.15 (0.55-10.20)	1.27 (0.38-4.48)
Age		1.11 (0.94-1.34)		1.14 (0.95-1.42)		1.14 (0.94-1.43)		1.18 (0.95-1.53)	1.10 (0.92-1.34)
Education (Master's vs. Bachelor's)			2.68 (0.83-9.74)	3.00 (0.89-11.88)		3.38 (0.94-14.86)		**4.69** (1.16-25.71)	
APOE-ε4 Status					2.49 (0.61-9.87)	2.66 (0.62-11.54)		3.57 (0.77-17.77)	2.28 (0.56-9.13)
Grammatical Complexity							0.44 (0.13-1.55)	0.26 (0.06-1.08)	

Bolded values are statistically significant.
[1] Based on diagnosis of AD according to CERAD criteria; non-cases defined as those without AD or dementia at their last cognitive assessment
[2] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[3] Model did not converge: quasi-complete separation of data detected
Abbreviations: AD= Alzheimer's disease; *APOE*-ε4= apolipoprotein E ε4 allele; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

F.2 Measures of the Association of Emotional Expressivity with AD Using Alternative Samples

F.2.1 Main Analysis: Low Idea Density

Table F11. Association of emotional expressivity with *AD* among individuals with *low idea density*, adjusted for age at diagnosis and *APOE*-ε4 status, in the analytic samples where the non-cases are defined as those with neither dementia nor AD neuropathology

	CERAD/DN (n=12)		NIA-RI/DN (n=19)	
	OR	**95% CI**	**OR**	**95% CI**
Emotional Expressivity				
Overall	2.00	0.02, 357.96	0.40	0.02, 5.21
Positive	6.26	0.12, 957.04	1.71	0.19, 19.44
Negative	1.70	0.003, 366.95	0.24	0.02, 2.56

Abbreviations: AD = Alzheimer's disease; *APOE*-ε4= apolipoprotein ε4; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; /DN= non-cases without dementia or neuropathology; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

F.2.2 Main Analysis: High Idea Density

Table F12. Association of emotional expressivity with *AD* among individuals with *high idea density*, adjusted for age at diagnosis and *APOE*-ε4 status, in the analytic samples where the non-cases are defined as those with neither dementia nor AD neuropathology

	CERAD/DN (n=40)		NIA-RI/DN (n=48)	
	OR	**95% CI**	**OR**	**95% CI**
Emotional Expressivity				
Overall	2.51	0.61, 12.13	1.60	0.39, 7.38
Positive	1.55	0.39, 6.50	1.19	0.29, 5.02
Negative	1.26	0.30, 6.09	1.82	0.42, 9.73

Abbreviations: AD = Alzheimer's disease; *APOE*-ε4= apolipoprotein ε4; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; /DN= non-cases without dementia or neuropathology; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

F.3 Sensitivity Analysis of Non-Stratified Models Using Alternative Samples

Table F13. Sensitivity analysis of the association of emotional expressivity with AD without stratification by idea density, in the analytic samples where the non-cases are defined as those with neither dementia nor AD neuropathology

	CERAD/D (n=78)		CERAD/DN (n=52)		NIA-RI/DN (n=67)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Emotional Expressivity						
Overall	1.57	0.54, 4.85	1.75	0.50, 6.70	1.44	0.46, 4.80
Positive	1.11	0.39, 3.14	1.56	0.45, 5.58	1.42	0.47, 4.47
Negative	1.10	0.37, 3.45	0.95	0.25, 3.75	1.01	0.33, 3.26
Low Positive	2.23	0.40, 17.50	2.25	0.35, 20.12	2.43	0.42, 20.38
High Positive	0.59	0.12, 2.98	0.17	0.01, 1.70	0.28	0.09, 2.49

Abbreviations: AD = Alzheimer's disease; *APOE*-ε4= apolipoprotein ε4; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CI= confidence interval; /D= non-cases without dementia; /DN= non-cases without dementia or neuropathology; NIA-RI= National Institute on Aging – Reagan Institute; OR= odds ratio

Appendix G. Sensitivity Analysis of the Association of Emotional Expressivity with Dementia using the Subset for the Analyses of AD

A sensitivity analyses was performed to investigate the association between emotional expressivity and dementia using the subset for the analyses of AD (n=85), which was limited by the availability of AD neuropathologic data. The purpose of this analysis was to allow a true comparison of the association of emotional expressivity with dementia to the association with AD. The full models generated in this sensitivity analysis, stratified by idea density, are found below (Tables G1-G6). In all, the association was very similar with dementia as it was with AD in this subset.

G.1 Sensitivity Analysis using the Subset Selected for the Analyses of AD: Low Idea Density

Table G1. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *dementia* among individuals with *low idea density* (n=19), OR (95% CI)

	Crude[1]	1B	1C	1D	Full[2]	Final
Variables						
High Overall EE	0.23 (0.01-2.02)	0.21 (0.01-1.95)	0.20 (0.01-2.02)	0.46 (0.02-7.10)	0.20 (0.003-3.97)	0.40 (0.02-5.20)
Age		1.05 (0.81-1.37)	1.00 (0.74-1.33)	0.87 (0.56-1.23)	0.97 (0.55-1.71)	1.00 (0.75-1.32)
Education (Master's vs. Bachelor's)			0.35 (0.03-3.44)	0.14 (0.002-2.35)	0.12 (0.002-2.53)	
APOE-ε4 Status				13.86 (0.82->999.9)	7.71 (0.40-971.86)	6.23 (0.59-150.38)
Grammatical Complexity[3]					**<0.001** (<0.001-0.58)	

Bolded values are statistically significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Model would not converge: quasi-complete separation of data detected.
[3] Grammatical complexity was not included in the final model, despite being statistically significant, because the model would not converge when it was included
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table G2. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *dementia* among individuals with *low idea density* (n=19), OR (95% CI)

	Crude[1]	1B	1C	1D	Full	Final
Variables						
High Positive EE	1.17 (0.16-8.59)	1.16 (0.16-8.61)	1.52 (0.19-14.63)	4.96 (0.35-188.53)	2.44 (0.15-97.19)	1.73 (0.19-19.66)
Age		1.01 (0.79-1.27)	0.94 (0.70-1.23)	0.80 (0.49-1.14)	0.94 (0.54-1.66)	0.99 (0.75-1.29)
Education (Master's vs. Bachelor's)			0.31 (0.02-3.18)	0.04 (<0.001-1.39)	0.10 (<0.001-2.62)	
APOE-ε4 Status				**34.14** (1.76->999.99)	9.62 (0.50-906.31)	8.98 (0.98-216.40)
Grammatical Complexity					<0.001 (<0.001-1.16)	

Bolded values are statistically significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table G3. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *low idea density* (n=19), OR (95% CI)

	Crude[1]	1B	1C	1D[2]	Full[2]	Final
Variables						
High Negative EE	0.31 (0.03-2.24)	0.26 (0.02-2.13)	0.24 (0.02-2.08)	<0.001 (<0.001-1.12)	**<0.001** (<0.001-0.20)	0.23 (0.01-2.44)
Age		1.06 (0.82-1.41)	1.01 (0.75-1.36)	0.91 (0.57-1.24)	1.58 (0.68-5.03)	1.05 (0.79-1.39)
Education (Master's vs. Bachelor's)			0.32 (0.02-3.19)	**<0.001** (<0.001-0.91)	**<0.001** (<0.001-0.39)	
APOE-ε4 Status				**>999.99** (2.37->999.9)	>999.99 (0.41->999.9)	8.74 (0.91-222.29)
Grammatical Complexity					**<0.001** (<0.001-0.15)	

Bolded values are statistically significant.
[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
[2] Model would not converge: quasi-complete separation of data detected.
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

G.2 Sensitivity Analysis using the Subset Selected for the Analyses of AD: High Idea Density

Table G4. Results of multivariate logistic regression analyses of the association between *overall emotional expressivity* and *dementia* among individuals with *high idea density* (n=66), OR (95% CI)

	Crude[1]	1B	1C	1D	Full	Final
Variables						
High Overall EE	2.00 (0.66-6.56)	2.00 (0.66-6.62)	2.30 (0.73-8.01)	2.62 (0.81-9.67)	3.01 (0.89-11.84)	2.72 (0.72-7.94)
Age		1.07 (0.92-1.26)	1.08 (0.92-1.29)	1.07 (0.91-1.28)	1.09 (0.92-1.33)	1.06 (0.90-1.25)
Education (Master's vs. Bachelor's)			2.17 (0.70-7.27)	2.20 (0.70-7.54)	2.48 (0.76-8.99)	
APOE-ε4 Status				2.22 (0.55-8.91)	2.63 (0.62-11.44)	2.19 (0.54-8.64)
Grammatical Complexity					0.36 (0.09-1.40)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table G5. Results of multivariate logistic regression analyses of the association between *positive emotional expressivity* and *dementia* among individuals with *high idea density* (n=66), OR (95% CI)

	Crude[1]	1B	1C	1D	Full	Final
Variables						
High Positive EE	1.36 (0.46-4.13)	1.40 (0.47-4.31)	1.60 (0.52-5.16)	1.64 (0.53-5.37)	1.84 (0.57-6.40)	1.42 (0.47-4.43)
Age		1.07 (0.92-1.26)	1.08 (0.92-1.28)	1.07 (0.91-1.28)	1.08 (0.92-1.31)	1.06 (0.91-1.26)
Education (Master's vs. Bachelor's)			2.04 (0.67-6.72)	2.05 (0.66-6.84)	2.31 (0.72-8.18)	
APOE-ε4 Status				1.84 (0.47-6.77)	2.11 (0.53-8.24)	1.84 (0.48-6.71)
Grammatical Complexity					0.40 (0.10-1.47)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio

Table G6. Results of multivariate logistic regression analyses of the association between *negative emotional expressivity* and *dementia* among individuals with *high idea density* (n=66), OR (95% CI)

	1A	1B	1C	1D	1E	Final
Variables						
High Negative EE	1.06 (0.36-3.21)	1.05 (0.35-3.22)	1.17 (0.38-3.71)	1.38 (0.43-4.78)	1.45 (0.44-5.21)	1.20 (0.39-3.92)
Age		1.06 (0.92-1.25)	1.07 (0.92-1.27)	1.06 (0.91-1.27)	1.07 (0.91-1.29)	1.06 (0.91-1.25)
Education (Master's vs. Bachelor's)			1.92 (0.63-6.22)	1.98 (0.64-6.58)	2.19 (0.69-7.75)	
APOE-ε4 Status				1.99 (0.49-7.77)	2.26 (0.54-9.28)	1.92 (0.48-7.37)
Grammatical Complexity					0.43 (0.12-1.55)	

[1] Crude, 1B, 1C… etc. correspond to models represented in the analytic strategy (Table 2)
Abbreviations: *APOE*-ε4= apolipoprotein E ε4 allele; CI= confidence interval; EE= emotional expressivity; OR= odds ratio