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The Influence of Widowhood and Sociodemographic Moderators on Dementia and Alzheimer's Disease Risk

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THE INFLUENCE OF WIDOWHOOD AND SOCIODEMOGRAPHIC MODERATORS ON DEMENTIA AND ALZHEIMER'S DISEASE RISK

by

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ABSTRACT

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by

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Dementia and Alzheimer's disease (AD) are highly debilitating conditions that afflict millions of elderly persons. In recent decades, biological evidence has implicated chronic stress in the etiology of these conditions. As a result, the relationship between widowhood, one of the most stressful life events, and dementia and AD has also received attention. However, studies are mixed regarding this association, and few have investigated whether this relationship is moderated by the context surrounding widowhood. This study extends this literature by investigating whether widowhood increases risk for dementia and AD and whether this risk is moderated by contextual factors including age at widowhood, remarriage after widowhood, manner of death, number of dependent and adult children at the time of widowhood, gender, presence of ε4 allele of apolipoprotein E (APOE), and history of depression and antidepressant use. To do this, this investigation utilized data from the Cache County Memory Study (CCMS), a large population-based epidemiological study of dementia and AD, and the Utah

Population Database (UPDB), one of the world's foremost linked genealogical databases. In Cox regression analyses that modeled time to onset of dementia and AD, gender was found to moderate the relationship between incident widowhood and dementia (*HR* = 1.74, 95% *CI*: 0.97-3.10), in that widowhood trended towards decreased risk among men (*HR* =0.72, *CI*: 0.45-1.16) but increased risk among women (*HR* = 1.21, *CI*: 0.83-1.75) in stratified models. In addition, history of depression and antidepressant use moderated the association between incident widowhood and dementia (*HR* = 2.63, 95% *CI*: 1.26-5.50) and AD (*HR* = 1.68, 95% *CI*: 1.11-2.53), in that widowhood was associated with decreased risk for dementia and AD among the never depressed (*HR* = 0.66, *CI*: 0.42-1.02 and *HR* = 0.54, *CI*: 0.31-0.92, respectively), a trend towards increased risk for AD among those with a history of antidepressant use but no depression (*HR* = 1.80, *CI*: 0.86-3.75), and with increased risk for dementia and AD among those with a history of both (*HR* = 1.93, *CI*: 0.98-3.81 and *HR* = 1.89, *CI*: 0.80-4.43). These findings advance clinical and scientific knowledge concerning the effects of widowhood on risk for dementia and AD, and underscore the importance of context in understanding this relationship.

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PUBLIC ABSTRACT

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Dementia and Alzheimer's disease (AD) are dramatic public health problems. In recent years, researchers have uncovered evidence demonstrating that chronic stress can lead to these conditions. Because of this, researchers have also investigated whether widowhood, one of the most stressful life events, may also lead to dementia and AD. However, these studies are conflicting, and few have investigated whether the influence of widowhood on dementia and AD varies in different contexts associated with aging and widowhood. For instance, evidence suggests that widowhood may exert greater influence among males and among those with a history of depression. Other such contextual factors include the age at which one is widowed, whether one remarries after widowhood, whether one's spouse died of natural causes or by accident or suicide, the number and age of children at the time of widowhood, and whether one carries one or more copies of the Apolipoprotein ε4 allele—a genetic factor known to increase risk for dementia and AD. The purpose of this dissertation was to further investigate whether widowhood increased risk for dementia and AD and whether this risk depends on these contextual factors.

This dissertation utilized data from the Cache County Memory Study (CCMS), a

large-scale epidemiological study of dementia and AD, and the Utah Population Database, one of the world's foremost genealogical databases, to assess whether the occurrence of widowhood is related to the timing at which dementia and AD occurs, and to assess whether this relationship varies in different contexts. Findings indicated that widowed persons who are male and widowed persons with a history of severe depression are at increased risk for dementia and AD. These findings may help clinicians identify elderly persons at higher risk for these conditions, and will help epidemiological researchers to better understanding elderly populations.

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CHAPTER 1

INTRODUCTION

Alzheimer's disease (AD, also referred to as "dementia of the Alzheimer's type") and other dementias profoundly impact individuals and their families, communities, and the nation. These conditions are highly debilitating, with those affected having memory impairments and other cognitive impairments severe enough to cause significant impairment in social or occupational functioning (American Psychiatric Association, 1994). These conditions are very common, with dementia prevalence ranging from 2% to 22% for men and 1% to 31% for women and AD prevalence ranging from 1% to 18% for men and 1% to 24% for women, across ages 65 to 90+ years (Lobo et al., 2000). Dementia and AD (referred to hereafter as dementia unless otherwise specified) are also highly costly. In 2009 alone, the direct costs (resources used in dementia caregiving, such as institutionalization) and indirect costs (resources lost in dementia caregiving, such as work time lost assisting demented person with instrumental activities of daily living such as preparing food, shopping, and laundry) of dementia in the U.S. was estimated to be $97.4 billion (Wimo, Winblad, & Jönsson, 2010). This is particularly concerning given that the elderly segment of the population in the developed world is growing, such that by 2030, one in five persons will be over the age of 65 (U.S. Census Bureau, 2008).

Much research has been done to understand the etiology of dementia. A number of mechanisms have been forwarded to explain the etiology of AD, the most common form of dementia, which is characterized pathologically by neuritic plaques and neurofibrillary tangles (Cummings & Cole, 2002). AD has been linked to β amyloid

deposition, which derives from amyloid precursor protein (APP), produced by the APP gene on the 21st chromosome (J. A. Hardy & Higgins, 1992). β amyloid has been found to lead to neuritic plaques, to hyperphosphorylated tau protein and resulting neurofibrillary tangles, and to cell loss, vascular damage, and dementia (J. A. Hardy & Higgins, 1992). Other factors have also been implicated in AD pathology, such as lipid metabolism (Frears, Stephens, Walters, Davies, & Austen, 1999; Hofman et al., 1997; Jick, Zornberg, Jick, Seshadri, & Drachman, 2000); genes (Hollingworth et al., 2011), such as APOE ε4 allele (Breitner et al., 1999; Knopman, Mosley, Catellier, & Coker, 2009; Packard et al., 2007; Tyas et al., 2007); neuroinflammation (Cummings & Cole, 2002; Ringman & Cummings, 2006; Wenk, 2003); the loss and alteration of cholinesterases (Ringman & Cummings, 2006; Shen, 2004); and oxidative stress (Zhu et al., 2004).

Researchers have also explored the deleterious effects of chronic stress on central nervous system (CNS) damage and AD pathology. Though temporary stress enables physiological reactions that promote survival (Pedersen, Wan, & Mattson, 2001), chronic stress leads to physiological processes, such as the glucocorticoid cascade (Sapolsky, Krey, & McEwen, 1986), that lead to adverse health outcomes, including degeneration of brain regions such as the hippocampus, associated with learning and memory. In addition, chronic stress has been linked with neuritic plaques and neurofibrillary tangles (Dong et al., 2004; Green, Billings, Roozendaal, McGaugh, & LaFerla, 2006; Kang, Cirrito, Dong, Csernansky, & Holtzman, 2007; Sotiropoulos et al., 2011).

A number of animal and human studies have found that chronic stress damages the hippocampus and leads to AD pathology. In one such study (Sousa, Madeira, &

Paula-Barbosa, 1998), researchers found that rats given daily injections of corticosterone, a stress hormone endemic to these animals, had lower overall brain weight and lower hippocampal volume than rats not given these injections, and that increasing the length of time during which they were given these daily injections led to increasingly lower overall brain weight and hippocampal volume. Similar evidence was found by other authors, who found that mice or rats subjected to corticosterone treatment or stressful conditions exhibited fewer new endothelial cells in the hippocampus (Ekstrand, Hellsten, & Tingstrom, 2008), less area covered by the synaptic vesicles in the hippocampus (Magariños, García Verdugo, & McEwen, 1997), increased phosphorylation of TAU at certain regions of the hippocampus (Sotiropoulos et al., 2011), as well as greater amyloid β levels (Green et al., 2006; Kang et al., 2007) and many more neuritic plaques throughout the brain (Dong et al., 2004).

Human studies have also found stress to be associated with hippocampal damage, and with memory impairment, mild cognitive impairment (MCI), and AD. For instance, studies have found that persons with high stress levels (Lupien et al.,1998) had lower hippocampal volumes than participants with lower cortisol levels, and that persons with post-traumatic stress disorder (PTSD) had higher cortisol levels (Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006) and lower hippocampal volume (Bremner et al., 2003; Lindauer et al., 2006; Villarreal et al., 2002) than similar persons without PTSD. Other studies have found stress to be associated with memory impairment. Researchers have found stressful life events (Peavy et al., 2007), high cortisol levels (Lupien et al., 1998), and participation in a stressful public speaking task (Lupien et al, 1997) to be associated with various measures of memory, such as delayed memory, spatial memory, and

declarative memory. In addition, increased cortisol production (Rasmuson et al., 2001) and decreased feedback sensitivity to stress (Elgh et al., 2006) are associated with mild to moderate AD and diminished performance on the spatial span section of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), respectively. Also, other studies have found an association between proneness to distress, as defined by high neuroticism scores, and increased likelihood of mild cognitive impairment (MCI; Wilson et al., 2007) and AD (Wilson et al., 2005).

Among all psychosocial stressors that may increase risk for adverse cognitive outcomes, studies have found widowhood to be rated as one of the most stressful (S. E. Hardy, Concato, & Gill, 2002; Holmes & Rahe, 1967). Studies have found widowhood to be associated with increased cortisol levels (Buckley et al., 2009; Gerritsen et al., 2009), as well as other signs of chronic stress, including increased depression (Buckley et al., 2009; Hughes & Waite, 2009) and anger, and anxiety, and reduced sleep (Buckley et al., 2009). In addition, studies have linked widowhood with a number of adverse health outcomes, including increased chronic medical conditions, mobility limitations, poorer self-rated health (Hughes & Waite, 2009), increased physical pain (Bradbeer, Helme, Yong, Kendig, & Gibson, 2003), and stroke (Engström et al., 2004; Maselko, Bates, Avendaño, & Glymour, 2009; Öhgren et al., 2000; Simons, McCallum, Friedlander, & Simons, 1998). Risk of mortality was also increased in the first year after bereavement (Manor & Eisenbach, 2003; Schaefer, Quesenberry, & Wi, 1995).

Since widowhood is associated with chronic stress and adverse health outcomes, and since chronic stress is associated with damages to brain areas associated with learning and memory, as well as with AD pathology and impaired memory, it has been

hypothesized that widowhood would increase one's risk for greater cognitive impairment and dementia. Hakansson and colleagues (2009) found that those widowed at mid-life had higher risk of any cognitive impairment and MCI, but not AD, than those living with a partner (married or cohabitating) at midlife, and that those widowed at both midlife and later life were at particularly high risk for any cognitive impairment and AD, suggesting that widowhood has a more pronounced association with AD among widowed person who do not remarry. Aartsen and colleagues (2005) found that among men, those who were widowed between baseline and an 8-year follow-up were more likely to have diminished immediate and delayed word recall at follow-up than those who had not been widowed. They also found that this association was moderated by depression, in that widowed persons who were more depressed at baseline declined more than widowed persons who were not depressed at baseline. Van Gelder and colleagues (2006) found that widowed or divorced persons exhibited greater cognitive decline over their course of their 10-year study than persons who remained married. Karlamangla and colleagues (2009) found that total cognition scores, and in particular word recall scores, declined faster among widowed persons than among married persons.

Other studies found only a moderated relationship between widowhood and cognitive decline. For instance, Rosnick, Small, and Burton (2010) found a significant bereavement by age interaction on some measures of cognitive functioning, in which the discrepancy in cognitive functioning between bereaved and nonbereaved persons grew increasingly greater with decreasing age. They also found a significant bereavement by gender interaction, in which bereaved men, but not bereaved women, had lower scores on this measure than their nonbereaved counterparts. Sachs-Ericsson, Sawyer, Corsentino,

Collins, and Blazer (2010) found that number of negative life events, which included widowhood, predicted cognitive impairment in those with at least one APOE ε4 allele but not among those without at least one APOE ε4 allele. Other factors may also moderate the relationship between widowhood and dementia, since they have been found to moderate the relationship between widowhood and other conditions. For instance, it has been demonstrated that those who remarry after widowhood are less depressed and more satisfied with life than those who do not remarry after widowhood (Williams, 2003). Manner of death may also moderate this relationship. One study (Carr, House, Wortman, Nesse, & Kessler, 2001) found that persons whose spouses had died suddenly had more intrusive thoughts about their deceased spouse and lower anxiety, and men whose wives died suddenly had considerably lower feelings of yearning for their deceased wife than men whose wives did not die suddenly. Also, some evidence indicates that widowed women with more dependent children are at higher risk of mortality than widowed women with fewer dependent children (Alter, Dribe, & Van Poppel, 2007). In addition, one study found that widowed men with adult children are less likely to be institutionalized than widowed men without adult children, suggesting that widowhood led to increased risk of dementia, which in turn necessitated institutionalization (Noël-Miller, 2010).

Other studies on widowhood and AD found that this relationship was not robust to inclusion of covariates. For instance, Ward, Mathias, and Hitchings (2007) found that an initially significant relationship between bereavement and various measures of cognitive impairment became nonsignificant after controlling for depression, anxiety and stress, suggesting that these factors mediate the relationship between widowhood and

cognitive status. Fratiglioni, Wang, Ericsson, Maytan, and Winbald (2000) found that being widowed was associated with increased risk for incident dementia in unadjusted models, but not in models adjusted for living arrangements (living with someone versus living alone); frequency of contact with children, relatives, and friends; and satisfaction with such contact, which may suggest that these factors moderate the relationship between widowhood and cognitive status. Still other studies (Comijs, van den Kommer, Minnaar, Penninx, & Deeg, 2011; Helmer et al., 1999; Rosnick, Small, McEvoy, Borenstein, & Mortimer, 2007) found no association between widowhood and dementia. Differences in study characteristics between previous studies may help explain why some found relationships, or moderated relationships, between widowhood and dementia, while others did not. In general, studies that found statistically significant relationships or moderated relationships assessed marital history and dementia status over longer periods of time.

Studies that have assessed the relationship between widowhood and AD are few and have several methodological limitations. In all of these studies, marital status was assessed at limited time points, and was measured via self-report. This may produce biased findings in persons with compromised cognitive functioning. Also, some widowed persons, particularly widowed females, may be reluctant to disclose living alone because of safety reasons. Also, many of these studies used relatively small periods of dementia observation, which may not capture the number of dementia cases that could be captured if a longer period of observation were used. In addition, with the exception of Fratiglioni et al. (2000), Hakansson and colleagues (2009), and Helmer and colleagues (1999), who used dementia or AD as outcomes, most studies used only cognitive functioning as an

outcome, which limits the conclusions that can be made concerning associations between widowhood and dementia.

Much research has been conducted to understand the etiology of Alzheimer's disease and other dementias. A number of possible mechanisms have been explored, including chronic stress, which has been found to lead to CNS damage, including reduction in hippocampal volume, and to memory impairment. Widowhood has been found to be related to chronic stress and conditions related to chronic stress, including anger, anxiety, reduced sleep, and depression, as well as to various adverse health outcomes, and mortality. A number of studies have also found a relationship between widowhood and late-life cognitive functioning. Those that did find a relationship tended to use more complete marital history and to use longer periods in which to observe cognitive decline and dementia. However, most of these studies assessed marital histories at limited time points, and all but one (Hakansson et al., 2009) assessed marital history in late-life only. In addition, these studies assessed marital history using self-report, which may produce biased findings in elderly samples. Moreover, most of these studies used cognitive functioning as the outcome rather than dementia and AD, and few accounted for the moderating effect of contextual variables.

The proposed study will pursue the following research objectives. It will determine the extent to which widowhood increases risk for AD and all-cause dementia, and whether effects are stronger at various stages in the lifespan. Additionally, in order to identify particularly vulnerable subpopulation(s), the proposed study will also examine a focused set of potential moderators that have been identified in the widowhood literature on various health-related outcomes, to determine whether they also moderate the

widowhood/dementia association. These moderator variables will include both characteristics of the widowed person as well as contextual factors. The proposed study will accomplish this by use of extant data from the Cache County Memory Study (CCMS), a 12-year epidemiological study of dementia in an initial population of 5,092 persons. Unlike the majority of studies conducted to date, which assessed marital status and dementia for shorter periods of time, which assessed marital history via self-report, and which tended to used cognitive function as the outcome, the proposed study will utilize full, objective marital history records, and 12 years of dementia ascertainment from a large, population-based dataset, thus greatly extending our understanding of how this potentially severe stressor impacts dementia risk.

CHAPTER 2

LITERATURE REVIEW

Public Health Significance of Dementia

Dementia generally and Alzheimer's disease specifically profoundly affects individuals and families. These conditions are highly common. A review of data pooled from 11 studies conducted in eight European countries found dementia prevalence among those 65-69, 70-74, 75-79, 80-84, 85-89, and 90 or more years old to be 1.6%, 2.9%, 5.6%, 11%, 12.8%, and 22.1%, respectively, among men and 1.0%, 3.1%, 6%, 12.6%, 20.2%, and 30.8% among women, and AD prevalence to be 0.6%, 1.5%, 1.8%, 6.3%, 8.8%, and 17.6% among men and 0.7%, 2.3%, 4.3%, 8.4%, 14.2%, and 23.6% among women (Lobo et al., 2000). Incidence rates were also high; using pooled data, one study found that among those 65-69, 70-74, 75-79, 80-84, and 85-89 years old, 2.4%, 5.0%, 10.5%, 17.7%, and 27.5% acquired moderate dementia, and 1.6%, 3.5%, 7.8%, 14.8%, and 26.0% acquired moderate AD (Jorm & Jolley, 1998). In the CCMS, , those 90-92 years old, and 93 and older, had an incidence of 121.7 and 110.0 per 1,000 person years for all-cause dementia and 96.1 and 73.6 for AD (Miech et al., 2002). This is particularly concerning given the growing number of elderly persons. According to U.S. Census (2008) estimates, by 2030 one in five persons will be over age 65. Moreover, dementia is devastating and debilitating. This condition is characterized by memory impairment, as well as multiple other cognitive impairments, which could include aphasia, apraxia, agnosia, or impairment in executive functioning (Diagnostic and Statistical Manual of

Mental Disorders IV [DSM-IV]; American Psychiatric Association, 1994). In addition, dementia is marked by significant impairment in social or occupational functioning. Dementia and AD impose dramatic financial burden on families and the nation as well. One study estimated the average cost of each dementia case in North America to be $26,860 in 2009, and the total cost of dementia care in the U.S to be $97.4 billion in 2009 (Wimo et al., 2010).

Hypothesized Mechanisms Causing Dementia

Much research has been conducted to understand the causes of dementia. By far the most common form of dementia in late life is AD (Jorm & Jolley, 1998). This disease is characterized by two pathological features: neuritic plaques and neurofibrillary tangles. Neuritic plaques consist of a core of β amyloid proteins, surrounded by astrocytes and microglia, which aid in the destruction of damaged cells, and neurons with degenerated axons and dendrites (Cummings & Cole, 2002). Neurofibrillary tangles consist of paired helical filaments of abnormally phosphorylated tau protein. Normally, tau proteins bind with microtubules to help them form the transport system of neurons. In AD patients, excessive amounts of phosphate ions bind to tau, rendering them unable to bind to microtubules, thus breaking down the cell's transport system. After the cell dies, the twisted filaments of hyperphosphorylated tau protein remain. Additional pathological features of AD, including reductions in synaptic density, loss of neurons, and granulovacuolar degeneration in hippocampal neurons, while not required for a diagnosis, are often found in AD cases.

A number of mechanisms have been proposed to explain the etiology of AD.

Neuritic plaques and neurofibrillary tangles can be linked to β amyloid deposition. Accumulation of β amyloid leads to neuritic plaques, as well as cell death, oxidation of lipids and disruption of cell membranes, inflammation, and neurofibrillary tangles (Cummings & Cole, 2002; Hardy & Higgins, 1992; Nikolaev, McLaughlin, O'Leary, & Tessier-Lavigne, 2009). Various lines of evidence support this theory. Though rare, mutations in APP gene (which controls β amyloid production) lead to both neuritic plaques and neurofibrillary tangles (Farlow et al., 1994; Martinez, Campion, Babron, & Clerget-Darpoux, 1993; Price & Sisodia, 1998). Other researchers propose that abnormal tau leads to AD pathology. As evidence for this, researchers have found that hyperphosphorylation of tau leads to failure of tau to bind to microtubules, and that the resulting failure to form microtubules leads to cell death (Iqbal et al., 2005; Mudher & Lovestone, 2002). However, researchers have found that mutations in tau lead to only neurofibrillary tangles, whereas mutations in APP lead to both neuritic plaques and neurofibrillary tangles (Mudher & Lovestone, 2002), and that transgenic mice with mutant APP and mutant tau have more tangles than transgenic mice with only mutant tau (Lewis et al., 2001; Mudher & Lovestone, 2002), suggesting that aggregation of β amyloid precedes tau pathology.

Other mechanisms have also been proposed. Some research suggests that lipid metabolism is related to AD pathology. The finding that the APOE ε4 allele increases risk for AD (Breitner et al., 1999) supports this theory, in that this allele makes a glycoprotein involved in transporting cholesterol through the blood (Mahley & Rall, 2000). Also, the finding that vascular risk factors, including atherosclerosis (Hofman et al., 1997), are associated with dementia, that cholesterol in cell cultures increases the

amount of β amyloid produced from APP (Frears et al., 1999), and that statins, which are designed to lower cholesterol, also lower one's risk for dementia (Jick et al., 2000), also support this theory. Genetic explanations have also been explored. AD (Gatz et al., 2006) and β amyloid deposition (Hinrichs et al., 2010) are highly heritable. Though APOE ε4 allele accounts for only 26% of the variation in the heritability in β amyloid deposition, it has been found to strongly relate to AD (Breitner et al., 1999; Tyas et al., 2007) and cognitive decline (Knopman et al., 2009; Packard et al., 2007). Neuroinflammation has also been implicated, in that β amyloid deposition leads to neuroinflammation (Cummings & Cole, 2002; Wenk, 2003), and nonsteroidal anti-inflammatory drugs (NSAIDs) reduce risk of AD (Lim et al., 2000; Ringman & Cummings, 2006; Wenk, 2003). The neurotransmitter acetylcholine also plays a role, in that parts of the brain that sustain neuronal loss during AD tend to use acetylcholine (Ringman & Cummings, 2006) and lower levels of acetylcholine are associated with neuritic plaques and neurofibrillary tangles, and neuroinflammation (Shen, 2004). Further, cholinesterase inhibitors, which inhibit the breakdown of acetylcholine, are somewhat effective in delaying cognitive decline (Ringman & Cummings, 2006). Oxidative stress, produced when imbalances in biochemical processes produce reactive oxygen species (ROS), is also implicated in AD. Older persons are at increased risk for oxidative stress, and are more vulnerable to its effects (Zhu et al., 2004). One way in which β amyloid becomes toxic to cells is by generating oxidative stress. Perhaps because of this, signs of oxidative stress can be seen in neuritic plaques and neurofibrillary tangles, and in other cells at risk of death.

Chronic Exposure to Stress: Another Biological Mechanism

Evidence indicates that chronic stress, including life stress associated with life stressors such as widowhood, may contribute to AD pathology as well. While stress responses enable physiological reactions that promote survival in the immediate presence of a stressor, chronic activation of these responses can lead to adverse health outcomes, including degeneration of brain areas associated with learning and memory, such as the hippocampus (Pedersen et al., 2001). Sapolsky and colleagues (1986) originally formulated the glucocorticoid cascade hypothesis, an explanation of how chronic stress leads to this degeneration. These researchers noted that some areas of the brain, including the hippocampus, inhibit the release of stress hormones, called glucocorticoids (corticosterone in rodents and cortisol in humans), and that sustained release of glucocorticoids permanently decreases the number of glucocorticoid receptors in the hippocampus, leading to impaired glucocorticoid feedback of the stress response, which in turn leads to hypersecretion of glucocorticoids and further reduction of hippocampal receptors. Indeed, a number of studies using animals and humans have found that chronic stress leads to changes in the hippocampus. In addition, in recent years researchers have found that chronic stress can contribute to AD pathology, though the mechanisms behind this are not well understood (Green et al., 2006).

Animal Studies

In a study of rats, Sousa and colleagues (1998) found hippocampal changes among both neonatal rats (30 days old) and adult rats (180 days old) treated with corticosterone. Rats treated with daily injections of corticosterone for 30 days had lower

overall brain weight, $M = 1.19$ g, $SD = 0.04$ g; $F(2,21) = 16.06$, $p < .0005$, than a control group of rats maintained under standard laboratory conditions during the 30 days ($M = 1.35$ g, $SD = 0.02$) and a control group of rats given daily injections of sesame oil during the 30 days ($M = 1.28$ g, $SD = 0.05$). This group also had lower overall hippocampal volume, $M = 22.3$ mm^3, $SD = 0.18$; $F(2,21) = 4.91$, $p < .018$, than the control group under standard lab conditions ($M = 27.4$ mm^3, $SD = 0.13$) and the control group given daily injections of sesame oil ($M = 26.1$ mm^3, $SD = 0.14$). The authors also found similar effect sizes in lower brain weight and lower hippocampal volume among adult rats (age 180 days) treated with corticosterone at various life periods (days 1-89, 90-180). However, rats that were given the 0-30 day corticosterone treatments and thereafter given no treatments (the "recovery" group) did not have lower overall brain weight. Findings from this study indicate that corticosterone treatments decrease overall brain weight and hippocampal volume in neonatal and adult rats, and that increasing amounts of this hormone lead to increased damage.

Other animal studies explain how this reduction of the hippocampus occurs. Ekstrand and colleagues (2008) found that rats treated daily with injections of corticosterone (40 mg per kg of body weight) in sesame oil for 2 weeks had fewer new endothelial cells in the hippocampus than rats in the control group, who received injections of only sesame oil for same length of time (corticosterone group: $M = 100$, $SD = 15$, control group: $M = 1{,}294$, $SD = 128$; $t = 8.9$, $p < 0.0001$). Another study (Magariños et al., 1997) found that compared to a control group of rats kept in a cage for 3 weeks, rats restrained in a wire mesh restraint fastened to their head and tail 6 hours a

day for 3 weeks had less area covered by the synaptic vesicles in their hippocampi (M = 5.05 mm^2, SD = 0.32 and M = 1.84 mm^2, SD = 0.15, respectively, $p < .01$, t value not reported).

Chronic stress has also been linked to memory impairment in animal studies. Sotiropoulos and colleagues (2011) found that stress, especially stress in the presence of amyloid β, leads to diminished hippocampus-dependent spatial reference memory in a Morris Water Maze. This procedure involves placing rats a circular tank with black water and a small black platform 1 cm below the surface of the water. Because rats are naturally averse to swimming, they tend to swim only as long as necessary to find the platform. After having rats practice for four trials per day for four days, stressed rats that were given amyloid β injections ($p < .05$) and rats that were given amyloid β and glucocorticoid injections ($p < .00001$) swam longer than control rats.

Stress is also linked to AD pathology. For instance, Sotiropoulos and colleagues (2011) found that, compared to a control group of rats who were kept in a cage for 1 month, rats receiving daily stressors for 1 month, which stressors included doses of hypertonic saline (1 ml per 100 g of body weight), overcrowding for 1 hour, being placed in a confined environment, and being placed on a vibrating and rocking platform, had increased phosphorylation of TAU at the pSer202, pThr231, pSer396/404, and pSer409 regions of the hippocampus, which pathology mediates the relationship between amyloid deposition and senile plaque formation, and leads to neurofibrillary tangles. In addition, Kang and colleagues (2007) found that APP transgenic mice subjected to isolation stress by being kept alone for 3 months in a cage a third the size of a standard cage had 84% greater amyloid β levels in brain interstitial fluid than APP transgenic control mice kept

in standard conditions—with 2-5 mice in a standard-sized cage for the same period of time. Green and colleagues (2006) found that APP transgenic mice given daily injections of dexamethasone, a synthetic glucocorticoid, had 60% greater amyloid β levels than APP transgenic control mice. Also, Dong and colleagues (2004) found that APP transgenic mice subjected to the same isolation stress as the mice in Kang and colleagues had many more neuritic plaques than APP transgenic control mice; isolated group: M = 279, SD = 21; control group: M = 13, SD = 6; $F(3) = 22.4$, $p < .001$, MS not reported.

Human Studies

Studies conducted among humans also found chronic stress to be associated with changes to the central nervous system. Lupien and colleagues (1998) assessed cortisol levels among elderly persons during a 24-hour period once a year for 5 years and found that persons classified as having high cortisol levels at baseline and whose cortisol levels increased during the study period had lower hippocampal volume; $M = 4.0$ cm^3, SE = 0.08 $t(9) = 25.1$, $p < 0.001$, than persons classified as having moderate cortisol levels at baseline and whose cortisol levels decreased during the study period ($M = 4.54$ cm^3, SE = 0.13). Lindauer and colleagues (2006) found that police officers with PTSD had smaller left and right hippocampal volume than age/gender-matched control officers who did not have PTSD but had experienced traumatic events; $F(2)= 5.18$, $p = .015$; left hemisphere: $M = 2.0$ cm^3, $SD = 0.3$ in officers with PTSD versus $M = 2.4$ cm^3, $SD = 0.2$ in officers without PTSD; right hemisphere: $M = 2.2$ cm^3, $SD = 0.2$ versus 2.4 cm^3, $SD = 0.3$. Other studies have also linked PTSD and hippocampal volume. Villarreal and colleagues (2002) found that PTSD patients had lower left (PTSD patients: $M = 2.95$ cm^3, $SD = .31$;

controls: $M = 3.38$ cm^3, $SD = .49$, $p = 0.044$) and right (PTSD patients: $M = 3.01$ cm^3, $SD = .29$; controls: $M = 3.35$ cm^3, $SD = .37$, $p = 0.024$) absolute hippocampal volume than controls matched on age, gender, race, height, years of education, estimated intelligence quotient, handedness and lifetime weeks of alcohol intoxication. Bremner and colleagues (2003) found that women with early childhood sexual abuse and PTSD had left hippocampal volumes that were 15% smaller than women with early childhood sexual abuse but without PTSD ($M = 973$ mm^3, $SD = 162$ and $M = 1150$ mm^3, $SD = 189$, respectively) and 17% smaller than women without abuse or PTSD ($M = 1160$ mm^3, $SD = 205$). These women also had right hippocampal volumes that were 16% smaller than women with abuse but not PTSD ($M = 915$ mm^3, $SD = 179$ and $M = 1101$ mm^3, $SD = 174$) and 22% smaller than women without abuse or PTSD ($M = 1180$ mm^3, $SD = 213$).

Similar to animal studies, studies on humans found chronic stress to be related to diminished performance on cognitive tests. In a sample of elderly participants ($M = 78.6$ years, $SD = 6.0$), Peavy and colleagues (2007) found that subjects with one or more high stress events on the Life Events/Difficulties Scale (LEDS) exhibited slightly worse performance on the long delay free recall section of the California Verbal Learning Test (CVLT); high stress groups (means reported separately for ε4 positive and ε4 negative, respectively): $M = 7.1$, $SD = 4.3$ and $M = 6.9$, $SD = 3.2$; versus low stress groups: $M = 9.5$, $SD = 4.6$ and $M = 8.6$, $SD = 3.2$; $F(1,83) = 6.0$, $p = .02$. This stressed group also showed poorer performance on the visual reproduction delay section of the Wechsler Memory Scale-Revised (WMS-R); high stress groups: $M = 5.6$, $SD = 4.3$ and $M = 9.7$, $SD = 4.3$ versus low stress groups: $M = 9.1$, $SD = 4.3$ and $M = 10.3$, $SD = 3.6$; $F(1,82) = 4.4$, $p = .04$;, and on the memory subscale of the Dementia Rating Scale (DRS); high stress

groups: $M = 22.3$, $SD = 3.2$ and $M = 23.9$, $SD = 1.7$ versus low stress groups: $M = 23.9$, $SD = 2.3$ and $M = 24.1$, $SD = 0.88$; $F(1,83) = 3.9$, $p = .05$. The authors also found a significant stress by APOE ε4 allele interaction, with those having high overall stress on the LED and at least one APOE ε4 allele exhibiting the worst performance. This ε4 positive, high stressed group had WMS-R immediate memory means (and standard deviations) of 19.2 (7.2), compared to 26.2 (8.2), 26.4 (10.4), and 25.6 (7.5) for those who were high stress ε4 negative, low stress ε4 positive, and low stress ε4 negative, respectively; $F(1,83) = 5.2$, $p = .03$). They also had MWS-R delayed memory means and standard deviations of 14.1 (9.3), compared to 21.5 (9.4), 23.3 (12.7), and 21.1 (8.5); $F(1,83) = 5.5$; $p = .02$, and CVLT Recognition False-Positive means and standard deviations of 4.7 (4.4), compared to 2.0 (2.5), 2.7 (4.5), and 3.2 (3.3), $F(1,83) = 4.3$,$p = .04$), again as compared to those who were high stress ε4 negative, low stress ε4 positive, and low stress ε4 negative, respectively. Another study (Starkman, Giordani, Berent, Schork, & Schteingart, 2001) found that persons with Cushing's disease (CD), a condition marked by elevated cortisol levels, had lower scores than controls on all cognitive measures tested. This included the WAIS-R verbal IQ (CD patients: $M = 96.2$, $SD = 13.0$; controls: $M = 106.2$, $SD = 9.2$; $F = 12.8$, $p < .001$), the WAIS-R performance IQ (CD patients: $M = 97.7$, $SD = 12.7$; controls: $M = 108.4$, $SD = 12.1$; $F = 16.4$, $p < .0001$), and the Wechsler Memory Scale (WMS) memory quotient (CD patients: $M = 104.2$, $SD = 16.4$; controls: $M = 119.3$, $SD = 14.9$; $F = 23.4$, $p < .0001$).

Other human studies have also found a relationship between stress and memory impairment. Lupien and colleagues (1998) found that persons classified as having high cortisol levels at baseline and whose cortisol levels increased during the study period

performed worse on a test of delayed memory, $F(1,7) = 17.5$, $p < .01$, and had diminished spatial memory, $F(1,8) = 8.4$, $p < .05$, compared to persons classified as having moderate cortisol levels at baseline and whose cortisol levels decreased during the study period. In another study (Lupien et al., 1997) of elderly persons (men: $M = 73.3$, $SD = 7.9$ years old, women: $M = 71.3$, $SD = 5.9$ years old), scores on a declarative memory task decreased after subjects participated in a stressful task; public speaking: $F(1,12) = 6.11$; $p = 0.03$, but not after a nonstressful task (computer-generated activity in which participants identified a target on the screen). Rasmuson and colleagues (2001) found that those with mild to moderate AD had increased cortisol production ($M = 8727$ μ gram/24 hours, *SD* not reported) relative to healthy controls ($M = 2919$ μ gram/24 hours, *SD* not reported, $p < .01$). Another study (Elgh et al., 2006) found that among AD patients, decreased feedback sensitivity to stress, as measured by cortisol levels the morning after subjects were given an injection of dexamethasone (a synthetic glucocorticoid), was significantly related to the spatial span section of the WAIS-R neuropsychological instrument (WAIS-R NI; $r = .52$, $p = .037$).

Increased stress has also been linked with MCI and AD. Wilson and colleagues (2007) found that every one unit increase in the neuroticism scale of the NEO Five Factor Inventory, a measure the authors used to assess proneness to psychological distress, was associated with 2% increased risk of MCI (*RR* = 1.02; 95% *CI*: 1.01, 1.04). Individuals who were more prone to distress (those above the 90th percentile on the NEO) were 42% more likely to develop MCI than those not prone to distress (those below the 10th percentile). The authors also found a significant interaction between gender and neuroticism ($p = 0.02$); in which the association between these factors was stronger

among men. Wilson and colleagues (2005) obtained similar findings for AD. Using the same measure of neuroticism, this study found that every one unit increase in the neuroticism scale was associated with 6% increased risk of AD (*OR* = 1.06; 95% *CI*: 1.01, 1.11), with those prone to distress being 2.4 times more likely to develop AD than those not prone to distress. They also found a significant interaction between race and neuroticism; among White persons, every one unit increase in neuroticism was associated with a 12% increased risk of AD (*OR* = 1.12; 95% *CI*: 1.05, 1.19); whereas, among African American persons, neuroticism was not related to risk of AD (*OR* = 1.02; 95% *CI*: 0.97, 1.08).

Widowhood: A Profound Stressor Affecting Health Outcomes

Widowhood and Chronic Stress

In a hallmark study of stressful life events, Holmes and Rahe (1967) found that out of a list of 43 life events, including divorce, personal injury or illness, and being fired at work, respondents ranked death of a spouse as the life event requiring the most social readjustment. Similarly, S.E. Hardy and colleagues (2002) found that out of several late life stressors, including personal injury or illness, injury or illness of a friend, or some other nonmedical event (victimization, changing residence, divorce, unemployment), elderly participants most commonly (42%) reported death of a family member or friend as the most stressful event they had experienced in the previous 5 years.

Additional studies provide further evidence that widowhood is associated with increased stress and stress-related conditions, such as depression. One study (Gerritsen et al., 2009) found that elderly persons who had endured at least two stressful late life

events, with widowhood being one event that participants could select, exhibited higher morning cortisol levels than elderly persons who had endured fewer than two stressful life events (*OR* = 1.12, $p < .05$). Buckley and colleagues (2009) found that mid-to-late aged bereaved persons (*M* = 65.2, range 33-84), the majority of whom had lost spouses, were more angry (Range 15-60, bereaved: Median= 16.0, interquartile range [IQR]: 16.0-37.0; nonbereaved: Median = 15.0, IQR: 15.0-15.0, $p < .001$) and anxious (range 20-80; bereaved: *M* = 47.4, *SE* = 2.0; nonbereaved: *M* = 28.2, *SE* = 1.4, $p < .001$) on the Spielberger State Anxiety and Anger scales, compared to nonbereaved persons (*M* = 61.6 years old, range 36-87). Additionally, those experiencing recent bereavement slept fewer hours (bereaved: *M* = 5.88 hours, *SE* = 0.21; nonbereaved: *M* = 7.22 hours, *SE* = 0.16, $p < .001$) and had higher cortisol levels (in millimoles per liter: mmol/L; bereaved: *M* = 306 mmol/L, IQR: 247-414; nonbereaved: *M*= 266 mmol/L, IQR: 220-338, $p = .003$) at 2-weeks following their loved one's death than similarly aged nonbereaved persons. Importantly, among bereaved persons cortisol levels (Median=326 mmol/L, IQR: 236-390) remained high at six months following death, suggesting lasting associations between bereavement, particularly spousal bereavement, and these outcomes. However, one study (Gersten, 2008) found that widowhood did not lead to increased stress, as assessed by neuroendocrine allostatic load (NAL), an indicator of the overall burden on the body imposed by cumulative stress, which is assessed by measuring levels of cortisol, epinephrine, and norepinephrine. The authors found that widowed persons did not have increased NAL, and that length of widowhood was not related to NAL.

A number of studies have found a link between widowhood and depression. Buckley et al. (2009) found that mid-to-late aged bereaved persons were more depressed

on the 60-point Centre for Epidemiological Studies-Depression (CES-D) questionnaire (M = 26.7, SD = 1.7) than nonbereaved persons (M = 5.9, SD = 0.7, $p < .001$), and that among bereaved persons depression levels remained high at six months following death (M = 16.8, SD = 6.2). Hughes and Waite (2009) found that widowed and divorced people had worse CES-D depression symptoms (OR = 1.2, $p < .001$) than currently married persons. De Beurs and colleagues (2001) found that among a group of initially nondepressed elderly persons, those who lost a spouse between baseline and a 3-year follow-up were more likely to develop depression, than elderly persons who had not lost a spouse (OR = 2.5, 95% CI: 1.2-5.2). Schultz and colleagues (2001) found that depression status after widowhood depended on caregiver status. Using a sample of widowed persons, they found that widowed persons who were not caregivers before their spouses' deaths exhibited increased depression on a 10-item version of the 30-point CES-D; prebereaved: M = 4.74, SD = 3.87 and postbereaved: M = 8.25, SD = 6.64, $F(1, 116)$ = 14.33, $p < .001$; as did also caregivers who were not strained (those whose spouses had at least one ADL or IADL and who reported helping their spouse with this activity, but who reported that this assistance did not cause mental or emotional strain); prebereaved: M = 4.94, SD =5.44 and postbereaved: M = 7.13, SD = 5.38, $F(1, 116)$ = 4.35, p = .04). However, caregivers who were strained did not exhibit increased depression, possibly because depression was already high before their spouses died, such that depression decreased slightly after the caregiving duties ended (prebereaved: M = 9.44, SD = 6.04 and postbereaved: M = 9.19, SD = 5.87).

Evidence also suggests that this relationship is moderated by gender. Lee, DeMaris, Bavin, and Sullivan (2001) found that in unadjusted models, widowhood

interacted with gender (β = 4.29, $p < .05$), in that scores on a 12 item version of the CES-D (range 0-84) were higher in men who were widowed at baseline, compared to men who were married at baseline (M =17.37 and 11.15, respectively, SDs not reported), but were not higher in women widowed at baseline, compared to women married (M = 17.22 and 15.29). In models adjusted for time since widowhood, frequency of church attendance, and dislike of domestic labor, this interaction lost significance. Together, these findings suggest that death of a spouse is associated with chronic stress and conditions related to chronic stress, such as anxiety, anger, reduced sleep, and depression. This is particularly concerning given that a recent meta-analysis (Otte et al., 2005) found that older persons also tend to have higher cortisol responses to drugs that elicit a stress response (e.g., Dexamethasone) and psychological challenges (e.g., mental arithmetic in front of an audience, a cognitive computer-based task) than younger persons.

Widowhood and Adverse Health Outcomes

In addition to being linked to increased stress, several studies have found widowhood to be related to various adverse health outcomes (see Stroebe, Schut, & Stroebe, 2007), including stroke (Engström et al., 2004; Maselko et al., 2009; Öhgren et al., 2000; Simons et al., 1998), and to diminished self-care (Shahar, Schultz, Shahar, & Wing, 2001). For instance, Hughes and Waite (2009) found that widowed and divorced people had more chronic conditions (OR = 1.2, $p < .001$), more mobility limitations (OR = 1.23, $p < .001$), poorer self-rated health (OR = 1.52, $p < .001$), and worse CES-D depression symptoms (OR = 1.2, $p < .001$) than currently married persons. Using logistic regression models that controlled for sex, educational status, and whether the subject

lived alone, Bradbeer and colleagues (2003) found that compared with nonwidowed subjects, widowed subjects were more likely to report that they were currently experiencing moderate to severe pain (*OR* = 3.1, 95% *CI*: 1.6-5.8) and strong to severe current pain (*OR* = 3.4, 95% *CI*: 1.1-10.4), and that pain limited their daily activities (*OR* = 1.5, 95% *CI*: 1.1-1.9). The authors also used path analysis to explore the relationship between widowhood and physical pain. They found that widowhood led to mood disturbance ($r = .21$, $p < 0.001$), as assessed by a 12-item subscale of the Psychogeriatric Assessment Scales and two questions about the frequency of positive and negative mood, and that this mood disturbance in turn led to pain severity ($r = .42$, $p < 0.001$), with this model accounting for 17% of the variance. The authors speculated that these relationships could be attributed to social changes and mood changes associated with widowhood, such as living alone, lack of an intimate companion, depression, and endorphin activity.

Studies have also found widowhood to be related to stroke. In Maselko and colleagues (2009), researchers found that among men, widowhood was associated with increased risk for stroke (*HR* = 1.53, 95% *CI*: 1.24, 1.89), even after inclusion of SES factors, behavioral risk factors, and chronic conditions, though the strength of this association was reduced with inclusion of these factors. Among women, widowhood was also associated with increased risk for stroke (*HR* = 1.33, 95% *CI*: 1.17-1.51), though this association lost significance with inclusion of chronic conditions. Simons and colleagues (1998) found that those who were currently married were 30% and 54% less likely to suffer an ischemic stroke or a fatal ischemic stroke, respectively, than those who were widowed, divorced, or never married (*HR* = 0.70, 95% *CI*: 0.54-0.91 and *HR* = 0.46, 95% *CI*: 0.28-0.76). They also found that marital status interacted with gender in predicting

ischemic stroke, in that women (*HR* = 0.54, 95% *CI*: 0.36-0.82) but not men (*HR* = 0.85, 95% *CI*: 0.60-1.25) who were currently married were at decreased risk, relative to women and men who were widowed, divorced, or never married. Another study (Öhgren et al., 2000) also found that those who were widowed, divorced, or never married were at increased risk of stroke relative to those who were married (*OR* = 2.0, 95% *CI*: 1.04-3.9). Engström and colleagues (2004) found that widowed women were at greater risk for stroke than married women (*RR* = 1.13, 95% *CI*: 1.02-1.24). Among men, this association had an equivalent effect size but was nonsignificant (*RR* = 1.13, 95% *CI*: 0.99-1.28). These studies indicate that widowhood is associated with stroke. This is particularly concerning given that stroke can lead to vascular dementia (Barba et al., 2000), which is a common type of dementia (Dubois & Hebert, 2001).

Studies have found widowhood to be associated with diminished self-care as well. In a longitudinal study by Shahar and colleagues (2001) it was found that in the year after widowhood, and in the 6 years between baseline and follow-up, widowed persons lost 2.03 lb (*SD* = 8.13) and 1.4 lb (*SD* = 4.38) on average; whereas, married persons matched on age, sex, and race gained .41 lb (*SD* = 4.0) and 2.4 lb (*SD* = 0.8, $p < .045$ and $p < .02$). The authors also found that widowed persons consumed less vitamin A; widowed: *M* = 3,625 international units (IU), *SD* = 5,757; married: *M* = 5,404 IU, *SD* = 5,757; $p = .04$, and vitamin E; widowed: *M* = 67.5 IU, *SD* = 146.7; married: *M* = 149.8 IU, *SD* = 146.7; $p = .01$). In addition, widowed persons ate more meals alone per week; widowed: *M* = 15.9, *SD* = 6.7; married: *M* = 3.8, *SD* = 4.5; $p < .001$), ate more commercially prepared meals per week; widowed: *M* = 2.0, *SD* = 1.0; married: *M* = 1.0, *SD* = 0.77; $p = .04$), ate fewer homemade foods per week (widowed: *M* = 3.7, *SD* = 0.78; married: *M* = 4.3, *SD* =

1.28; p = .002), and reported that they enjoyed eating less; widowed: M = 3.8, SD = 0.65; married: M = 4.21, SD = 0.45; p = .003).

Widowhood and Late-Life Cognitive Status

Association of Widowhood with Cognitive Functioning and Rate of Decline

Aartsen and colleagues (2005) looked at the relationship between widowhood and memory functioning in a sample of elderly persons (M = 70.3 years, SD = 6.6), as assessed by the 15 Words Test, which measures immediate recall of words and recall of words after a 20-minute delay. The authors found that among men, but not women, those who were widowed between baseline and an 8-year follow-up were more likely to have diminished immediate and delayed word recall at follow-up than those who had not been widowed (men: chi square = 6.4, $p < .05$; women: chi square = 2.3, p = .13). However, when these same outcomes were measured with continuous scales, gender no longer significantly moderated the effect of widowhood. In addition, researchers also found that length of widowhood was not related to the rate of change in memory performance in structural equation models, and that this association did not depend on gender. However, these models did find that this association depended on depression, in that widowed persons who were more depressed at baseline declined more than widowed persons who were not depressed at baseline.

Van Gelder and colleagues (2006) found that in a sample of elderly men (mean age at baseline = 76.1, standard deviation not reported), change in marital status in the 5 years previous to the study was related to increased decline in cognitive functioning over

the course of a 10-year observation period, as assessed by changes in Mini-Mental State Examination scores (MMSE, range 0-30). Using multiple regression models, they found that those who were married at both times exhibited a 1.1 point decrease in cognitive functioning (1990 MMSE: *M* = 25.8, *SD* = 2.7; 2000 MMSE: *M* = 24.7, *SD* not reported), and that those who were divorced or widowed during the 5 years preceding the study (1985-1990) exhibited 1.0 point additional decline on the MMSE (95% *CI*: 0.1-1.9; 1990 MMSE: *M* = 25.4, *SD* = 2.7; 2000 MMSE: *M* = 23.7, *SD* not reported) over the subsequent 10 years than persons who remained married.

Other studies also found a relationship between widowhood and cognitive decline. An 8-year longitudinal study (Karlamangla et al., 2009) found that total cognition scores, as well as word recall scores, as assessed by the telephone interview for cognitive status, declined faster among widowed persons (total cognition: β = -0.79, 95% *CI*: -1.5, -.08; word recall: β = -0.64, 95% *CI*: -1.15, -0.13) than among married persons. They also found that this association did not depend on gender. In a 12 year longitudinal study, Lee and colleagues (2011) found that in a sample of married persons without dementia, persons experiencing death of spouse after baseline had Modified Mini Mental State (3MS; Teng & Chui, 1987), scores that were 1.5 points higher on average immediately after widowhood than married person. However, subsequent to this period widowed persons exhibited faster rate of cognitive decline (0.3 points faster per year on average) than married persons ($p < 0.0001$). They also found that this relationship was not moderated by history of depression, as assessed by the Diagnostic Interview Schedule, or presence of one or two ε4 alleles at APOE.

Some studies did not find an overall association between widowhood and

cognitive decline, but did find significant moderation of this relationship. Rosnick and colleagues (2010) conducted a longitudinal study that compared persons bereaved at baseline and at a 6-month follow-up with persons who were not bereaved at either of these points, and who were matched to bereaved persons on age and sex. Cognitive performance was assessed via measures of episodic memory (immediate and delayed story recall), spatial memory, verbal ability (Boston Naming Test), reasoning (Similarities task of the WAIS-R), and visuospatial ability (copying objects), with standardized scores from each of the tests summed to produce an overall cognitive score. They found that bereavement was not related to any measure of cognitive performance. However, they did find a significant bereavement by age interaction on immediate story recall ($\beta = 0.34$, $p < .001$) and delayed story recall ($\beta = 0.31$, $p < .001$), in which the magnitude of the difference between bereaved and nonbereaved persons increased with decreasing age. They also found a significant bereavement by gender interaction on immediate story recall ($\beta = 0.93$, $p < .01$), in which bereaved men, but not bereaved women, had lower scores on this measure than their nonbereaved counterparts. To further understand these interactions, the authors compared males and females, and younger versus older persons (age groups dichotomized at the median age), in terms of social support, spouse's age at death, duration of time in which they knew that their spouse was dying, whether they cared for the dying spouse, the stressfulness of caregiving, and self-rated health. The authors did not report statistics for these analyses, but reported that there were no significant relationships. Sachs-Ericsson and colleagues (2010) found that APOE status (ε4 carrier versus noncarrier) moderated the relationship between number of negative life events (including widowhood) and cognitive impairment (as per the Short

Portable Mental Status Questionnaire, $OR = 1.3$, $p < .01$ for interaction). In stratified models, number of negative life events predicted cognitive impairment ($OR = 1.32$, $p < .017$) among APOE ε4 carriers, but not among APOE ε4 noncarriers.

Some studies found a relationship between widowhood and cognitive decline, but also found that this relationship was not robust to inclusion of covariates. Ward and colleagues (2007) found significant relationships between bereavement and various measures of cognitive function, including attention (visual elevator subtest of the Test of Everyday Attention—TEA); speed, sequencing, mental flexibility, visual search, and motor function (Trail Making Test, versions A and B); verbal fluency (Controlled Oral Word Association Test-COWA); and information processing (Symbol Digit); though most of these associations were not robust to adjustment for mood (the Depression Anxiety Stress Scales—DASS). In this study, researchers compared recently bereaved persons (past 18 months) with persons not bereaved during that time (matched on age, gender, education, and estimated premorbid IQ). Bereaved persons had poorer scores than nonbereaved persons on the visual elevator subtest of the TEA, $t(48) = 2.11$, $p < 0.05$, Cohen's $d = 0.6$; on the Trail Making Test versions A, $t(48) = 2.48$, $p < 0.05$, Cohen's $d = 0.7$; and B, $t(48) = 2.28$, $p < 0.05$, Cohen's $d = 0.7$; and on the COWA, $t(48) = 2.50$, $p < 0.05$, Cohen's d=0.7; and Symbol Digit, $t(48) = 3.20$, $p < 0.01$, Cohen's d =0.9, tests. However, when these associations were tested in hierarchical regression models that controlled for aspects of mood (depression, anxiety, or stress) that were related to the various measures of cognitive function in Pearson correlations, the association between bereavement and these cognitive tests was no longer significant. These results may indicate that widowhood is associated with cognitive status via

increases in depression, anxiety, and stress that in turn affect cognitive functioning.

Still other studies found no relationship between widowhood and cognitive decline. A cross-sectional study by Rosnick and colleagues (2007) looked at the associated between 54 negative life events, including widowhood, with events rated in terms of their occurrence in the previous year and their impact (1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = strong effect), and measures of episodic memory (Hopkins Verbal Learning Test), psychomotor speed (Trailmaking Test, Versions A and B), and attention (Stroop Test). The authors found that occurrence of widowhood and the subjective rating of its impact were not related to any measure of cognitive performance in correlational analyses. Also, Comijs and colleagues (2011) conducted a study including two waves of cognitive assessment spaced 4 years apart, testing the effect of death or divorce (categories were combined) on rate of cognitive decline, as assessed by changes on the Mini-Mental State Examination (MMSE), a Dutch version of the Auditory Verbal Learning Test (AVLT), and information processing speed, as assessed by the Alphabet Coding Task-15. The authors found that continuously married persons did not significantly differ from widowed/divorced persons on these measures of decline.

Widowhood Association with Dementia

Other studies examining the relationship between widowhood and cognitive status focused on dementia as the outcome. In one prospective longitudinal study (Hakansson et al., 2009), researchers found significant relationships between marital history at two time points (mid-life and later life) and dementia at later life. Mild cognitive impairment (MCI) and AD were assessed via a three-stage dementia diagnosis protocol, consisting of

a screening phase (MMSE), a clinical phase (various cardiovascular, neurological, and neuropsychological assessments; an expert review board that reviewed this testing), and a differential diagnostic phase (MRI of the brain, final diagnosis from review board). In addition to MCI and AD, the authors designated a category that consisted of persons with any cognitive impairment. Using logistic regression models, they found that persons living without a partner (single, widowed, or divorced) at mid-life had higher risk of any cognitive impairment (*OR* = 2.09, 95% *CI*: 1.3 to 3.4) and MCI (*OR* = 2.14, 95% *CI*: 1.2 to 3.8), but not AD, than those living with a partner (married or cohabitating) at midlife. This risk appeared to be higher for those who were widowed at midlife than for those who were single or divorced at midlife (any cognitive impairment: *OR* = 2.76, 95% *CI*: 1.5 to 5.2; MCI: *OR* = 3.0, 95% CI: 1.6 to 6.9; AD not significant). The study also found that persons with a partner at midlife but not in later life were somewhat more likely to have any cognitive impairment (*OR*: 1.60, 95% *CI*: 1.0 to 2.7) but not more likely to have MCI or AD, compared to persons living without a partner at midlife. Given that this OR is lower than the OR of persons who lacked a partner at midlife, this suggests that lack of a partner at midlife is more detrimental than lack of a partner in later life. In addition, persons without a partner, and especially those who were widowed, at midlife and later in life were at particularly high risk relative to those cohabitating at both times (no partner at both times: any cognitive impairment *OR*=2.89, CI= 1.7 to 5.0; MCI: *OR*= 3.17, *CI*: 1.7 to 60; AD *OR* = 2.83, *CI*= 1.1 to 7.4; widowed at both times: any cognitive impairment *OR* = 3.53, *CI*= 1.7 to 7.4; AD *OR* = 7.67, *CI* = 1.6 to 40.0), suggesting that being continuously without a partner, especially being continuously widowed, is associated with greater risk than being without a partner only at midlife.

Another study (Fratiglioni et al., 2000) found a relationship between widowhood and dementia, but this relationship was not robust to inclusion of covariates. In this study, researchers found that being widowed at baseline was associated with increased risk for incident dementia over a 3-year follow-up period in unadjusted (*RR* = 1.6, 95% *CI*: 1.1-2.3) models. However, the association was no longer significant after adjustment for social network variables, which included living arrangements (living with a partner, children, siblings, or other persons, or living alone); frequency of contact with children, relatives, and friends; and satisfaction with such contact. These findings indicate that increased frequency of and satisfaction with social support may buffer the association between widowhood and dementia or AD. Helmer and colleagues (1999) looked at the association between time-varying marital status measurement and risk for dementia and AD, with AD assessed via a multistage diagnosis protocol, including standardized questionnaires (names of questionnaires not specified) measuring memory impairment, other cognitive functioning, and social and occupational functioning, and review by a neurologist. While being never married was associated with higher risk for dementia (*RR* = 1.91, 95% *CI*: 1.12, 3.25) and AD (*RR* = 2.68, 95% *CI*: 1.49, 4.81), being widowed was not associated with increased risk for either.

Reconciling Conflicts Among Previous Findings

Differences in subject and study characteristics between previous studies may explain why some found relationships, or moderated relationships, between widowhood and cognitive outcomes including AD and dementia, while others did not. In general, studies that used more complete marital histories found significant associations between

widowhood and cognitive impairment (see Table 2.1; Aartsen et al., 2005; Hakansson et al., 2009; Karlamangla et al., 2009; H. B. Lee et al., 2011; Van Gelder et al., 2006), while studies that used shorter/less complete marital histories found only moderated associations or no associations between widowhood and cognitive functioning (Comijs et al., 2011; Fratiglioni et al., 2000; Rosnick et al., 2007, 2010; Sachs-Ericsson et al., 2010; Ward et al., 2007).

Presence of relationships or moderated relationships between widowhood and dementia or AD also depended on length of cognitive follow-up (Table 2.1). Studies that used longer periods of cognitive follow-up found significant associations, or moderated relationships, between widowhood and cognitive impairment (Aartsen et al., 2005; Karlamangla et al., 2009; H. B. Lee et al., 2011; Sachs-Ericsson et al., 2010; Van Gelder et al., 2006). In contrast, studies that used shorter periods of cognitive observation found no associations between widowhood and cognitive functioning (Comijs et al., 2011; Fratiglioni et al., 2000; Rosnick et al., 2007; Ward et al., 2007).

Other subject and study characteristics, including sample mean age and percentage of sample that was female (Table 2.2), and the types of covariates entered into the models, did not seem to be related to significance of the association between widowhood and cognitive outcomes. For instance, age was controlled for in studies that found relationships or moderated relationships (Aartsen et al., 2005; Hakansson et al., 2009; Karlamangla et al., 2009; Rosnick et al., 2010; Sachs-Ericsson et al., 2010; Van Gelder et al., 2006) as well as in studies that didn't find relationships (Comijs et al., 2011; Fratiglioni et al., 2000; Helmer et al., 1999; Rosnick et al., 2007; Ward et al., 2007). Inclusion of education, gender, and depression was similarly unrelated to outcome.

Table 2.1

Studies of Widowhood and Cognitive Outcomes: Length of Observation Period and Study Outcome

Study	Span of marital history (Hx) [a]	Observation period, in years [a] (number of measurement points)	Widowhood related to cognitive impairment?	Widowhood related to dementia or AD?
Aartsen et al. (2005)	6 years (during period of observation)	6 (3)	Yes	
Comijs et al. (2011)	4 years (during period of observation)	4 (2)	No	
Fratiglioni et al. (2009)	1 time point (baseline)	3 (2)		Not in adjusted models
Hakannson et al. (2009)	Midlife and later life (baseline)	cross-sectional		Yes
Helmer et al. (1999)	5 years (during period of observation)	5 (3)		No
Karlamanga et al. (2009)	8 years (during period of observation)	8 (4)	Yes	
H.B. Lee et al. (2011)	10 years (during period of observation)	10 (3)	Yes	
Rosnick et al. (2007)	1 year	1 measurement point	No	
Rosnick et al. (2010)	1 time point (baseline)	1 measurement point	Moderated relationship only	
Sachs-Ericsson et al. (2010)	1 year	10 (4)	Moderated relationship only	
Van Gelder et al. (2006)	5 years	10 (3)	Yes	
Ward et al. (2007)	18 months	1 measurement point	Not in adjusted models	

[a] All periods of marital history observation occurred prior to observation period unless otherwise specified.

Table 2.2

Mean Age, Percent Female, and Study Outcome

Study	Mean age at baseline[a]	Percent female	Widowhood related to cognitive impairment?
Aartsen et al. (2005)	70.3	41.3	yes
Comijs et al. (2011)	72.5	51.3	no
Fratiglioni et al., 2009	75+	74.6	not in adjusted models
Hakannson et al. (2009)	71.3	62.0	yes
Helmer et al. (1999)	65+	58.0	no
Karlamanga et al. (2009)	74.9	63.4	yes
H.B. Lee et al. (2011)	65+	N/S[b]	yes
Rosnick et al. (2007)	73	50.5	no
Rosnick et al. (2010)	70	85.0	moderated relationship only
Sachs-Ericsson et al. (2010)	65+	67.0	moderated relationship only
Van Gelder et al. (2006)	75.2	0.0	yes
Ward et al. (2007)	71.1	72.0	not in adjusted models

[a]Minimum eligible age reported for studies that did not report mean age.
[b]N/S = not specified.

Limitations of Previous Findings

The above studies are few in number and have several methodological limitations. Although some studies assessed marital history more fully than others, in all of these studies, marital status was assessed at limited time points. Not incorporating full marital history can result in failure to capture all widowhood experiences that, while years in the past, may have lingering adverse effects on health. Also, each of these studies used self-report to assess marital status. This poses a problem in that accurately assessing full marital history can be difficult among elderly persons with compromised cognitive functioning and when negative stigma might result in underreporting of prior marital changes. Also, these studies tended to use short periods of dementia observation, which

limits the number of AD or other dementia cases that can be studied and compromises statistical power, especially in tests of moderation (i.e., interaction effects).

In addition, although Helmer and colleagues (1999), Hakansson and colleagues (2009), and Fratiglioni and colleagues (2000) used dementia or AD as an outcome, the other studies (Aartsen et al., 2005; Comijs et al., 2011; Karlamangla et al., 2009; H. B. Lee et al., 2011; Rosnick et al., 2007, 2010; Sachs-Ericsson et al., 2010; Van Gelder et al., 2006; Ward et al., 2007) used cognitive decline as an outcome. Thus, inference regarding the association between widowhood and dementia or AD onset is not possible for the latter studies. Also, Sachs Ericsson and colleagues used only one measure of cognitive decline—the 10-item Short Portable Mental Status Questionnaire (SPMSQ). Finally, Van Gelder and colleagues used a sample of only males, which limits the study's ability to generalize findings to females.

Context of Widowhood

A number of widowhood-related factors may moderate the relationship between widowhood and adverse health outcomes, including dementia or AD. Studies have found that the relationships between bereavement and mortality (Manor & Eisenbach, 2003; Martikainen & Valkonen, 1996), and between bereavement and cognitive impairment (Rosnick et al., 2010), are more pronounced in younger people than in older people, indicating perhaps that bereavement is more normative in older populations, and thus less likely to be related to chronic stress and associated health impairments among older persons. Also, remarriage after widowhood may buffer this association, since men (but not women) who remarry after divorce or widowhood tend to be less depressed and more

satisfied with life than men who remain divorced or widowed (Williams, 2003). This may suggest that those who are able to remarry have personality traits, such as extraversion, that are associated with lower depression and greater marital quality. Alternatively, it may suggest that acquiring a new spouse lowers depression and increases life satisfaction, or perhaps that the new spouse monitors and intervenes in health-related issues. Manner of death may also moderate this relationship. One study (Carr et al., 2001) found that persons whose spouses had died suddenly had more intrusive thoughts about their deceased spouse and lower anxiety, and men whose wives died suddenly had considerably lower feelings of yearning for their deceased wife than men whose wives did not die suddenly. Another study (Miyabayashi & Yasuda, 2007) found that persons whose spouses had committed suicide had poorer general health on the General Health Questionnaire (GHQ), higher depression on the Self-Rating Questionnaire for Depression (SRQ-D), and felt more grief for the deceased spouse on the Miyabayashi Grief Measurement (MGM) scale than those whose spouse died because of illness. Number of dependent children at the time of widowhood may also moderate this relationship, in that having dependent children may exacerbate the stress associated with losing one's spouse. This is supported by findings indicating that widowed women with more dependent children are at higher risk of mortality than widowed women with fewer dependent children (Alter et al., 2007). In contrast, persons with adult children at the time of widowhood may be at decreased risk for dementia, given that older children could provide social support to buffer stress associated with widowhood. This hypothesis is supported by findings indicating that having more positive relationship experiences is associated with decreased allostatic load (Seeman, Singer, Ryff, Dienberg Love, & Levy-

Storms, 2002) and that among women, presence of male friend during an acute psychological stressor (the paced auditory serial addition test [PASAT], in which participants are instructed to complete arithmetic problems at increasingly faster rates over time) attenuates cardiovascular response (systolic blood pressure, diastolic blood pressure, and heart rate; Phillips, Gallagher, & Carroll, 2009). In addition, one recent study (Noël-Miller, 2010) found that widowed men with adult children were less likely to be institutionalized than widowed men without adult children, suggesting that support from adult children buffers the association between widowhood and institutionalization.

Other factors may also moderate this relationship. For instance, evidence suggests that widowhood has a stronger association with increased depression (G. R. Lee et al., 2001) and with diminished cognitive functioning (Aartsen et al., 2005; Rosnick et al., 2010) among men than among women. Genetic factors, such as ε4 allele at APOE, could also moderate this relationship, in that stress (Peavy et al., 2007) and negative life events, including widowhood (Sachs-Ericsson et al., 2010), have stronger associations with diminished memory performance in persons with at least one APOE ε4 allele. This relationship may also depend on distress proneness. Depression, which is somewhat common among the elderly (5.1% in women and 3.2% in men for any depression and 4.4% in women and 2.7% in men for major depression; Steffens et al., 2000) may indicate such proneness, in that persons with depression are less likely to use effective coping skills (Greenglass, Fiksenbaum, & Eaton, 2006) and would thus be less able to cope with stress. Indeed, Aartsen and colleagues (2005) found that cognitive functioning declined more among widowed persons who were depressed at baseline than among widowed persons who were not depressed at baseline. On the other hand, some evidence

suggests that antidepressant treatment can protect against hippocampal shrinkage (Sheline, Gado, & Kraemer, 2003) thus protecting against dementia, suggesting the need to examine depression with and without antidepressant treatment as potential moderators.

Summary

Due to their prevalence, their profound impact on quality of life, burden to families and their dramatic costs, dementia and AD are urgent public health problems. Past research has explored many of the mechanisms of AD, including β amyloid deposition; hyperphosphorylated tau; lipid metabolism; genes, including the APOE ε4 allele; neuroinflammation; cholinesterase; and oxidative stress. In addition to these mechanisms, research has also focused on the deleterious effects of chronic stress on CNS functioning. Though temporary stress is normal and promotes survival, chronic stress leads to hippocampal damage, hyperphosphorylated tau in the hippocampus, amyloid β deposition, and memory impairments. Studies have found widowhood to be ranked as the most stressful life event, and to be linked with chronic stress and a number of adverse health outcomes. This increased risk for adverse health outcomes among widowed persons may be due to the chronic stress and instrumental and social adaptations one must make after loss of spouse. Indeed, some studies, particularly those that utilized more complete marital histories and longer periods of dementia observation, have found widowhood to lead to dementia and AD, though methodological limitations in these studies preclude firm conclusions. To understand the relationship between widowhood and dementia or AD, it is crucial that studies use data from prospective, population-based studies that utilize a comprehensive clinical assessment protocol for

diagnosing dementia, and that they use full, objective marital histories. Studies on this relationship also benefit from inclusion of moderating contextual factors. A number of widowhood-related factors, such as age at widowhood, remarriage, manner of spousal death, and number of dependents at time of widowhood, as well as other factors, such as gender, ε4 allele at APOE, and distress proneness, as indicated by history of depression, have been found to moderate the relationship between widowhood and adverse health outcomes or dementia.

Research Questions

The study sought to answer the following research questions.

1. Do those who are widowed have higher risk of dementia or AD than persons who are never widowed? (Each outcome to be investigated separately.)

2. Does the association between widowhood and dementia or AD depend on the life stage during which the widowhood occurs, in that those who were widowed at younger ages are at greater risk for dementia or AD relative to those were never widowed than those at older ages?

3. Does the association between widowhood and dementia or AD depend on remarriage after widowhood, in that those who remarry after widowhood experience similar risk for dementia and AD as those who never widowed; whereas, those who do not remarry after widowhood experience increased risk?

4. Does the association between widowhood and dementia or AD depend on the spouse's manner of death, in that those whose spouse's death was anticipated (natural death) experienced the same or slightly higher risk for dementia or AD compared to those

who never married, whereas those whose spouse's death was unanticipated (homicide/ suicide/accidental death) have significantly higher risk of dementia or AD compared to those who were never widowed?

5. Does the association between widowhood and dementia or AD depend on number of dependent children at the time of widowhood, in that those with two or more children at widowhood have the highest risk of dementia or AD compared to those who never widowed?

6. Does the association between widowhood and dementia or AD depend on number of adult children at the time of widowhood, in that those with none or few adult children at widowhood have higher risk of dementia or AD compared to those who never widowed, whereas those with more adult children at widowhood do not have higher risk of dementia or AD?

7. Does the association between widowhood and dementia or AD depend on gender, in that widowed men have higher risk of dementia or AD compared with men who never widowed; whereas, widowed women do not have higher risk?

8. Does the association between widowhood and dementia or AD depend on presence of ε4 allele at APOE, in that widowed persons who have at least one APOE ε4 allele have higher risk of dementia or AD compared with persons who never widowed, whereas widowed persons who do not have an APOE ε4 allele do not have higher risk?

9. Does the association between widowhood and dementia or AD depend on history of depression and antidepressant use, in that widowed persons with a history of depression untreated with antidepressants have increased risk for dementia or AD compared to those who never widowed, whereas widowed persons who either have no

depression history or have received antidepressant treatment for their depression do not have increased risk for dementia or AD?

CHAPTER 3

METHODS

Subjects

This study utilized data from the CCMS, a large population-based study of the prevalence and incidence of AD and other dementias, as well as the genetic and environmental determinants of these conditions. CCMS was funded continuously from 1994-2011 by the National Institute on Aging (R01-AG-11380). Eligible participants included all residents of Cache County, Utah, aged 65 or older as of January 1, 1995. Participants were identified from Medicare enrollee lists provided by the Health Care Financing Administration (HCFA). Five thousand six hundred seventy-seven persons were invited to participate in this study, of which 5,092 (90%) agreed. This high rate of participation greatly reduces non-response bias, because non-responders tend to be less educated and tend to have greater cognitive impairment (Norton, Breitner, Welsh, & Wyse, 1994), known risk factors for AD and other dementias. Utilizing data from a population-based sample is also advantageous, in that these samples are more representative than clinic-based samples, which tend to over-represent persons who are married and have higher socioeconomic status (Kokmen, Özsarfati, Beard, O'Brien, & Rocca, 1996).

Characteristics of the population in Cache County make this sample well suited to prospective, longitudinal study. Persons in Cache County have low average rates of cancer (Merrill & Lyon, 2005), and high life expectancy (88.1 years and 85.7 years among females and males, respectively, compared to the national average of 78.5 and

71.5; Murray, Michaud, & McKenna, 1998) in part because of low poverty and high rates of physical activity in this region (Welsh-Bohmer et al., 2006), and in part because the majority of its seniors (91%) are members of The Church of Jesus Christ of Latter-day Saints (also known as the LDS or Mormon Church), which proscribes alcohol and tobacco use (Norton et al., 2006). Cache County also has low rates of chronic disease, which simplifies the differential diagnosis of dementia, particularly among the oldest old, as well as large families, which provide more opportunities for informant interviews, and low rates of in-and-out migration, which facilitate longitudinal data collection (Welsh-Bohmer et al., 2006).

Of the 5,092 persons who originally participated in CCMS, 359 prevalent dementia cases and 188 cases who did not complete the multi-stage dementia ascertainment protocol, were excluded. Also, in order to ensure that enough observation time has transpired to assess whether the outcome event has occurred, Cox regression removes cases whose observation period is shorter than the shortest survival time. This removed 573 cases that dropped out before the shortest survival time to dementia. These exclusions resulted in a sample of 3,972 subjects at baseline. To explore bias associated with missing marital history, I retained persons with missing or incomplete marital history. After these analyses were conducted, I excluded these 339 persons, resulting in 3,633 participants (548 participants with dementia and 3,085 participants without dementia) for models of all-cause dementia risk. In analyses assessing risk of AD, 179 cases with dementia but not AD were excluded in order to assess the specificity of effects to the neurodegenerative process of AD as compared to all-cause dementia, which incorporates other etiologies such as vascular dementia (also linked to stress). Removal

of these cases resulted in 3,454 persons (369 participants with AD and 3,085 participants without dementia). For analyses of incident widowhood exposure, I excluded persons who experienced a prevalent widowhood so as to study only initial exposure. This reduced the sample to 2,545 and 2,419 persons for analyses of all-cause dementia (344 participants with dementia and 2,201 participants without dementia) and AD (218 participants with AD and 2,201 participants without dementia).

Design

This dissertation is a prospective study of extant longitudinal data that explores the association between widowhood as the primary predictor variable and either AD or all-cause dementia as the outcome, in a population of elderly persons observed at four triennial "waves" of measurement spanning 13 years. Because this is a study of incident dementia, prevalent dementia cases have been removed.

Measurement

AD and Other Dementias

In each of the four CCMS triennial waves, three stages of dementia screening protocol were conducted: a cognitive screening, a clinical assessment, and a physician evaluation, which included laboratory tests and diagnostic imaging. At the cognitive screening, participants were administered a self-report 3MS examination (Tschanz et al., 2002), a 100-point adaptation of the Mini-Mental State Examination. If subjects were unable to complete this assessment, an informant was administered an Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE; Jorm, 1994). Individuals

who were screen positive on either 3MS or IQCODE were given a comprehensive clinical assessment (CA), as were persons selected to be in a designated control panel via a sampling procedure stratified by age, gender, and APOE genotype. The CA consisted of a brief neurological exam, a clinical history and Neuropsychiatric Inventory (NPI) from an informant, and a battery of neuropsychological testing administered by a trained psychometrician. After these tests were reviewed by a board-certified geriatric psychiatrist and a neuropsychologist with CCMS researchers in "case staffing" meetings, these physicians assigned participants working diagnoses of dementia (according to DSM-III-R criteria), other cognitive impairment that did not meet criteria for dementia, or non-case. Differential diagnoses of dementia included the following categories: definite AD, probable AD, possible AD (according to National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA; McKhann et al., 1984] criteria), or other categories of dementia. Those with a working diagnosis of dementia or prodromal AD were sent on to the physician evaluation and laboratory studies stage, after which physicians assigned participants a new working diagnosis. Following this, an expert panel consisting of a board-certified geriatric psychiatrist and a board-certified neurologist, neuropsychologist, and neuroscientist assigned final consensus diagnoses to participants from a list of 30 differential diagnostic categories. Where available (162 cases), diagnoses from neuropathological examination of donated brain tissue was also reviewed in the final expert consensus meeting. For purposes of this dissertation project, participants receiving any of the dementia codes as primary, secondary, tertiary, or quaternary diagnosis are considered positive for dementia, and participants receiving any of the codes for AD in

any diagnosis are considered positive for AD.

Widowhood

To assess widowhood, this study utilized the Utah Population Database (UPDB), one of the world's foremost linked genealogical databases. The central feature of this dataset is an extensive set of Utah family histories, derived from genealogical records of LDS and non-LDS persons amassed by the LDS church, which are linked with other data sets such as medical records, cancer records, birth and death certificates, driver's license records, and census records. UPDB linkage to CCMS has been completed, in which 99% of CCMS participants were successfully linked. A large advantage of this database is its objective birth, marriage, divorce, and death data, including dates, eliminating the need to rely on self-report with known problems of recall bias. UPDB contains a record for each marriage, with its accompanying marriage date, and divorce or widowhood date where applicable. A number of measures were undertaken to prepare this data for analysis. Because widowhood is being considered as an exposure variable, data restrictions were put in place to consider only widowhood events that preceded dementia onset. Also, because the UPDB contains death dates of spouses that do not distinguish between deaths of ex-spouses (i.e., spouses whom the participant had divorced) and deaths of current spouses (true widowhoods) programming was written to distinguish between these two types of spousal deaths, so as to include only true widowhoods.

For this study, I conducted separate analyses for prevalent versus incident widowhood exposure. Examining incident widowhood allowed me to characterize widowhood as a time-varying covariate, so as to capture persons not at risk at baseline

but at risk thereafter. In analyses of prevalent widowhood, all participants who experienced divorce, but not widowhood, were included in a separate category so as to distinguish them from continuously married persons. For prevalent widowhood, I used the following categories: those who had no prevalent widowhood exposures, those who had divorced but had no prevalent widowhood exposures, and persons who had one or more prevalent widowhood exposures. I also included a category for those with missing or incomplete marital histories, so as to assess in exploratory data analyses whether missingness is related to any variable of interest.

Context of Widowhood

Variables reflecting the context of widowhood were also derived. The timing of initial prevalent widowhood was examined by comparing those who were never widowed with those who were widowed at various ages, using age intervals that corresponded with developmental life stages. These stages included emerging adulthood, young adulthood, middle adulthood, and late-life (widowed at age 24 or younger, 25-45, 46-64, 65 or older). Programming work also indicated whether remarriage after widowhood had occurred. Taken together, categories for this variable included: never widowed, divorced but never widowed, widowhood without remarriage, and widowhood with remarriage. In addition to marriage and widowhood dates, the UPDB also includes data on manner of death for decedents. This permitted the creation of a "manner of death" contextual variable with categories including: never widowed, divorced but never widowed, widowhood due to natural causes, widowhood due to homicide/suicide/accidental death. In addition, the UPDB furnishes birth and death dates for participants' children. These

were compared to subject's date of widowhood to determine whether, at the time of spouse's death, the subject had none, one, or two or more children 18 or younger ("dependents"), or none, one or two, three or four, or five or more adult children.

Additional CCMS and UPDB variables were explored as potential moderators. Gender was noted at the Wave 1 CCMS screening visit. APOE genotype was also assessed at the Wave 1 screening visit through collection of buccal DNA, processed through polymerase chain reaction (PCR) amplification and a restriction isotyping method described by Saunders and colleagues (1993). In addition to being tested as a potential moderator, this factor was entered as a covariate.

To assess history of depression and antidepressant use, I used the Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, & Ratcliff, 1981) and the CCMS medication inventory, respectively. The DIS was collected at the Wave 1 screening visit. This measure yields lifetime and recent diagnoses of depression. Robins and colleagues found that the DIS achieved adequate agreement with depression diagnosis from a psychiatrist ($\kappa = .63$), as well as adequate sensitivity (80%) and specificity (84%). Participants were considered to have a history of depression if they had an episode of major depression before the onset of dementia. Because depression is a common symptom of dementia, and because some measurement error may occur in dating dementia onset, only major depressive episodes and antidepressant use that occurred at least 1 year before dementia onset was used to indicate a history of depression (Norton et al., 2006). At the Wave 1 screening visit, antidepressant use from birth to Wave 1 was recorded, and at each of three additional triennial waves of dementia ascertainment antidepressant use in the preceding interval was recorded, yielding a lifetime history of

antidepressant use. All references to "antidepressant use" thenceforth in this document pertain to lifetime use. Table 3.1 lists the antidepressant medications that indicated antidepressant use. History of depression was combined with antidepressant use, by categorizing participants into one of four groups based on whether or not they met major depression criteria per DIS and whether or not they had ever taken antidepressants.

Covariates

Exploratory data analyses (EDA) were used to assess whether potential confounders were included in Cox models. Potential confounders were entered as covariates if they correlated with both prevalent widowhood and dementia or AD. Because education and occupation may confound the relationship between widowhood and dementia or AD, these factors were assessed in EDA. Information on these variables was obtained at the Wave 1 screening visit. To assess occupation, subjects were asked to list all occupations they worked in for more than 5 years. Of these, the occupation of longest duration was identified, and the Dictionary of Occupational Titles (U.S. Department of Labor, 1991) was used to categorize this into one of nine groups: professional, technical, and managerial; clerical and sales; service; agricultural, fishery, forestry, and related occupations; processing; machine trades; benchwork; structural work; and miscellaneous. In addition, a tenth category was added to identify persons who never had a job outside of the home. Age and gender were also assessed, since evidence indicates not only that these factors may moderate the relationship between widowhood and dementia and AD, but also that they may confound this relationship, since risk of both widowhood and dementia and AD tend to increase with age and female gender.

Table 3.1

Antidepressant Medications Defining "Antidepressant Use"

Drug name	Brand names
Bupropion Hydrochloride	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban SR
Duloxetine Hydrochloride	Cymbalta
Nefazodone Hydrochloride	Serzone
Trazodone Hydrochloride	Desyrel, Desyrel Dividose
Venlafaxine Hydrochloride	Effexor, Effexor XR
Isocarboxazid	Marplan
Phenelzine Sulfate	Nardil
Tranylcypromine Sulfate	Parnate
Citalopram Hydrobromide	Celexa
Escitalopram Oxalate	Lexapro
Fluoxetine Hydrochloride	Prozac, Prozac Weekly, Rapiflux, Sarafem
Fluvoxamine Maleate	Luvox
Olanzapine, Fluoxetine Hydrochloride	Symbyax
Paroxetine Hydrochloride	Paxil, Paxil CR, Pexeva
Sertraline Hydrochloride	Zoloft
Maprotiline Hydrochloride	Ludiomil
Mirtazapine	Remeron, Remeron SolTab
Amitriptyline Hydrochloride	Elavil, Vanatrip
Amitriptyline Hydrochloride, Chlordiazepoxide	Limbitrol, Limbitrol DS
Amitriptyline Hydrochloride, Perphenazine	Duo-Vil, Etrafon, Etrafon Forte
Amoxapine	Asendin
Clomipramine Hydrochloride	Anafranil
Desipramine Hydrochloride	Norpramin
Doxepin Hydrochloride	Prudoxin, Sinequan, Zonalon
Imipramine Hydrochloride	Tofranil
Imipramine Pamoate	Tofranil-PM
Nortriptyline Hydrochloride	Aventyl HCl, Pamelor
Protriptyline Hydrochloride	Vivactil
Trimipramine Maleate	Surmontil

Presence of any ε4 allele at APOE was also assessed, since this factor is highly related to dementia and AD and may also relate to widowhood.

I also explored number of chronic conditions as a potential confounder. This variable was assessed at the Wave 1 screening visit. Subjects were asked whether they had ever had the following conditions: stroke, hypertension, myocardial infarction, diabetes, high cholesterol, or a coronary artery bypass graft. To assess shared environment and lifestyle as a potential confounder, I looked at diet, exercise, current alcohol consumption, and smoking history. To measure diet, adherence to the Dietary Approaches to Stop Hypertension (DASH) diet was assessed, which is based on the U.S. Department of Agriculture's (2010) Dietary Guidelines for Americans. This measure asks subjects how often they ate 142 different kinds of foods in the last year. Points were given for high intake of fruits, vegetables, low-fat dairy products, nuts and legumes, and whole grains; and low intake of sodium, sweets and sweetened beverages, and red and processed meat. Exercise was assessed by asking participants how many hours per week they spent doing light activities (e.g., walking), and the frequency with which they engaged in moderate (e.g., bowling, golfing; usually every day, 2-6 times a week, about once a week, a few times a month, a few times a year, rarely or never) and vigorous activity (e.g., jogging, tennis). Persons who engaged in five or more hours of light activity a week and who engaged in moderate or physical activity at least once a week were considered "physically active." Current consumption of alcohol was defined as two or more drinks per week, with a drink defined as 12 oz. of beer (12.8g of alcohol), 4 oz. of wine (11g of alcohol), or 1.5 oz. of liquor (14g of alcohol). Smoking was defined as having smoked 100 or more cigarettes during one's lifetime. These variables were all

assessed at the baseline screening visit.

Procedure

Data Acquisition and Cleaning

This dissertation is a secondary data analysis project. After gaining IRB approval, I inquired with the director of the UPDB as to whether there were substantial updates of vital statistics and residence address information since the latest UPDB datasets received at USU. Several data cleaning measures were undertaken. Incomplete marital histories were identified. This was done by aggregating each participant's entire marital history chronologically, which identified marriage patterns that did not conform to expectations. For instance, if a subject had a widowhood date was followed chronologically by another widowhood date with no intervening marriage date, this subject was assumed to have an incomplete marital history. Quality assurance and data clean-up work, in collaboration with personnel at the University of Utah who manage the UPBD, were completed, in order to resolve many of these cases. For cases whose marital history included a marriage date followed by another marriage date, a divorce to the first spouse was imputed if either of two conditions were met. In some cases, death certificate data from the UPDB did not include the date in which subjects divorced a particular spouse, but did indicate that they divorced that spouse. For these subjects, divorce to the first spouse was imputed. Divorce was also imputed if UPDB data indicated that the first spouse died after marriage to the second spouse occurred, since this scenario negated the possibility that the first marriage dissolved via widowhood. If the death date of the first spouse was missing, this missing death date was used to indicate that this spouse was still living, provided that the birth

date for that spouse was not missing, which scenario indicated a pattern of missing date for that spouse. To further identify missing data, lifetime never-married status was cross-checked between UPDB and CCMS self-report data sources for further quality assurance. For the variable that assesses the timing of initial widowhood, presence of outliers (widowed at 16 years of age or younger) was assessed. Since only one participant met this criteria (16.6 years old at widowhood), this person was retained in analyses.

Exploratory Data Analysis

Exploratory data analyses were conducted to assess missingness bias, potential for confounding, and bivariate relationships. For these analyses, I used chi-square analyses for categorical variables, and independent samples *t* tests and ANOVA for continuous variables. To assess missingness bias associated with missing marital history, I examined whether subjects with missing or incomplete marital histories differ from subjects with complete marital histories on any of the covariates and moderators (education, occupation, age at baseline, gender, presence of any ε4 allele at APOE, number of chronic conditions, diet, exercise, alcohol consumption, smoking, death during observation period, and history of depression) or on dementia or AD. After conducting these analyses, subjects with missing or incomplete marital history data were excluded from further exploratory analyses and models. To assess missingness bias associated with death or drop out, exploratory investigations were conducted to examine whether subjects who were diagnosed with dementia, subjects who died before Wave 4, subjects who otherwise dropped out before Wave 4, and subjects who were right censored differed on prevalent exposure (occurrence of any widowhood), incident exposure, covariates and

moderators, and on rate of cognitive decline per year. Cognitive decline was measured at each triennial wave using the 3MS (Tschanz et al., 2002), a 100-point adaptation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) that assesses orientation, memory, attention, abstract verbal reasoning and verbal fluency. To assess potential for confounding and bivariate relationships, I assessed whether covariates and moderators related to prevalent and incident exposure; and whether prevalent exposure variables (occurrence of any widowhood, the timing of initial widowhood, remarriage after widowhood, manner of death, widowhood with dependent children, and widowhood with adult children), incident exposure, and covariates and moderators related to dementia and AD. During exploratory data analysis I also determined the number of persons who divorced or remarried after baseline in order to assess whether there were a sufficient number of such persons to include them in a separate category. Given that, of the 2,545 participants used for Cox model regressing dementia on incident widowhood, only 41 remarried after incident widowhood, a separate category was not created for these persons.

Statistical Analysis

After exploratory data analyses were conducted, Cox Regression models were computed. This analysis is advantageous because it can account for persons whose dementia status is censored, either because they left the study early or they endured the entire period of observation without acquiring dementia, but are still living and may yet develop dementia at some future date. In addition, Cox regression is advantageous over logistic regression because it models time to dementia onset (handling varying lengths of

observation between subjects), rather than a simple dichotomy indicating whether subjects ever received a dementia diagnosis.

Before computing models, the assumptions of Cox Regression analysis were tested. Cox regression assumes that hazards remain proportional across the observation period (Garson, 2012). To test this assumption, an interaction between each predictor variable and time was computed to determine whether the association between the predictor and the outcome depends on the amount of time that has elapsed during the observation period. Each such interaction term was entered initially by itself. All interaction terms that were significant when tested separately were then entered in a final model. In this model, only the interaction term involving gender remained statistically significant. Because of this, this interaction term was included in all models in which gender was entered. Cox regression also assumes that no multicollinearity occur among predictor variables. To test this assumption, bivariate statistics were conducted for all predictor variables. Given that none of the resulting correlation coefficients exceeded .58, this assumption was deemed satisfied.

Because of the interest in studying all-cause dementia due to its overall public health burden (these analyses also have more cases, hence greater statistical power) as well as AD (greater specificity), separate analyses were conducted for these two outcomes. In addition, separate analyses were also conducted for prevalent and incident widowhood exposure, both before and after inclusion of covariates, moderators, and their interaction with widowhood. To explore prevalent exposure, I entered each of the prevalent exposure variables (occurrence of any widowhood, the timing of initial widowhood, remarriage after widowhood, manner of death, widowhood with dependent

children, and widowhood with adult children) in separate models. For each of these prevalent exposures, I entered covariates, one at a time, with a final model including all covariates, in order to fully understand effects of each covariate separately on widowhood/dementia association. To assess the moderating effect of gender, ε4 allele at APOE, and history of depression, I interacted each of these with the exposure variable assessing occurrence of any widowhood, with each moderator entered in a separate model, followed by a final model that includes covariates.

Incident exposure was assessed via a time-varying variable, in which all subjects were set to 0 at baseline, were changed to 1 upon occurrence of widowhood and remained set to 1 thereafter. In order to investigate the unique effect of incident widowhood, all persons who experienced prevalent widowhood were excluded from models of incident exposure. To explore incident exposure, I entered incident exposure alone into the model. Each of the covariates were then entered, one at a time, followed by a final model including all covariates. I then assessed the moderating effect of gender, ε4 allele at APOE, and history of depression by interacting each of these with incident exposure, with each moderator entered in a separate model, followed by a final model that includes all covariates. In a final model, I included significant prevalent exposures, incident exposures, significant covariates, and significant moderators. The entire sequence of models was conducted for all-cause dementia as the outcome, and then repeated for AD as the outcome.

CHAPTER 4

RESULTS

This chapter reports results of statistical analyses described in the previous chapter. It begins with results of exploratory data analyses. These include analyses assessing bias associated with missing marital history, and bias associated with death. Exploratory analyses also addressed the potential for confounding and bivariate relationships, which assess whether covariates and moderators relate to prevalent and incident exposure; and whether prevalent exposure variables (occurrence of any widowhood, the timing of initial widowhood, remarriage after widowhood, manner of death, widowhood with dependent children, and widowhood with adult children), incident exposure, and covariates and moderators relate to dementia and AD. Results of Cox regression models assessing whether prevalent and incident exposure relate to dementia and AD, and whether these relationships are moderated by the context of widowhood will then be presented.

Exploratory Data Analysis

Missingness Bias

Tables A.1 and A.2 in the appendix present results of analyses assessing bias associated with missing or incomplete UPDB marital history, and death. For analyses involving missing or incomplete UPDB marital history, persons with missing UPDB marital history who were never married as per CCMS self-report at Wave 1 were put into a separate category so as to separate them from those who were married at some point but

had missing or incomplete data in the UPDB. Because there were so few persons who never married (n = 49), for these analyses the following categories of the occupation of longest duration variable were collapsed: blue collar workers (processing, machine work, benchwork, structural), miscellaneous, and never worked outside of home. Table A.1 indicates that those who had never married had slightly more years of education (M = 14.3, SD = 3.4) than those with missing marital histories (M = 13.1, SD = 3.2) and those with complete marital histories (M = 13.3, SD = 2.8). This Table also indicates that persons in the service industry, as well as females, current drinkers, and persons with a history of smoking, were more likely to be missing marital history, while persons in the agricultural industry were less likely to be missing this data. Table A.2 indicates that persons with one or more prevalent widowhoods; persons in the agricultural, processing, structural, and miscellaneous industries; males; those not physically active; and those with a history of smoking were more likely to die during the course of the study, while persons with no incident widowhoods, those with one or more ε4 alleles at APOE, and those with a history of depression with and without antidepressant use were less likely to die. Persons who died were also older (M = 77.7, SD = 7.1 years), had more chronic conditions (M = 1.4, SD = 1.2), lower DASH scores (M = 25.2, SD = 5.7), and faster 3MS cognitive decline (M = 0.47, SD = 2.2 points per year).

Confounding/Bivariate Relationships

Tables A.3 through A.6 in the appendix present results examining potential for confounding and bivariate relationships. In Tables A.3 and A.4, analyses are presented that assess whether prevalent or incident exposure, respectively, relates to covariates and

moderators. Table A.3 indicates that persons with one or more prevalent widowhoods had fewer years of education (*M* = 12.6, *SD* = 2.5) than persons with no prevalent widowhoods (*M* = 13.6, *SD* = 2.9), and were older (*M* = 78.5, *SD* = 6.9 and *M*=72.9, *SD* = 5.8, respectively). Those in the service, processing, and benchwork industries; those who never worked outside the home; females; those who died during the observation period; and those with a history of depression with and without antidepressant use were more likely to have experienced widowhood before baseline, and those in the professional/technical/managerial, agricultural, and structural industries; those with one or more ε4 alleles at APOE; those who were physically active; and those with a history of smoking were less likely to have any prevalent widowhoods. Table A.4 indicates that those with one or more incident widowhoods had slightly fewer years of education (*M* = 13.3, *SD* = 2.8) than those with no incident widowhoods (*M* = 13.9, *SD* = 3.0). It also indicates that those in the service, processing, and benchwork industries; those who never worked outside the home; females; those who died during the course of the study; and those with a history of antidepressant use with or without depression were more likely to have one or more incident widowhood, while those in the machine work and structural industries, and persons who had ever smoked were less likely to have one or more incident widowhood.

Table A.5 and A.6 in the Appendix present analyses assessing whether dementia or AD, respectively, relates to exposure variables, covariates and moderators. Table A.5 indicates that persons with one or more prevalent widowhoods; prevalent widowhood at 65 years of age or older; prevalent widowhood with no remarriage; prevalent widowhood from natural causes; no dependent children or two or more dependent children at the time

of prevalent widowhood; 1-2, 3-4, and 5 or more adult children at the time of prevalent widowhood; and one or more incident widowhoods were more likely to acquire dementia. It also indicates that persons who acquired dementia were older than persons who did not acquire dementia (M = 77.5, SD = 6.7 years versus M = 74.0, SD = 6.5 years, respectively). In addition, Table A.5 indicates that persons in the service and agricultural industries, persons with one or more ε4 alleles at APOE, and persons with a history of antidepressant use without depression were more likely to acquire dementia, while persons in the structural and miscellaneous industries were less likely to develop dementia. Similar factors increased risk for AD. Table A.6 indicates that persons with one or more prevalent widowhoods; prevalent widowhood at 65 years of age or older; prevalent widowhood with no remarriage; prevalent widowhood from natural causes; no dependent children or two or more dependent children at the time of prevalent widowhood; 3-4, and 5 or more adult children at the time of prevalent widowhood; one or more incident widowhoods; females; those with one or more ε4 alleles at APOE; and those with a history of antidepressant use without depression were more likely to acquire AD, while those with a history of depression without antidepressant use were less likely to develop AD. Persons with AD were also older (M = 78.0, SD = 6.6) than persons without dementia (M = 74.0, SD = 6.5) and had slightly fewer chronic conditions (AD: M = 1.0, SD = 1.0 versus no dementia: M = 1.2, SD = 1.1).

Summary

These exploratory data analyses reveal some bias associated with missing marital history and death, and reveal that some factors confound the relationship between

widowhood and dementia or AD. Results from missingness analyses indicate that the sample of persons with complete marital history used in this dissertation for Cox models slightly underrepresents persons in the service industry, females, consumers of alcohol, and smokers. However, given that 3,633 participants had complete marital histories while only 290 were excluded because of incomplete marital histories, and thus that 92.6% of the total possible sample (290/290 + 3,633) had complete histories, this slight underrepresentation is unlikely to affect results. These analyses also found a number of factors to be related to death. Given that the likelihood of death is highly related to age, age at baseline was used as a covariate in this study. Of the variables tested as potential confounders, only occupation, age, gender, and presence of ε4 allele at APOE were related to both prevalent or incident widowhood and dementia or AD. Because of this, only these factors were used as covariates.

Cox Regression Models

Dementia Regressed on Prevalent Widowhood

Prevalent widowhood, overall. The assumption of proportional hazards was met for all predictors except gender (p = .05). Accordingly, in all Cox models with this predictor, the gender by time interaction term was included. Table 4.1 reports results from Cox regression models regressing dementia on prevalent widowhood. In the model without covariates (Model 1), those with one or more prevalent widowhoods were at increased risk for dementia (*HR* = 1.75, 95% *CI*: 1.47-2.08). Risk was also increased when occupation was added as a covariate (Model 2; *HR* = 1.76, 95% *CI*: 1.47-2.10).

Table 4.1

Cox Regression: Dementia Regressed on Prevalent Widowhood

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	CI[a]	*HR*	CI	*HR*	CI	*HR*	CI	*HR*	CI
Prevalent widowhood[b]										
1+ prevalent divorce, no widowhood	0.67	0.38-1.17	0.71	0.40-1.23	0.73	0.42-1.27	0.73	0.42-1.27	0.65	0.37-1.16
1+ widowhood	1.75	1.47-2.08	1.76	1.47-2.10	1.00	.82-1.21	0.99	0.81-1.21	0.99	0.81-1.22
Occupation of longest duration[c]										
Clerical, sales			0.83	0.65-1.07	0.88	0.69-0.11	0.89	0.68-1.15	0.89	0.69-1.16
Service			1.50	1.13-1.99	1.35	1.02-1.79	1.34	1.0-1.80	1.30	0.97-1.75
Agricultural			1.45	1.13-1.87	1.22	0.95-1.57	1.24	0.94-1.60	1.31	1.0-1.70
Processing			1.29	0.70-2.38	1.01	0.55-1.87	1.02	0.55-1.87	1.06	0.57-1.96
Machine work			1.07	0.63-1.81	0.86	0.51-1.46	0.86	0.50-1.48	0.86	0.50-1.48
Benchwork			0.68	0.38-1.23	0.71	0.40-1.29	0.71	0.39-1.29	0.76	0.42-1.38
Structural			0.96	0.61-1.53	0.93	0.59-1.48	0.94	0.59-1.51	0.94	0.58-1.50
Miscellaneous			0.84	0.44-1.59	0.79	0.42-1.50	0.80	0.42-1.52	0.75	0.40-1.43
Never worked outside home			1.16	0.85-1.58	0.99	0.72-1.35	0.98	0.70-1.36	0.99	0.71-1.38
Age					1.12	1.11-1.14	1.12	1.11-1.14	1.13	1.11-1.14
Gender[d]: Female							1.53	0.99-2.37	1.68	1.07-2.62
Presence of 1+ APOE ε4 allele[e]									1.95	1.64-2.32

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

However, prevalent widowed was not related to risk for dementia when age was added as a covariate (Model 3; *HR* = 1.0, 95% *CI*: 0.82-1.21), or in subsequent models.

Timing of widowhood. A similar pattern was found in other prevalent exposure variables. Table 4.2 presents results of Cox models regressing dementia on the timing of prevalent widowhood. In the model without covariates (Model 1), increased risk was found among those who were widowed between ages 46-64 (*HR* = 1.35, 95% *CI*: 1.01-1.79) and among those widowed at age 65 or older (*HR* = 2.21, 95% *CI*: 1.80-2.70). These increased risks were also significant when occupation was controlled for (Model 2; ages 46-64: *HR* =1.38, 95% *CI*: 1.04-1.83). However, these risks were not statistically significant when age was entered into the model (Model 3; 46-64: *HR* = 1.05, 95% *CI*: 0.78-1.39; 65+: *HR* = 1.0, 0.80-1.26) and when the rest of the covariates were entered into the model.

Remarriage after widowhood. In Table 4.3, results are presented for Cox models regressing dementia on prevalent widowhood with remarriage. When tested without covariates (Model 1), and when tested with occupation as a covariate (Model 2), widowhood without remarriage was associated with 86% and 90% increased risk for dementia, respectively (Model 1: *HR* = 1.86, 95% *CI*: 1.55-2.23; Model 2: *HR* = 1.90, 95% *CI*: 1.57-2.29), but when tested with age, widowhood without remarriage became nonsignificant (*HR* = 1.04, 95% *CI*: 0.85-1.28), and remained so when the other covariates were entered.

Manner of death of spouse. In Table 4.4 results for Cox models regressing dementia on prevalent widowhood with manner of death are presented. On this variable, a substantial number of participants (*n* = 812) were missing manner of death. These

Table 4.2

Cox Regression: Dementia Regressed on Timing of Prevalent Widowhood

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Timing of prevalent widowhood[b]										
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.70	0.40-1.23	0.73	0.42-1.27	0.73	0.42-1.27	0.65	0.37-1.16
45 or younger	0.98	0.56-1.71	0.97	0.56-1.69	0.80	0.46-1.40	0.80	0.46-1.39	0.86	0.49-1.50
46-64	1.35	1.01-1.79	1.38	1.04-1.83	1.05	0.78-1.39	1.04	0.77-1.39	1.03	0.77-1.39
65 or older	2.21	1.80-2.70	2.22	1.81-2.73	1.0	0.80-1.26	0.99	0.79-1.25	1.0	0.79-1.26
Occupation of longest duration[c]										
Clerical, sales			0.82	0.64-1.06	0.89	0.69-1.14	0.89	0.68-1.16	0.90	0.69-1.16
Service			1.49	1.12-1.98	1.35	1.01-1.79	1.35	1.0-1.81	1.30	0.97-1.75
Agricultural			1.42	1.10-1.82	1.22	0.94-1.57	1.24	0.95-1.61	1.31	1.0-1.70
Processing			1.28	0.69-2.36	1.0	0.55-1.86	1.01	0.55-1.86	1.05	0.57-1.95
Machine work			1.04	0.61-1.76	0.86	0.50-1.46	0.86	0.50-1.48	0.86	0.50-1.48
Benchwork			0.64	0.35-1.15	0.71	0.39-1.27	0.70	0.39-1.27	0.76	0.42-1.37
Structural			0.94	0.59-1.50	0.93	0.59-1.48	0.94	0.58-1.51	0.93	0.58-1.50
Miscellaneous			0.85	0.45-1.60	0.79	0.41-1.49	0.80	0.42-1.51	0.75	0.39-1.42
Never worked outside home			1.10	0.80-1.51	0.98	0.71-1.35	0.97	0.70-1.36	0.98	0.71-1.37
Age					1.12	1.11-1.14	1.12	1.11-1.14	1.13	1.11-1.15
Gender[d]: Female							1.53	0.99-2.37	1.68	1.07-2.62
Presence of 1+ APOE ε4 allele[e]									1.95	1.64-2.32

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.3

Cox Regression: Dementia Regressed on Prevalent Widowhood with Remarriage

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood with remarriage[b]										
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.70	0.40-1.23	0.73	0.42-1.27	0.72	0.42-1.26	0.65	0.36-1.16
1+ widowhood, no remarriage	1.86	1.55-2.23	1.90	1.57-2.29	1.04	0.85-1.28	1.04	0.84-1.29	1.05	0.85-1.30
1+ widowhood, with remarriage	1.28	0.86-1.89	1.21	0.81-1.81	0.78	0.52-1.17	0.78	0.52-1.17	0.77	0.51-1.17
Occupation of longest duration[c]										
Clerical, sales			0.82	0.64-1.06	0.88	0.68-1.13	0.89	0.68-1.15	0.90	0.69-1.17
Service			1.48	1.11-1.96	1.34	1.01-1.78	1.34	1.0-1.80	1.30	0.97-1.75
Agricultural			1.46	1.14-1.88	1.23	0.96-1.59	1.24	0.96-1.62	1.32	1.01-1.71
Processing			1.27	0.69-2.34	1.01	0.55-1.86	1.01	0.55-1.87	1.06	0.57-1.96
Machine work			1.07	0.63-1.82	0.88	0.52-1.50	0.88	0.51-1.51	0.87	0.51-1.50
Benchwork			0.65	0.36-1.17	0.69	0.38-1.25	0.70	0.38-1.26	0.75	0.41-1.36
Structural			0.96	0.60-1.53	0.93	0.58-1.48	0.93	0.58-1.49	0.92	0.57-1.48
Miscellaneous			0.85	0.45-1.60	0.80	0.42-1.52	0.81	0.43-1.54	0.76	0.40-1.44
Never worked outside home			1.14	0.83-1.56	0.97	0.71-1.33	0.97	0.70-1.36	0.98	0.71-1.37
Age					1.12	1.11-1.14	1.12	1.11-1.14	1.13	1.11-1.14
Gender[d]: Female							1.50	1.0-2.32	1.63	1.04-2.56
Presence of 1+ APOE ε4 allele[e]									1.95	1.64-2.32

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.4

Cox Regression: Dementia Regressed on Prevalent Widowhood: Manner of Death

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood: Manner of Death[b]										
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.71	0.41-1.23	0.73	0.42-1.27	0.73	0.42-1.27	0.65	0.37-1.16
Widowed, Natural Causes	1.64	1.26-2.13	1.66	1.27-2.17	0.98	0.75-1.29	0.98	0.74-1.29	1.0	0.76-1.32
Widowed, Accident or suicide	1.16	0.37-3.61	1.15	0.37-3.59	0.79	0.25-2.47	0.78	0.25-2.45	0.75	0.24-2.34
Widowed, Missing manner of death	1.84	1.50-2.25	1.84	1.50-2.26	1.01	0.81-1.26	1.0	0.79-1.26	1.0	0.79-1.26
Occupation of longest duration[c]										
Clerical, sales			0.83	0.65-1.07	0.89	0.69-1.14	0.89	0.68-1.16	0.90	0.69-1.17
Service			1.50	1.13-2.0	1.35	1.02-1.80	1.35	1.0-1.81	1.31	0.97-1.75
Agricultural			1.45	1.13-1.87	1.22	0.95-1.57	1.24	0.95-1.61	1.31	1.0-1.70
Processing			1.28	0.70-2.37	1.01	0.55-1.87	1.01	0.55-1.87	1.06	0.57-1.96
Machine work			1.07	0.63-1.81	0.86	0.51-1.46	0.86	0.50-1.49	0.86	0.50-1.48
Benchwork			0.68	0.38-1.24	0.71	0.40-1.29	0.71	0.39-1.29	0.76	0.42-1.38
Structural			0.96	0.61-1.53	0.93	0.59-1.48	0.94	0.59-1.51	0.94	0.58-1.50
Miscellaneous			0.83	0.44-1.57	0.79	0.42-1.50	0.80	0.42-1.52	0.75	0.40-1.43
Never worked outside home			1.16	0.85-1.59	0.99	0.72-1.35	0.98	0.70-1.37	0.99	0.71-1.38
Age					1.12	1.11-1.14	1.12	1.11-1.14	1.13	1.11-1.14
Gender[d]: Female							1.53	0.99-2.37	1.68	1.07-2.62
Presence of 1+ APOE ε4 allele[e]									1.95	1.64-2.32

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

participants were placed into a separate category to assess whether missingness on this factor was associated risk for dementia and AD. In Model 1, in which no covariates were added, and in Model 2, in which occupation was added, those whose prevalent widowhood stemmed from natural causes were at 64% and 66% increased risk for dementia (Model 1: *HR* = 1.64, 95% *CI*: 1.26-2.13; Model 2: *HR* = 1.66, 95% *CI*: 1.27-2.17). In addition, those with missing manner of death were at 84% increased risk in Models 1 and 2 (Model 1: *HR* = 1.84, 95% *CI*: 1.50-2.25; Model 2: *HR* = 1.84, 95% *CI*: 1.50-2.26). In Model 3, in which age was controlled, the statistical effect for prevalent widowhood by natural causes became nonsignificant (*HR* = 0.98, 95% *CI*: 0.75-1.29) as did the statistical effect for missing manner of death (*HR* = 1.01, 95% *CI*: 0.81-1.26). These remained nonsignificant when the remaining covariates were entered into the model.

Number of dependent children at time of widowhood. Table 4.5 presents results for models regressing dementia on prevalent widowhood with number of dependent children. In Model 1, persons with no dependent children, and two or more dependent children, at the time of prevalent widowhood experienced 85% and 74% increased risk for dementia (no dependent children: *HR* = 1.85, 95% *CI*: 1.54-2.22; two or more dependent children: *HR* = 1.74, 95% *CI*: 1.07-2.84). Results were similar in Model 2 (no dependent children: *HR* = 1.86, 95% *CI*: 1.54-2.24; two or more dependent children: *HR* = 1.76, 95% *CI*: 1.08-2.88). In Model 3, a slight trend was observed for those with two or more children at the time of prevalent widowhood (*HR* = 1.37, 95% *CI*: 0.84-2.23). This trend persisted with inclusion of all covariates (*HR* = 1.42, 95%

Table 4.5

Cox Regression: Dementia Regressed on Prevalent Widowhood with Dependent Children

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood with dependent children[b]										
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.71	0.40-1.23	0.73	0.42-1.28	0.73	0.42-1.27	0.65	0.37-1.16
Widowed, no dependents	1.85	1.54-2.22	1.86	1.54-2.24	0.99	0.81-1.21	0.98	0.79-1.21	0.98	0.79-1.21
Widowed, 1 dependent	0.88	0.46-1.71	0.89	0.46-1.73	0.71	0.37-1.39	0.71	0.36-1.39	0.75	0.38-1.46
Widowed, 2+ dependents	1.74	1.07-2.84	1.76	1.08-2.88	1.37	0.84-2.23	1.34	0.82-2.20	1.42	0.87-2.32
Occupation of longest duration[c]										
Clerical, sales			0.83	0.65-1.07	0.89	0.69-1.14	0.89	0.68-1.15	0.89	0.69-1.16
Service			1.49	1.12-1.98	1.36	1.02-1.81	1.36	1.01-1.82	1.31	0.98-1.76
Agricultural			1.46	1.13-1.88	1.22	0.94-1.57	1.23	0.95-1.61	1.30	1.0-1.69
Processing			1.26	0.68-2.33	1.01	0.55-1.87	1.01	0.55-1.87	1.06	0.57-1.96
Machine work			1.06	0.63-1.80	0.86	0.51-1.47	0.87	0.51-1.49	0.87	0.50-1.49
Benchwork			0.67	0.37-1.22	0.73	0.41-1.32	0.73	0.40-1.32	0.78	0.43-1.41
Structural			0.97	0.61-1.54	0.94	0.59-1.50	0.95	0.59-1.52	0.95	0.59-1.52
Miscellaneous			0.84	0.45-1.60	0.78	0.41-1.48	0.79	0.42-1.50	0.75	0.39-1.41
Never worked outside home			1.16	0.84-1.58	0.99	0.72-1.36	0.99	0.71-1.37	0.99	0.71-1.39
Age					1.12	1.11-1.14	1.12	1.11-1.14	1.13	1.11-1.15
Gender[d]: Female							1.53	0.99-2.36	1.67	1.07-2.61
Presence of 1+ APOE ε4 allele[e]									1.95	1.64-2.32

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

CI: 0.87-2.32), which suggested these persons were 42% more likely to develop dementia as those with no prevalent widowhoods.

Number of adult children at time of widowhood. Table 4.6 reports models regressing dementia on prevalent widowhood with adult children. In Model 1, persons with 1-2, 3-4, and 5 or more adult children at the time of prevalent widowhood were 71%, 81%, and 97% more likely to develop dementia (1-2 adult children: *HR* = 1.71, 95% *CI*: 1.30-2.25; 3-4 adult children: *HR* = 1.81, 95% *CI*: 1.40-2.35; 5 or more adult children: *HR* = 1.97, 95% *CI*: 1.47-2.62). Results were similar in Model 3 (1-2 adult children: *HR* = 1.74, 95% *CI*: 1.32-2.30; 3-4 adult children: *HR* = 1.82, 95% *CI*: 1.40-2.37; 5 or more adult children: *HR* = 1.95, 95% *CI*: 1.46-2.61). In Model 3, these statistical effects became nonsignificant (1-2 adult children: *HR* = 0.95, 95% *CI*: 0.71-1.27; 3-4 adult children: *HR* = 1.02, 95% *CI*: 0.77-1.33; 5 or more adult children: *HR* = 1.11, 95% *CI*: 0.82-1.50), and remained so with inclusion of remaining covariates.

Tests of interaction effects. Tables 4.7-4.9 present results of Cox models in which dementia is regressed on interactions between prevalent widowhood and gender, ε4 allele at APOE, and history of depression, respectively. For each moderator, prevalent widowhood alone is presented in Model 1. In Model 2, the main effect of each moderator and its interaction with prevalent widowhood is presented. In Model 3, the remaining covariates are added. Table 4.7 indicates that the main effect of gender and its interaction with prevalent widowhood are not significant (main effect: *HR* = 1.42, 95% *CI*: 0.92-2.20; one or more prevalent widowhoods by female gender: *HR* = 1.42, 95% *CI*: 0.92-2.20). In Model 3, which controlled for occupation, age, and presence of one or more ε4

Table 4.6

Cox Regression: Dementia Regressed on Prevalent Widowhood with Adult Children

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood with adult children[b]										
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.70	0.40-1.23	0.73	0.42-1.27	0.73	0.42-1.26	0.65	0.37-1.16
Widowed, no adult children	1.33	0.86-2.07	1.34	0.86-2.08	0.86	0.55-1.35	0.85	0.54-1.34	0.87	0.54-1.38
Widowed, 1-2 adult children	1.71	1.30-2.25	1.74	1.32-2.30	0.95	0.71-1.27	0.94	0.70-1.27	0.93	0.69-1.25
Widowed, 3-4 adult children	1.81	1.40-2.35	1.82	1.40-2.37	1.02	0.77-1.33	1.0	0.76-1.32	1.0	0.75-1.32
Widowed, 5+ adult children	1.97	1.47-2.62	1.95	1.46-2.61	1.11	0.82-1.50	1.10	0.80-1.49	1.14	0.84-1.55
Occupation of longest duration[c]										
Clerical, sales			0.83	0.65-1.07	0.89	0.69-1.14	0.89	0.69-1.16	0.90	0.69-1.17
Service			1.50	1.13-1.99	1.35	1.02-1.80	1.35	1.01-1.81	1.31	0.97-1.76
Agricultural			1.44	1.12-1.86	1.21	0.94-1.57	1.23	0.95-1.60	1.30	1.0-1.69
Processing			1.27	0.69-2.35	1.01	0.55-1.87	1.01	0.55-1.87	1.06	0.57-1.96
Machine work			1.07	0.63-1.81	0.85	0.50-1.45	0.86	0.50-1.47	0.86	0.50-1.47
Benchwork			0.68	0.38-1.23	0.72	0.40-1.30	0.72	0.40-1.30	0.78	0.43-1.41
Structural			0.96	0.60-1.52	0.93	0.59-1.48	0.94	0.58-1.51	0.93	0.58-1.49
Miscellaneous			0.83	0.44-1.57	0.79	0.42-1.49	0.80	0.42-1.51	0.75	0.40-1.42
Never worked outside home			1.14	0.83-1.56	0.97	0.71-1.33	0.96	0.69-1.35	0.97	0.70-1.36
Age					1.12	1.11-1.14	1.12	1.11-1.14	1.13	1.11-1.14
Gender[d]: Female							1.53	0.99-2.37	1.67	1.07-2.61
Presence of 1+ APOE ε4 allele[e]									1.96	1.65-2.33

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.7

Cox Regression: Dementia Regressed on Prevalent Widowhood by Gender

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood[b]						
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.78	0.40-1.53	0.68	0.33-1.38
1+ widowhood	1.75	1.47-2.09	1.67	1.18-2.36	0.90	0.62-1.29
Gender[c]: Female			1.42	0.92-2.20	1.60	1.0-2.56
Prevalent widowhood x Gender						
1+ prevalent divorce, no widowhood; Female			.064	0.19-2.12	0.88	0.26-2.98
1+ widowhood; Female			1.11	0.74-1.66	1.15	0.76-1.75
Occupation of longest duration[d]						
Clerical, sales					0.89	0.69-1.16
Service					1.30	0.97-1.75
Agricultural					1.31	1.01-1.71
Processing					1.05	0.57-1.95
Machine work					0.88	0.51-1.53
Benchwork					0.75	0.42-1.37
Structural					0.93	0.58-1.50
Miscellaneous					0.75	0.40-1.43
Never worked outside home					0.99	0.71-1.37
Age					1.13	1.11-1.14
Presence of 1+ APOE ε4 allele[e]					1.95	1.64-2.32

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

alleles at APOE, the main effect of gender approached significance (*HR* = 1.60, 95% *CI*: 1.0-2.56) and its interaction with prevalent widowhood remained nonsignificant (*HR* = 1.15, 95% *CI*: 0.76-1.75). In Table 4.8, results indicate that the main effect of having one or more ε4 alleles at APOE is significant (*HR* = 1.61, 95% *CI*: 1.30-2.0), but its interaction with prevalent widowhood was not significant (*HR* = 1.06, 95% *CI*: 0.74-1.52). After adding occupation, age, and gender, the main effect of ε4 alelle at APOE

Table 4.8

Cox Regression: Dementia Regressed on Prevalent Widowhood by APOE ε4

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood[b]						
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.39	0.14-1.04	0.450	.17-1.21
1+ widowhood	1.75	1.47-2.09	1.75	1.40-2.20	0.96	0.74-1.23
Presence of 1+ APOE ε4 allele[c]			1.61	1.30-2.0	1.86	1.50-2.3
Prevalent widowhood x APOE ε4 allele						
1+ prevalent divorce, no widowhood; 1+ APOE ε4 allele			2.34	0.69-7.92	1.88	0.55-6.39
1+ widowhood; 1+ APOE ε4 allele			1.06	0.74-1.52	1.10	0.77-1.57
Occupation of longest duration[d]						
Clerical, sales					0.90	0.69-1.17
Service					1.31	0.98-1.76
Agricultural					1.32	1.01-1.72
Processing					1.06	0.57-1.96
Machine work					0.87	0.50-1.49
Benchwork					0.77	0.42-1.39
Structural					0.94	0.59-1.52
Miscellaneous					0.76	0.40-1.44
Never worked outside home					1.00	0.71-1.39
Age					1.13	1.11-1.14
Gender[e]: Female					1.68	1.07-2.62

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: 0 APOE ε4 alleles.
[d] Reference category: professional, technical, managerial.
[e] Reference category: Male.

remained significant (*HR* = 1.86, 95% *CI*: 1.50-2.30) and its interaction with prevalent widowhood remained nonsignificant (*HR* = 1.10, 95% *CI*: 0.77-1.57). Table 4.9 indicates that the main effect for history of depression is significant, in that those with a history of antidepressant use without depression were at 91% increased risk for dementia (*HR* = 1.91, 95% *CI*; 1.46-2.50). However, the interaction between this factor and prevalent widowhood was not significant. In Model 3, which controlled for occupation, age, gender, and presence of ε4 allele at APOE, the main effect for history of depression

Table 4.9

Cox Regression: Dementia Regressed on Prevalent Widowhood by Depression History

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood[b]						
1+ prevalent divorce, no widowhood	0.67	0.39-1.17	0.65	0.29-146	0.50	0.20-1.21
1+ widowhood	1.75	1.47-2.09	2.10	1.66-2.65	1.15	0.89-1.49
History of depression[c]						
Depression hx/no antidepressant hx			0.87	0.59-1.27	0.86	0.59-1.26
No depression hx/antidepressant hx			1.91	1.46-2.50	2.11	1.61-2.76
Depression hx/antidepressant hx			1.19	0.85-1.67	1.59	1.13-2.25
Prevalent widowhood x History of depression						
1+ prevalent divorce, no widowhood by depression hx/no antidepressant hx			0.95	0.18-4.94	1.90	0.35-10.27
1+ prevalent divorce, no widowhood by no depression hx/antidepressant hx			2.23	0.66-7.53	3.0	0.84-10.74
1+ prevalent divorce, no widowhood by depression hx/antidepressant hx			0		0	
1+ widowhood by Depression hx/no antidepressant hx			0.53	0.29-1.0	0.69	0.37-1.29
1+ widowhood by No depression hx/ antidepressant hx			0.84	0.54-1.31	0.79	0.50-1.23
1+ widowhood by Depression hx/antidepressant hx			0.68	0.40-1.16	0.68	0.39-1.18
Occupation of longest duration[d]					0.92	0.71-1.20
Clerical, sales					1.39	1.03-1.87
Service					1.35	1.04-1.77
Agricultural					1.11	0.60-2.06
Processing					0.80	0.47-1.39
Machine work					0.83	0.46-1.50
Benchwork					0.95	0.59-1.52
Structural					0.83	0.44-1.57
Miscellaneous					0.96	0.69-1.34
Never worked outside home					0.95	0.59-1.52
Structural					1.13	1.12-1.15
Age					1.56	0.99-2.44
Gender[e]: Female					2.02	1.70-2.40
Presence of 1+ APOE ε4 allele[f]						

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: no depression hx/no antidepressant hx.
[d] Reference category: professional, technical, managerial.
[e] Reference category: male.
[f] Reference category: 0 APOE ε4 alleles.

remained significant, with those with a history of antidepressant use without depression having over double the risk for dementia (*HR* =2.11, 95% *CI*: 1.61-2.76), and those with a history of antidepressant use and depression having 59% increased risk (*HR* =1.59, 95% *CI*: 1.13-2.25). The interaction between this factor and prevalent widowhood in this model was also nonsignificant.

AD Regressed on Prevalent Widowhood

Prevalent widowhood, overall. Table 4.10 presents results for Cox models regressing AD on prevalent widowhood. In Model 1, in which only prevalent widowhood is entered, persons with one or more prevalent widowhoods experienced over two fold risk of dementia relative to person with no prevalent widowhood (*HR* = 2.05, 95% *CI*: 1.66-2.53). Results were similar in Model 2, in which occupation was entered (*HR* = 2.06, 95% *CI*: 1.66-2.55). When age was entered (Model 3), prevalent widowhood became nonsignificant (*HR* = 1.11, 95% *CI*: 0.88-1.40). Prevalent widowhood remained nonsignificant when gender was entered (Model 4: *HR* = 1.04, 95% *CI*: 0.82-1.33) and when presence of one or more ε4 alleles at APOE was entered (Model 5: *HR* = 1.04, 95% *CI*: 0.82-1.33).

Timing of widowhood. Results were similar for other exposure variables. Table 4.11 presents results for Cox models regressing AD on age at prevalent widowhood. In Model 1, those widowed between 46-64 years of age, and 65 years of age or older, were 62% and 2.61 times more likely to develop AD (46-64 years old: *HR* = 1.62, 95% *CI*: 1.17-2.24; 65+ years old: *HR* = 2.61, 95% *CI*: 2.05-3.31) than those who did not experience a prevalent widowhood. Results were similar for Model 2 (46-64 years old:

Table 4.10

Cox Regression: AD Regressed on Prevalent Widowhood

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood[b]										
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.67	0.33-1.36	0.69	0.34-1.40	0.70	0.34-1.42	0.59	0.28-1.25
1+ widowhood	2.05	1.66-2.53	2.06	1.66-2.55	1.11	0.88-1.40	1.04	0.82-1.33	1.04	0.82-1.33
Occupation of longest duration[c]										
Clerical, sales			0.80	0.59-1.10	0.86	0.63-1.17	0.80	0.58-1.10	0.82	0.60-1.14
Service			1.45	1.02-2.06	1.27	0.89-1.80	1.17	0.82-1.68	1.17	0.82-1.68
Agricultural			1.47	1.08-2.01	1.19	0.87-1.62	1.30	0.94-1.80	1.41	1.02-1.97
Processing			1.67	0.87-3.21	1.24	0.65-2.37	1.19	0.62-2.28	1.26	0.66-2.42
Machine work			1.25	0.69-2.26	0.93	0.51-1.69	1.05	0.57-1.94	1.04	0.56-1.93
Benchwork			0.71	0.36-1.41	0.73	0.37-1.44	0.68	0.34-1.35	0.76	0.38-1.51
Structural			1.05	0.60-1.84	1.04	0.60-1.81	1.18	0.67-2.09	1.16	0.66-2.06
Miscellaneous			0.86	0.40-1.84	0.79	0.37-1.69	0.83	0.39-1.79	0.77	0.36-1.65
Never worked outside home			1.16	0.79-1.70	0.93	0.63-1.36	0.84	0.56-1.25	0.86	0.58-1.28
Age					1.14	1.12-1.15	1.14	1.12-1.15	1.14	1.13-1.16
Gender[d]: Female							1.75	1.02-3.00	1.82	1.06-3.14
Presence of 1+ APOE ε4 allele[e]									2.32	1.88-2.86

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.11

Cox Regression: AD Regressed on Timing of Prevalent Widowhood

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Timing of prevalent widowhood[b]										
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.67	0.33-1.36	0.69	0.34-1.40	0.70	0.34-1.42	0.59	0.28-1.25
Widowed at 45 or younger	0.95	0.47-1.93	0.95	0.47-1.92	0.78	0.38-1.58	0.72	0.35-1.47	0.81	0.40-1.66
Widowed at 46-64	1.62	1.17-2.24	1.66	1.19-2.30	1.21	0.87-1.69	1.13	0.80-1.59	1.11	0.78-1.57
Widowed at 65 or older	2.61	2.05-3.31	2.61	2.04-3.33	1.11	0.85-1.46	1.05	0.80-1.39	1.04	0.79-1.38
Occupation of longest duration[c]										
Clerical, sales			0.79	0.58-1.08	0.87	0.63-1.18	0.81	0.59-1.11	0.83	0.60-1.14
Service			1.44	1.01-2.04	1.27	0.89-1.80	1.17	0.82-1.68	1.18	0.82-1.69
Agricultural			1.42	1.04-1.95	1.19	0.87-1.63	1.30	0.94-1.81	1.41	1.02-1.97
Processing			1.65	0.86-3.16	1.22	0.64-2.35	1.18	0.61-2.26	1.24	0.65-2.39
Machine work			1.20	0.66-2.19	0.93	0.51-1.70	1.05	0.57-1.94	1.04	0.56-1.94
Benchwork			0.66	0.33-1.31	0.72	0.36-1.42	0.67	0.33-1.33	0.75	0.38-1.50
Structural			1.03	0.59-1.80	1.04	0.59-1.80	1.17	0.66-2.08	1.16	0.65-2.05
Miscellaneous			0.86	0.40-1.84	0.78	0.36-1.67	0.82	0.38-1.77	0.76	0.35-1.63
Never worked outside home			1.09	0.75-1.60	0.92	0.63-1.36	0.83	0.56-1.24	0.86	0.58-1.28
Age					1.14	1.12-1.15	1.14	1.12-1.15	1.14	1.13-1.16
Gender[d]: Female							1.75	1.02-3.00	1.82	1.06-3.14
Presence of 1+ APOE ε4 allele[e]									2.31	1.87-2.84

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

HR = 1.66, 95% *CI*: 1.19-2.30; 65+ years old: *HR* = 2.61, 95% *CI*: 2.04-3.33). In Model 3, these statistical effects became nonsignificant (46-64 years old: *HR* = 1.21, 95% *CI*: 0.87-1.69; 65+ years old: *HR* =1.11, 95% *CI*: 0.85-1.46) and remained significant in subsequent models.

Remarriage after widowhood. Table 4.12 presents results for Cox models in which AD is regressed on prevalent widowhood with remarriage. Model 1 indicates that those with a prevalent widowhood who did not remarry experienced over two fold risk for dementia (*HR* = 2.23, 95% *CI*: 1.79-2.77). Results were similar in Model 2 (*HR* = 2.28, 95% *CI*: 1.82-2.85). Prevalent widowhood without remarriage approached significance in Model 3 (*HR* = 1.21, 95% *CI*: 0.95-1.54) and was nonsignificant in Models 4 and 5, which controlled for gender and presence of ε4 allele at APOE (Model 4: *HR* = 1.14, 95% *CI*: 0.88-1.46; Model 5: *HR* = 1.12, 95% *CI*: 0.87-1.45).

Manner of death of spouse. Table 4.13 reports findings from models regressing AD on manner of death of prevalent widowhood. Model 1 indicates that persons whose spouse died of natural causes had over double the risk of AD as persons who did not experience prevalent widowhood (*HR* = 2.13, 95% *CI*: 1.59-2.86). The model shows that persons missing the manner of death of prevalent widowhood were at increased risk (*HR* = 2.03, 95% *CI*: 1.59-2.59). Results were similar in Model 2 (prevalent widowhood by natural causes: *HR* = 2.17, 95% *CI*: 1.61-2.93; missing manner of death: *HR* = 2.02, 95% *CI*: 1.57-2.59). However, Model 3 shows the effects nonsignificant (prevalent widowhood by natural causes: *HR* = 1.23, 95% *CI*: 0.90-1.67; missing manner of death: *HR* = 1.05, 95% *CI*: 0.80-1.38), and remained so in Models 4 and 5.

Table 4.12

Cox Regression: AD Regressed on Prevalent Widowhood with Remarriage

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood with remarriage[b]										
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.67	0.33-1.36	0.69	0.34-1.40	0.69	0.34-1.41	0.59	0.28-1.25
Widowed, no remarriage	2.23	1.79-2.77	2.28	1.82-2.85	1.21	0.95-1.54	1.14	0.88-1.46	1.12	0.87-1.45
Widowed, with remarriage	1.22	0.74-2.03	1.12	0.67-1.90	0.67	0.39-1.14	0.66	0.39-1.13	0.70	0.41-1.19
Occupation of longest duration[c]										
Clerical, sales			0.79	0.58-1.08	0.85	0.62-1.16	0.80	0.58-1.11	0.83	0.60-1.14
Service			1.42	1.0-2.01	1.25	0.88-1.78	1.17	0.82-1.68	1.17	0.82-1.68
Agricultural			1.48	1.09-2.03	1.21	0.89-1.66	1.31	0.95-1.82	1.42	1.02-1.98
Processing			1.64	0.85-3.14	1.22	0.64-2.34	1.18	0.62-2.27	1.25	0.65-2.41
Machine work			1.26	0.70-2.29	0.99	0.54-1.80	1.09	0.59-2.02	1.06	0.57-1.98
Benchwork			0.67	0.34-1.33	0.69	0.34-1.37	0.65	0.33-1.30	0.74	0.37-1.47
Structural			1.05	0.60-1.83	1.03	0.59-1.79	1.15	0.65-2.03	1.13	0.64-2.0
Miscellaneous			0.86	0.40-1.85	0.80	0.37-1.71	0.83	0.39-1.79	0.76	0.35-1.64
Never worked outside home			1.13	0.77-1.66	0.90	0.61-1.32	0.83	0.55-1.23	0.86	0.57-1.27
Age					1.13	1.12-1.15	1.14	1.12-1.15	1.14	1.13-1.16
Gender[d]: Female							1.68	0.98-2.88	1.76	1.02-3.04
Presence of 1+ APOE ε4 allele[e]									2.30	1.87-2.84

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.13

Cox Regression: AD Regressed on Prevalent Widowhood: Manner of Death

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood: Manner of Death[b]										
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.67	0.33-1.36	0.69	0.34-1.40	0.70	0.34-1.42	0.59	0.28-1.25
Widowed, natural causes	2.13	1.59-2.86	2.17	1.61-2.93	1.23	0.90-1.67	1.18	0.86-1.61	1.19	0.87-1.62
Widowed, accident or suicide	1.25	0.31-5.03	1.23	0.30-4.95	0.87	0.21-3.51	0.83	0.20-3.34	0.84	0.21-3.39
Widowed, missing manner of death	2.03	1.59-2.59	2.02	1.57-2.59	1.05	0.80-1.38	0.97	0.74-1.29	0.96	0.73-1.28
Occupation of longest duration[c]										
Clerical, sales			0.80	0.59-1.09	0.86	0.63-1.18	0.80	0.58-1.10	0.83	0.60-1.14
Service			1.45	1.02-2.06	1.27	0.90-1.81	1.17	0.82-1.68	1.18	0.82-1.69
Agricultural			1.46	1.07-2.0	1.18	0.86-1.62	1.30	0.94-1.80	1.41	1.02-1.96
Processing			1.67	0.87-3.19	1.24	0.64-2.37	1.18	0.62-2.27	1.27	0.66-2.43
Machine work			1.26	0.69-2.29	0.95	0.52-1.73	1.08	0.58-2.01	1.08	0.58-2.02
Benchwork			0.70	0.36-1.40	0.72	0.36-1.42	0.66	0.33-1.32	0.75	0.38-1.49
Structural			1.05	0.60-1.83	1.04	0.60-1.81	1.19	0.67-2.09	1.17	0.66-2.07
Miscellaneous			0.86	0.40-1.85	0.79	0.37-1.71	0.84	0.39-1.82	0.78	0.36-1.66
Never worked outside home			1.16	0.79-1.70	0.93	0.64-1.37	0.84	0.56-1.25	0.86	0.58-1.28
Age					1.14	1.12-1.15	1.14	1.12-1.16	1.15	1.13-1.16
Gender[d]: Female							1.79	1.04-3.06	1.86	1.08-3.21
Presence of 1+ APOE ε4 allele[e]									2.32	1.88-2.86

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Number of dependent children at time of widowhood. Table 4.14, which reports results of models in which AD is regressed on prevalent widowhood with dependent children, found a trend toward increased risk among persons with two or more children at the time of prevalent widowhood. In Model 1, those with no dependent children, and two or more dependent children, were 2.15 and 2.24 times more likely to develop AD than persons who had no prevalent widowhoods (no dependent children: *HR* = 2.15, 95% *CI*: 1.73-2.68; two or more dependent children: *HR* = 2.24, 95% *CI*: 1.30-3.84). These results remained in Model 2 (no dependent children: *HR* = 2.16, 95% *CI*: 1.72-2.70; two or more dependent children: *HR* = 2.27, 95% *CI*: 1.32-3.90). In Model 3, prevalent widowhood with no dependent children became nonsignificant (*HR* = 1.09, 95% *CI*: 0.85-1.39) while prevalent widowhood with two or more dependent children approached significance (*HR* = 1.70, *CI*: 0.99-2.93). In Model 4, these effects were nonsignificant (no dependent children: *HR* = 1.02, 95% *CI*: 0.80-1.32; two or more dependent children: *HR* = 1.59, 95% *CI*: 0.92-2.76), whereas in Model 5, a trend among prevalent widowhood with two or more dependent children was found, in which these persons experienced 72% increased risk for AD relative to persons who never widowed (*HR* = 1.72, 95% *CI*: 0.99-2.98). Given that this factor nearly achieved statistical significance, and given that this factor was highly confounded with age, an alternative approach to controlling for age was pursued, in which Cox models regressing AD on prevalent widowhood with dependent children were stratified by narrow age ranges (65-69, 75-79, 85-89). However, because sample sizes were quite low for some cells (see Tables 4.15-4.17), these analyses were not conducted.

Table 4.14

Cox Regression: AD Regressed on Prevalent Widowhood with Dependent Children

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood with dependent children[b]										
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.67	0.33-1.36	0.69	0.34-1.41	0.70	0.34-1.42	0.59	0.28-1.25
Widowed, no dependents	2.15	1.73-2.68	2.16	1.72-2.70	1.09	0.85-1.39	1.02	0.80-1.32	1.0	0.78-1.30
Widowed, 1 dependent	0.92	0.41-2.08	0.94	0.42-2.11	0.74	0.33-1.67	0.69	0.30-1.56	0.76	0.33-1.71
Widowed, 2+ dependents	2.24	1.30-3.84	2.27	1.32-3.90	1.70	0.99-2.93	1.59	0.92-2.76	1.72	0.99-2.98
Occupation of longest duration[c]										
Clerical, sales			0.80	0.59-1.09	0.86	0.63-1.18	0.80	0.58-1.12	0.82	0.60-1.13
Service			1.44	1.01-2.04	1.29	0.91-1.83	1.19	0.83-1.71	1.19	0.83-1.71
Agricultural			1.48	1.08-2.02	1.18	0.86-1.61	1.30	0.93-1.80	1.40	1.0-1.95
Processing			1.64	0.85-3.14	1.24	0.65-2.38	1.19	0.62-2.28	1.27	0.66-2.43
Machine work			1.24	0.69-2.26	0.94	0.52-1.71	1.06	0.57-1.97	1.06	0.57-1.97
Benchwork			0.71	0.36-1.41	0.76	0.38-1.50	0.70	0.35-1.40	0.79	0.40-1.57
Structural			1.07	0.61-1.86	1.50	0.60-1.84	1.20	0.67-2.12	1.18	0.67-2.10
Miscellaneous			0.86	0.40-1.84	0.77	0.36-1.65	0.82	0.38-1.76	0.76	0.35-1.63
Never worked outside home			1.16	0.79-1.70	0.94	0.64-1.38	0.85	0.57-1.26	0.87	0.58-1.30
Age					1.14	1.12-1.15	1.14	1.12-1.16	1.15	1.13-1.16
Gender[d]: Female							1.75	1.02-2.99	1.82	1.06-3.13
Presence of 1+ APOE ε4 allele[e]									2.32	1.89-2.86

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.15

N *Sizes for AD Regressed on Prevalent Widowhood with Dependent Children Among 65-69 Year Olds*

Variable	No dementia	AD
Prevalent widowhood with dependent children		
No prevalent widowhoods	758	34
1+ prevalent divorce, no widowhood	60	2
Widowed, no dependents	87	3
Widowed, 1 dependent	17	1
Widowed, 2+ dependents	10	1

Table 4.16

N *Sizes for AD Regressed on Prevalent Widowhood with Dependent Children Among 75-79 Year Olds*

Variable	No dementia	AD
Prevalent widowhood with dependent children		
No prevalent widowhoods	404	59
1+ prevalent divorce, no widowhood	27	3
Widowed, no dependents	206	33
Widowed, 1 dependent	14	4
Widowed, 2+ dependents	16	1

Table 4.17

N *Sizes for AD Regressed on Prevalent Widowhood with Dependent Children Among 85-89 Year Olds*

Variable	No dementia	AD
Prevalent widowhood with dependent children		
No prevalent widowhoods	64	18
1+ prevalent divorce, no widowhood	1	0
Widowed, no dependents	103	33
Widowed, 1 dependent	4	0
Widowed, 2+ dependents	4	2

Number of adult children at time of widowhood. Table 4.18 reports models in which AD was regressed on prevalent widowhood with number of adult children. This indicates that those with 1-2, 3-4, and 5 or more adult children at the time of prevalent widowhood were 95%, 2.07 times, and 2.44 times more likely to develop AD as persons who did not experience prevalent AD (1-2 adult children: *HR* = 1.95, 95% *CI*: 1.40-2.71; 3-4 adult children: *HR* = 2.07, 95% *CI*: 1.52-2.82; 5+ adult children: *HR* = 2.44, 95% *CI*: 1.75-3.38). Results were similar for Model 2 (1-2 adult children: *HR* = 1.98, 95% *CI*: 1.41-2.76; 3-4 adult children: *HR* = 2.08, 95% *CI*: 1.52-2.84; 5 or more adults children *HR* = 2.42, 95% *CI*: 1.74-3.38). In Model 3, effects for 1-2 and 3-4 adult children became nonsignificant (1-2 adult children: *HR* = 1.01, 95% *CI*: 0.71-1.43; 3-4 adult children: *HR* = 1.01, 95% *CI*: 0.71-1.43) and the effect for five or more adult children approached significance (*HR* = 1.34, 95% *CI*: 0.95-1.89). In Models 4 and 5, these effects were nonsignificant.

Tests of moderating effects. Tables 4.19 through 4.21 report models regressing AD on the interaction between prevalent widowhood, and gender, presence of ε4 allele at APOE, and history of depression, respectively. In Model 1 of these analyses, AD is regressed on prevalent widowhood alone. In Model 2, AD is regressed on each moderator and its interaction with prevalent widowhood. In Model 3, the remaining covariates are added. Table 4.19 indicates that the main effect of gender is nonsignificant (*HR* = 1.42, 95% *CI*: 0.83-2.44) as is its interaction with prevalent widowhood (*HR* = 1.08, 95% *CI*: 0.66-1.77). These effects remained nonsignificant in Model 3, which controlled for occupation, age, and presence of ε4 allele at APOE. Table 4.20 presents models

Table 4.18

Cox Regression: AD Regressed on Prevalent Widowhood with Adult Children

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood with adult children[b]										
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.67	0.33-1.36	0.69	0.34-1.40	0.70	0.34-1.41	0.59	0.28-1.25
Widowed, no adult children	1.52	0.90-2.57	1.52	0.90-2.57	0.97	0.57-1.66	0.90	0.53-1.54	0.90	0.52-1.58
Widowed, 1-2 adult children	1.95	1.40-2.71	1.98	1.41-2.76	1.01	0.71-1.43	0.95	0.67-1.36	0.92	0.64-1.31
Widowed, 3-4 adult children	2.07	1.52-2.82	2.08	1.52-2.84	1.10	0.79-1.52	1.04	0.75-1.45	1.03	0.74-1.44
Widowed, 5+ adult children	2.44	1.75-3.38	2.42	1.74-3.38	1.34	0.95-1.89	1.23	0.87-1.78	1.29	0.91-1.84
Occupation of longest duration[c]										
Clerical, sales			0.80	0.59-1.09	0.86	0.63-1.18	0.81	0.59-1.11	0.83	0.60-1.15
Service			1.45	1.02-2.06	1.28	0.90-1.82	1.18	0.82-1.70	1.18	0.83-1.70
Agricultural			1.46	1.07-2.0	1.17	0.86-1.61	1.29	0.93-1.78	1.40	1.0-1.95
Processing			1.65	0.86-3.16	1.23	0.64-2.35	1.18	0.62-2.27	1.26	0.66-2.43
Machine work			1.25	0.69-2.27	0.92	0.51-1.68	1.04	0.56-1.92	1.03	0.56-1.93
Benchwork			0.71	0.36-1.42	0.74	0.37-1.48	0.69	0.35-1.38	0.79	0.40-1.57
Structural			1.04	0.60-1.82	1.03	0.59-1.80	1.17	0.66-2.07	1.15	0.65-2.03
Miscellaneous			0.85	0.40-1.82	0.78	0.37-1.68	0.83	0.39-1.79	0.77	0.36-1.66
Never worked outside home			1.13	0.77-1.66	0.91	0.62-1.34	0.82	0.55-1.22	0.84	0.57-1.26
Age					1.13	1.12-1.15	1.14	1.12-1.15	1.14	1.13-1.16
Gender[d]: Female							1.74	1.02-2.99	1.81	1.05-3.12
Presence of 1+ APOE ε4 allele[e]									2.33	1.89-2.88

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.19

Cox Regression: AD Regressed on Prevalent Widowhood by Gender

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood[b]						
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.87	0.38-1.98	0.70	0.28-1.70
1+ widowhood	2.05	1.66-2.53	1.92	1.25-2.93	0.91	0.58-1.42
Gender[c]: Female			1.42	0.83-2.44	1.72	0.96-3.05
Prevalent widowhood x Gender						
1+ prevalent divorce, no widowhood; Female			0.41	0.08-2.09	0.62	0.12-3.27
1+ widowhood; Female			1.08	0.66-1.77	1.20	0.72-2.01
Occupation of longest duration[d]						
Clerical, sales					0.83	0.60-1.14
Service					1.17	0.82-1.68
Agricultural					1.42	1.02-1.98
Processing					1.25	0.65-2.40
Machine work					1.09	0.58-2.04
Benchwork					0.75	0.38-1.49
Structural					1.16	0.65-2.05
Miscellaneous					0.76	0.36-1.65
Never worked outside home					0.86	0.58-1.28
Age					1.15	1.13-1.16
Presence of 1+ APOE ε4 allele[e]					2.32	1.88-2.85

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: male.
[d] Reference category: professional, technical, managerial.
[e] Reference category: 0 APOE ε4 alleles.

regressing AD on the interaction between prevalent widowhood and presence of ε4 allele at APOE. In Model 2, the main effect for ε4 allele at APOE was significant (*HR* = 1.97, 95% *CI*: 1.50-2.58) and the interaction between this and prevalent widowhood was not significant (*HR* = 0.95, 95% *CI*: 0.62-1.44). Results were similar in Model 3, which controlled for occupation, age, and gender. In this model, the effect of ε4 allele at APOE increased slightly (*HR* = 2.35, 95% *CI*: 1.79-3.09) and the interaction between this factor and prevalent widowhood remained nonsignificant (*HR* = 0.94, 95% *CI*: 0.61-1.43). In Table 4.21, Cox models regressing AD on the interaction between prevalent widowhood

Table 4.20

Cox Regression: AD Regressed on Prevalent Widowhood by APOE ε4

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood[b]						
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.33	0.08-1.32	0.39	0.10-1.58
1+ widowhood	2.05	1.66-2.53	2.17	1.64-2.88	1.07	0.79-1.46
Presence of 1+ APOE ε4 allele[c]			1.97	1.50-2.58	2.35	1.79-3.09
Prevalent widowhood x APOE ε4 allele						
1+ prevalent divorce, no widowhood; 1+ APOE ε4 allele			2.43	0.46-12.83	1.89	0.36-9.99
1+ widowhoodz; 1+ APOE ε4 allele			0.95	0.62-1.44	0.94	0.61-1.43
Occupation of longest duration[d]						
Clerical, sales					0.83	0.60-1.14
Service					1.18	0.82-1.69
Agricultural					1.41	1.02-1.97
Processing					1.26	0.66-2.43
Machine work					1.05	0.56-1.95
Benchwork					0.76	0.38-1.51
Structural					1.17	0.66-2.07
Miscellaneous					0.77	0.36-1.67
Never worked outside home					0.86	0.58-1.28
Age					1.14	1.13-1.16
Gender[e]: Female					1.82	1.06-3.14

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: 0 APOE ε4 alleles.
[d] Reference category: professional, technical, managerial.
[e] Reference category: male.

and history of depression are presented. Model 2 indicates that those with a history of antidepressant use without depression have a 74% increased risk of AD relative to those without a history of antidepressant use or depression (*HR* = 1.74, 95% *CI*: 1.23-2.47). However, the interaction of this factor with prevalent widowhood was not significant. In Model 3, which controlled for occupation, age, gender, and presence of ε4 allele at APOE, those with a history of antidepressant use without depression experienced twofold increased risk for AD (*HR* = 2.0, 95% *CI*: 1.40-2.84) and those with a history of depression and antidepressant use experienced 64% increased risk (*HR* = 1.64, 95%

Table 4.21

Cox Regression: AD Regressed on Prevalent Widowhood by Depression History

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Prevalent widowhood[b]						
1+ prevalent divorce, no widowhood	0.64	0.32-1.31	0.95	0.42-2.15	0.71	0.29-1.74
1+ widowhood	2.05	1.66-2.53	2.52	1.92-3.31	1.24	0.91-1.68
History of depression[c]						
Depression hx/no antidepressant hx			0.89	0.56-1.41	0.84	0.53-1.34
No depression hx/antidepressant hx			1.74	1.23-2.47	2.0	1.40-2.84
Depression hx/antidepressant hx			1.15	0.75-1.75	1.64	1.06-2.53
Prevalent widowhood x History of depression						
1+ prevalent divorce, no widowhood by depression hx/no antidepressant hx			0		0	
1+ prevalent divorce, no widowhood by no depression hx/antidepressant hx			1.20	0.23-6.17	1.82	0.34-9.88
1+ prevalent divorce, no widowhood by depression hx/antidepressant hx			0		0	
1+ widowhood by depression hx/no antidepressant hx			0.51	0.25-1.06	0.68	0.33-1.41
1+ widowhood by no depression hx/ antidepressant hx			0.86	0.50-1.48	0.81	0.47-1.40
1+ widowhood by depression hx/ antidepressant hx			0.51	0.25-1.01	0.46	0.23-0.94
Occupation of longest duration[d]						
Clerical, sales					0.86	0.62-1.18
Service					1.25	0.87-1.79
Agricultural					1.48	1.06-2.07
Processing					1.38	0.71-2.66
Machine work					0.94	0.50-1.75
Benchwork					0.82	0.41-1.64
Structural					1.14	0.64-2.03
Miscellaneous					0.84	0.39-1.81
Never worked outside home					0.82	0.55-1.22
Age					1.15	1.13-1.17
Gender[e]: Female					1.69	0.98-2.91
Presence of 1+ APOE ε4 allele[f]					2.40	1.94-2.97

[a] 95% confidence interval.
[b] Reference category: no prevalent widowhoods.
[c] Reference category: no depression hx/no antidepressant hx.
[d] Reference category: professional, technical, managerial.
[e] Reference category: male.
[f] Reference category: 0 APOE ε4 alleles.

CI: 1.06-2.53). In this final model, the interaction between prevalent widowhood and history of depression remained nonsignificant.

Dementia Regressed on Incident Widowhood

Tables 4.22 through 4.27 (each will be described and shown separately) report Cox models regressing dementia on incident widowhood (among subjects who had not yet been widowed as of baseline) and the interaction between this factor, and gender, presence of ε4 allele at APOE, and history of depression. Table 4.22 indicates that those with one or more incident widowhoods were 44% more likely to develop dementia as those who did not experience incident widowhood (*HR* = 1.44, 95% *CI*: 1.11-1.88). Results for incident widowhood were similar in Model 2, which controlled for occupation (*HR* = 1.47, 95% *CI*: 1.13-1.92). In Model 3, which controlled for age, the statistical effect of incident widowhood became nonsignificant (*HR* = 0.96, 95% *CI*: 0.72-1.26). In Models 4 and 5, which controlled for gender and presence of ε4 allele at APOE, respectively, the statistical effect of incident widowhood was also nonsignificant (Model 1: *HR* = 0.98, 95% *CI*: 0.74-1.31; Model 5: *HR* = 0.99, 95% *CI*: 0.75-1.32).

Moderation by gender. Table 4.23 reports models regressing dementia on the interaction between incident widowhood and gender. This indicates that the main effect of gender was not significant (*HR* = 1.26, 95% *CI*: 0.75-2.10), and that the interaction between gender and incident widowhood was also nonsignificant (*HR* = 1.63, 95% *CI*: 0.91-2.91). In Model 3, which controlled for occupation, age, and presence of ε4 allele at APOE, gender was nonsignificant (*HR* = 1.53, 95% *CI*: 0.89-2.63) and the interaction

Table 4.22

Cox Regression: Dementia Regressed on Incident Widowhood

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.44	1.11-1.88	1.47	1.13-1.92	0.96	0.72-1.26	0.98	0.74-1.31	0.99	0.75-1.32
Occupation of longest duration[c]										
Clerical, sales			0.79	0.58-1.09	0.90	0.65-1.23	0.91	0.65-1.27	0.93	0.66-1.29
Service			1.33	0.90-1.96	1.26	0.85-1.86	1.26	0.84-1.89	1.16	0.77-1.75
Agricultural			1.45	1.07-1.96	1.22	0.90-1.65	1.22	0.89-1.67	1.28	0.94-1.75
Processing			0.94	0.35-2.55	0.71	0.26-1.92	0.71	0.26-1.93	0.78	0.29-2.12
Machine work			1.15	0.61-2.20	1.08	0.57-2.06	1.08	0.56-2.08	1.15	0.60-2.22
Benchwork			0.99	0.44-2.25	1.17	0.52-2.67	1.16	0.51-2.63	1.18	0.52-2.69
Structural			0.94	0.56-1.58	0.90	0.53-1.52	0.90	0.53-1.53	0.89	0.52-1.51
Miscellaneous			1.19	0.58-2.43	1.11	0.54-2.27	1.12	0.55-2.30	1.09	0.53-2.25
Never worked outside home			0.91	0.58-1.42	0.94	0.60-1.46	0.95	0.60-1.52	0.92	0.57-1.48
Age					1.13	1.11-1.15	1.13	1.11-1.15	1.13	1.11-1.15
Gender[d]: Female							1.44	0.84-2.47	1.52	0.88-2.61
Presence of 1+ APOE ε4 allele[e]									1.90	1.53-2.36

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.23

Cox Regression: Dementia Regressed on Incident Widowhood by Gender

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.44	1.11-1.88	1.17	0.73-1.86	0.71	0.45-1.14
Gender[c]: Female			1.26	0.75-2.10	1.53	0.89-2.63
Incident widowhood x Gender			1.63	0.91-2.91	1.74	0.97-3.10
Occupation of longest duration[d]						
Clerical, sales					0.94	0.67-1.32
Service					1.16	0.77-1.75
Agricultural					1.30	0.95-1.78
Processing					0.82	0.30-2.23
Machine work					1.14	0.59-2.19
Benchwork					1.19	0.52-2.71
Structural					0.90	0.53-1.53
Miscellaneous					1.12	0.54-2.30
Never worked outside home					0.92	0.57-1.47
Age					1.13	1.11-1.15
Presence of 1+ APOE ε4 allele[e]					1.74	0.97-3.10

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: male.
[d] Reference category: professional, technical, managerial.
[e] Reference category: 0 APOE ε4 alleles.

between gender and incident widowhood, though not statistically significant, indicated a trend (*HR* = 1.74, 95% *CI*: 0.97-3.10). Following the convention of stratifying models after achieving statistical significance for an interaction term at least the p =.10 level, models stratified by gender were conducted (see Table 4.24). Because these analyses included a reduced number of dementia cases, the following categories of the occupation of longest duration variable were collapsed: blue collar workers (processing, machine work, benchwork, structural), miscellaneous, and never worked outside of home. These analyses indicate that although incident widowhood was not significantly related to risk among males or females, a trend toward opposite risk among them was found, in which

Table 4.24

Cox Regression: Dementia Regressed on Incident Widowhood, Stratified by Gender

	Males		Females	
Variables	*HR*	*CI*[a]	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	0.72	0.45-1.16	1.21	0.83-1.75
Occupation of longest duration[c]				
Clerical, sales	0.90	0.49-1.65	1.08	0.67-1.55
Service	1.26	0.57-2.79	1.19	0.72-1.96
Agricultural	1.28	0.90-1.80	1.28	0.58-2.84
Miscellaneous[d]	0.86	0.57-1.29	1.15	0.74-1.78
Age	1.12	1.10-1.15	1.14	1.11-1.17
Presence of 1+ APOE ε4 allele[e]	1.84	1.37-2.48	1.97	1.43-2.70

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Miscellaneous: blue collar (processing, machine work, benchwork, structural), miscellaneous, never worked outside of home
[e] Reference category: 0 APOE ε4 alleles

widowed men trended toward decreased risk for dementia relative to never-widowed men, whereas widowed women trended towards increased risk relative to never-widowed women.

Moderation by APOE genotype. Table 4.25, which displays results of models interacting incident widowhood with ε4 allele at APOE, indicates that the main effect of ε4 allele at APOE was significant (*HR* = 1.62, 95% *CI*: 1.27-2.07), while the interaction between this factor and incident widowhood was not significant (*HR* = 1.07, 95% *CI*: 0.64-1.77). Results were similar in Model 3, which controlled for occupation, age, and gender. In this model, the statistical effect of ε4 allele at APOE increased slightly (*HR* = 1.83, 95% *CI*: 1.43-2.33), while the interaction between this factor and incident widowhood remained nonsignificant (*HR* = 1.19, 95% *CI*: 0.71-1.98).

Table 4.25

Cox Regression: Dementia Regressed on Incident Widowhood by APOE ε4

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.44	1.11-1.88	1.41	0.99-2.00	0.92	0.63-1.33
Presence of 1+ APOE ε4 allele[c]			1.62	1.27-2.07	1.83	1.43-2.33
Incident widowhood x APOE ε4			1.07	0.64-1.77	1.19	0.71-1.98
Occupation of longest duration[d]						
Clerical, sales					0.93	0.66-1.30
Service					1.16	0.77-1.75
Agricultural					1.28	0.94-1.75
Processing					0.79	0.29-2.15
Machine work					1.16	0.60-2.23
Benchwork					1.18	0.52-2.69
Structural					0.89	0.52-1.51
Miscellaneous					1.10	0.53-2.25
Never worked outside home					0.92	0.57-1.48
Age					1.13	1.11-1.15
Gender					1.52	0.88-2.62

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: 0 APOE ε4 alleles
[d] Reference category: professional, technical, managerial.

Moderation by depression history. Table 4.26, which displays models regressing dementia on the interaction between incident widowhood and history of depression, indicates a significant interaction between these factors. This table indicates that the main effect of history of depression was significant, in that those with a history of antidepressant use without depression were 93% more likely to acquire dementia as those with no history of antidepressant use or depression (*HR* = 1.81, 95% *CI*: 1.35-2.44). However, in this model the interaction between history of depression and incident widowhood was not significant. In Model 3, which controlled for occupation, age, gender, and presence of ε4 allele at APOE, the interaction between history of depression

Table 4.26

Cox Regression: Dementia Regressed on Incident Widowhood by Depression History

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.44	1.11-1.88	1.10	0.74-1.64	0.70	0.46-1.06
History of depression[c]						
Depression hx/no antidepressant hx			0.76	0.49-1.18	0.81	0.52-1.26
No depression hx/antidepressant hx			1.81	1.35-2.44	1.93	1.43-2.61
Depression hx/antidepressant hx			0.88	0.58-1.36	1.16	0.74-1.82
Incident widowhood x History of depression						
1+ widowhood by Depression hx/no antidepressant hx			1.50	0.64-3.47	1.50	0.64-3.49
1+ widowhood by No depression hx/ antidepressant hx			1.50	0.79-2.83	1.90	1.00-3.60
1+ widowhood by Depression hx/ antidepressant hx			2.02	0.97-4.18	2.63	1.26-5.50
Occupation of longest duration[d]						
Clerical, sales					0.94	0.67-1.31
Service					1.24	0.82-1.87
Agricultural					1.33	0.97-1.82
Processing					0.82	0.30-2.25
Machine work					1.07	0.55-2.06
Benchwork					1.21	0.53-2.79
Structural					0.90	0.53-1.54
Miscellaneous					1.07	0.52-2.20
Never worked outside home					0.85	0.53-1.37
Age					1.14	1.12-1.16
Gender					1.52	0.88-2.63
Presence of 1+ APOE ε4 allele[e]					2.03	1.63-2.53

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: no depression hx/no antidepressant hx.
[d] Reference category: professional, technical, managerial.
[e] Reference category: 0 APOE ε4 alleles.

and incident widowhood was significant (*HR* = 2.63, 95% *CI*: 1.26-5.50). Given that this interaction was significant, models stratified by history of depression were run (see Table 4.27). These models indicate that among persons with no history of depression or antidepressant use, a trend was found in which those who experienced incident widowhood were 34% less likely to acquire dementia than those who did not experience incident widowhood (*HR* = 0.66, 95% *CI*: 0.42-1.02). Among persons with a history of

Table 4.27

Cox Regression: Dementia Regressed on Incident Widowhood, Stratified by Depression History

	No depression/no antidepressants[a]		Depression/no antidepressants[b]		No depression/ antidepressants[c]		Depression/ antidepressants[d]	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Incident widowhood[f]: 1+ widowhood	0.66	0.42-1.02	1.02	0.42-2.50	1.28	0.71-2.29	1.93	0.98-3.81
Occupation of longest duration[g]								
Clerical, sales	0.86	0.53-1.38	0.49	0.15-1.53	1.38	0.75-2.54	0.82	0.32-2.13
Service	1.40	0.83-2.36	0.13	0.02-1.00	1.81	0.68-4.83	0.88	0.29-2.66
Agricultural	1.46	0.97-2.19	0.67	0.25-1.80	1.17	0.54-2.52	1.25	0.48-3.25
Miscellaneous[h]	1.08	0.72-1.64	0.40	0.15-1.07	1.14	0.63-2.07	0.49	0.20-1.23
Age	1.14	1.11-1.17	1.18	1.10-1.26	1.13	1.08-1.17	1.14	1.06-1.21
Gender	1.82	0.93-3.57	0.50	0.09-2.68	1.60	0.46-5.57	1.14	0.14-9.04
Presence of 1+ APOE ε4 allele[i]	1.93	1.44-2.58	6.78	3.06-15.02	1.43	0.89-2.32	2.01	1.03-3.92

[a] No history of depression or antidepressant use.
[b] History of depression and no history of antidepressant use.
[c] No history of depression and history of antidepressant use.
[d] History of depression and antidepressant use.
[e] 95% confidence interval.
[f] Reference category: no incident widowhoods.
[g] Reference category: professional, technical, managerial.
[h] Miscellaneous: blue collar (processing, machine work, benchwork, structural), miscellaneous, never worked outside of home.
[I] Reference category: 0 APOE ε4 alleles.

depression and no history of antidepressant use, and persons with no history of depression and a history of antidepressant use, incident widowhood was not related to risk for dementia (*HR* = 1.02, 95% CI: 0.42-2.50; *HR* = 1.28, 95% *CI*: 0.71-2.29). In contrast, among those with a history of depression and antidepressant use, a trend was found in which those who experienced incident widowhood were 93% more likely to develop dementia (*HR* = 1.93, 95% *CI*: 0.98-3.81).

AD Regressed on Incident Widowhood

Tables 4.28-4.32 present Cox models in which AD is regressed on incident widowhood, and on the interaction of this factor with gender, ε4 allele at APOE, and history of depression. Table 4.28 indicates that those who experienced an incident widowhood experienced 64% increased risk of AD relative to those who did experience an incident widowhood (*HR* = 1.64, 95% *CI*: 1.19-2.26). Results for Model 2 were similar, with those with an incident widowhood having 67% increased risk (*HR* = 1.67, 95% *CI*: 1.21-2.31). In Model 3, this statistical effect lost significance (*HR* = 1.05, 95% *CI*: 0.75-1.47). Incident widowhood remained nonsignificant in Models 4 and 5.

Moderation by gender. Table 4.29 indicates that the main effect of gender was nonsignificant (*HR* = 1.09, 95% *CI*: 0.57-2.06) as was also the interaction of this factor with incident widowhood (*HR* = 1.44, 95% *CI*: 0.71-2.92). These effects remained nonsignificant in Models 4 and 5.

Moderation by APOE genotype. Table 4.30 presents results of models regressing incident widowhood on the interaction between this factor and presence of ε4 allele at APOE. This table indicates that the main effect of this factor was significant, in

Table 4.28

Cox Regression: AD Regressed on Incident Widowhood

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.64	1.19-2.26	1.67	1.21-2.31	1.05	0.75-1.47	1.01	0.71-1.42	1.0	0.71-1.42
Occupation of longest duration[c]										
Clerical, sales			0.81	0.55-1.21	0.94	0.63-1.39	0.87	0.58-1.32	0.88	0.58-1.34
Service			1.43	0.89-2.30	1.33	0.82-2.14	1.22	0.75-2.00	1.14	0.70-1.87
Agricultural			1.45	0.99-2.14	1.19	0.81-1.76	1.28	0.86-1.92	1.40	0.93-2.09
Processing			1.10	0.35-3.49	0.75	0.24-2.40	0.75	0.23-2.38	0.85	0.27-2.72
Machine work			1.31	0.60-2.84	1.22	0.56-2.65	1.34	0.61-2.94	1.49	0.68-3.29
Benchwork			1.05	0.39-2.88	1.27	0.47-3.48	1.20	0.44-3.30	1.27	0.46-3.48
Structural			1.05	0.56-1.98	1.06	0.57-2.00	1.16	0.61-2.22	1.14	0.60-2.19
Miscellaneous			1.39	0.61-3.20	1.26	0.55-2.90	1.34	0.58-3.11	1.32	0.57-3.04
Never worked outside home			0.70	0.37-1.32	0.69	0.37-1.30	0.62	0.32-1.20	0.60	0.31-1.15
Age					1.14	1.11-1.17	1.14	1.12-1.17	1.15	1.13-1.18
Gender[d]: Female							1.45	0.74-2.85	1.55	0.78-3.07
Presence of 1+ APOE ε4 allele[e]									2.41	1.84-3.17

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: professional, technical, managerial.
[d] Reference category: male.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.29

Cox Regression: AD Regressed on Incident Widowhood by Gender

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.64	1.19-2.26	1.37	0.77-2.42	0.77	0.42-1.35
Gender[c]: Female			1.09	0.57-2.06	1.55	0.78-3.06
Incident widowhood x Gender			1.44	0.71-2.92	1.57	0.77-3.20
Occupation of longest duration[d]						
Clerical, sales					0.90	0.59-1.36
Service					1.14	0.70-1.87
Agricultural					1.42	0.95-2.13
Processing					0.90	0.28-2.86
Machine work					1.48	0.67-3.25
Benchwork					1.28	0.47-3.52
Structural					1.15	0.60-2.21
Miscellaneous					1.34	0.58-3.11
Never worked outside home					0.59	0.31-1.15
Age					1.15	1.13-1.18
Presence of 1+ APOE ε4 allele[e]					2.43	1.85-3.19

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: male.
[d] Reference category: professional, technical, managerial.
[e] Reference category: 0 APOE ε4 alleles.

that those with one or more ε4 alleles at APOE were at twofold risk of developing AD as persons without such alleles (*HR* =2.03, 95% *CI*: 1.49-2.76). However, the interaction of this factor with incident widowhood was not significant (*HR* = 1.0, 95% *CI*: 0.54-1.84). Results were similar for Model 3, which controlled for occupation, age, and gender, with the main effect of ε4 allele at APOE increasing slightly (*HR* = 2.37, 95% *CI*: 1.73-3.24).

Moderation by depression history. Finally, Table 4.31 indicates that, when tested without covariates (Model 1), the interaction between incident widowhood and history of depression was not significant. However, after controlling for occupation, age, gender, and ε4 allele at APOE, this interaction became significant (*HR* = 1.68, 95%

Table 4.30

Cox Regression: AD Regressed on Incident Widowhood by APOE ε4

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.64	1.19-2.26	1.66	1.07-2.58	0.97	0.61-1.54
Presence of 1+ APOE ε4 allele[c]			2.03	1.49-2.76	2.37	1.73-3.24
Incident widowhood x APOE ε4			1.00	0.54-1.84	1.08	0.58-1.99
Occupation of longest duration[d]						
Clerical, sales					0.88	0.58-1.34
Service					1.14	0.70-1.87
Agricultural					1.40	0.93-2.10
Processing					0.86	0.27-2.74
Machine work					1.49	0.68-3.30
Benchwork					1.27	0.46-3.48
Structural					1.14	0.60-2.19
Miscellaneous					1.32	0.57-3.05
Never worked outside home					0.60	0.31-1.15
Age					1.15	1.13-1.18
Gender					1.55	0.78-3.07

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: 0 APOE ε4 alleles.
[d] Reference category: male.

CI: 1.11-2.53). Because this interaction was significant, models stratified by history of depression were run (Table 4.32). These results indicate that among persons with no history of depression or antidepressant use, those who experienced incident widowhood were 46% less likely to develop AD as persons who were never widowed (*HR* = 0.54, 95% *CI*: 0.31-0.92). Among persons with a history of depression and no history of antidepressant use, incident widowhood was not associated with risk for AD. A trend among persons with no history of depression and a history of antidepressant use, and persons with a history of depression and antidepressant use was observed, in which those who experienced incident widowhood were at higher risk for AD relative to those who

Table 4.31

Cox Regression: AD Regressed on Incident Widowhood by Depression History

	Model 1		Model 2		Model 3	
Variable	*HR*	*CI*[a]	*HR*	*CI*	*HR*	*CI*
Incident widowhood[b]: 1+ widowhood	1.64	1.19-2.26	1.07	0.65-1.76	0.59	0.35-0.99
History of depression[c]						
Depression hx/no antidepressant hx			0.64	0.36-1.14	0.66	0.37-1.19
No depression hx/antidepressant hx			1.46	0.97-2.19	1.68	1.11-2.53
Depression hx/antidepressant hx			0.73	0.41-1.30	1.12	0.62-2.02
Incident widowhood x History of depression						
1+ widowhood by Depression hx/no antidepressant hx			2.15	0.79-5.90	2.15	0.78-5.93
1+ widowhood by No depression hx/antidepressant hx			2.01	0.91-4.43	2.72	1.22-6.05
1+ widowhood by Depression hx/antidepressant hx			2.75	1.11-6.84	3.41	1.37-8.52
Occupation of longest duration[d]						
Clerical, sales					0.89	0.59-1.35
Service					1.20	0.73-1.97
Agricultural					1.49	0.99-2.25
Processing					0.92	0.29-2.94
Machine work					1.40	0.63-3.11
Benchwork					1.30	0.47-3.61
Structural					1.15	0.60-2.20
Miscellaneous					1.25	0.54-2.90
Never worked outside home					0.55	0.28-1.05
Age					1.16	1.13-1.19
Gender					1.59	0.80-3.16
Presence of 1+ APOE ε4 allele[e]					2.64	2.00-3.49

[a] 95% confidence interval.
[b] Reference category: no incident widowhoods.
[c] Reference category: no depression hx/no antidepressant hx.
[d] Reference category: professional, technical, managerial.
[e] Reference category: 0 APOE ε4 alleles.

Table 4.32

Cox Regression: AD Regressed on Incident Widowhood, Stratified by Depression History

	No depression/no antidepressants[a]		Depression/no antidepressants[b]		No depression/ antidepressants[c]		Depression/ antidepressants[d]	
Variable	*HR*	*CI*[e]	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Incident widowhood[f]: 1+ widowhood	0.54	0.31-0.92	1.06 0.	37-3.03	1.80	0.86-3.75	1.89	0.80-4.43
Occupation of longest duration[g]								
Clerical, sales	0.80	0.44-1.43	0.43	0.09-2.12	1.44	0.65-3.21	1.14	0.38-3.46
Service	1.38	0.75-2.56	0		1.86	0.52-6.66	0.94	0.24-3.71
Agricultural	1.54	0.93-2.55	1.04	0.30-3.63	1.14	0.35-3.71	0.90	0.23-3.47
Miscellaneous[h]	1.12	0.67-1.86	0.76	0.23-2.55	1.17	0.53-2.58	0.21	0.04-0.98
Age	1.17	1.14-1.21	1.20	1.11-1.30	1.10	1.03-1.17	1.19	1.08-1.30
Gender	1.89	0.86-4.14	0.21	0.01-4.80	1.22	0.24-6.22	2.50	0.03-225.2
Presence of 1+ APOE ε4 allele[i]	2.55	1.78-3.65	4.71	1.73-12.78	1.76	0.93-3.33	3.21	1.35-7.63

[a] No history of depression or antidepressant use.
[b] History of depression and no history of antidepressant use.
[c] No history of depression and history of antidepressant use.
[d] History of depression and antidepressant use.
[e] 95% confidence interval.
[f] Reference category: no incident widowhoods.
[g] Reference category: professional, technical, managerial.
[h] Miscellaneous: blue collar (processing, machine work, benchwork, structural), miscellaneous, never worked outside of home.
[I] Reference category: 0 APOE ε4 alleles.

never widowed (*HR* =1.80, 95% *CI*: 0.86-3.75 and *HR* = 1.89, 95% *CI*: 0.80-4.43, respectively).

Summary of Cox Models

This section presents Cox models which have assessed whether widowhood, and the context of widowhood, are related to risk for dementia or AD. Results of these analyses are summarized in Table 4.33. In general, the relationship between widowhood and dementia and AD was highly confounded with age. However, some variables reflecting the context of widowhood were statistically significant or showed trends towards statistical significance even after inclusion of age. This can be seen in models regressing dementia and AD on prevalent widowhood with number of dependent children. In these models, trends were found that suggested that those with two or more dependent children at the time of prevalent widowhood were 42% and 72% more likely to develop dementia and AD, respectively. Because this contextual factor nearly achieved statistical significance in models of AD, an alternative approach to controlling for age was attempted, which consisted of conducting models stratified by narrow age ranges (65-69, 75-79, 85-89). However, low sample sizes in these age ranges precluded these analyses. In models regressing dementia on the interaction between incident widowhood and gender, the convention of stratifying models in which the interaction term achieved significance at the $p < .10$ level was followed. These models indicated a trend towards opposing risk between males and females, which suggested that males who experienced incident widowhood were less likely than males who were never widowed to develop dementia, whereas females who experienced incident widowhood were more likely to

Table 4.33

Summary of Cox Regression Analyses: Dementia and AD on Widowhood, Contextual Variables, and Moderator Variables

Variable	All-cause dementia[a]	AD[a]
Prevalent widowhood	$p = .35$	$p = .35$
Prevalent widowhood, Age at first widowhood	$p = .65$	$p = .60$
Prevalent widowhood, with remarriage	$p = .25$	$p = .16$
Prevalent widowhood, with manner of death	$p = .67$	$p = .45$
Prevalent widowhood, with number of dependents[b]	$p = .29$	$p = .17$
Prevalent widowhood, with number of adult children[c]	p = .59	p = .41
Prevalent widowhood x Gender	$p = .77$	$p = .64$
Prevalent widowhood x Presence of APOE ε4 allele	$p = .55$	$p = .70$
Prevalent widowhood x History of depression	$p = .36$	$p = .45$
Incident widowhood	$p = .95$	$p = .99$
Incident widowhood x Gender	$p = .06$	$p = .21$
Incident widowhood: Males	$HR = 0.72$, $p = .18$	-
Incident widowhood: Females	$HR = 1.21$, $p = .32$	-
Incident widowhood x Presence of APOE ε4 allele	$p = .51$	$p = .81$
Incident widowhood x History of depression	$p = .05$	$p = .02$
No depression/No antidepressants[d]	$HR = 0.66$, $p = .059$	$HR = 0.54$, $p = .02$
Depression/No antidepressants[e]	$HR = 1.02$, $p = .96$	$HR = 1.06$, $p = .92$
No depression/Antidepressants[f]	$HR = 1.28$, $p = .41$	$HR = 1.80$, $p = .12$
Depression/Antidepressants[g]	$HR = 1.93$, $p = .059$	$HR = 1.89$, $p = .15$

[a] $p = p$ value associated with Wald statistic for each predictor or interaction term. Each exposure variable and interaction term was tested in a separate model with the following covariates: occupation, age, gender, and presence of ε4 allele at APOE.
[b] Number of dependent children at first prevalent widowhood.
[c] Number of adult children at first prevalent widowhood.
[d] No history of depression or antidepressant use.
[e] History of depression and no history of antidepressant use.
[f] No history of depression and history of antidepressant use.
[g] History of depression and antidepressant use.

develop dementia. In models of dementia and AD risk, significant interactions between incident widowhood and history of depression were found. In models of dementia stratified by history of depression, strong trends were found that suggested that among persons with no history of depression or antidepressant use, those who experienced

incident widowhood were 34% less likely to acquire dementia than those who did not experience incident widowhood, whereas those with a history of depression and antidepressant use were 93% more likely to develop dementia than those without incident widowhoods. Similar findings were observed in models of AD risk, such that among persons with no history of depression or antidepressant use, those who experienced incident widowhood were 46% less likely to develop AD, whereas among persons with a history of depression and no antidepressant use, persons who experienced incident widowhood were not more or less likely to develop AD, and among and persons with no history of depression and antidepressant use and persons with a history of depression and antidepressant use, trends suggested that those who experienced incident widowhood were 80% and 89% more likely to develop AD, respectively, than those who did not experience incident widowhood.

CHAPTER 5

DISCUSSION

This study thoroughly investigated the strength of association between widowhood, arguably one of the most stressful and severe life stressors (Holmes & Rahe, 1967), and dementia or AD. Gender was found to moderate the association between incident widowhood and dementia, in that opposing risk trends were found between men and women, with widowhood associated with decreased risk for dementia among men but increased risk among women. History of depression and antidepressant use also moderated this relationship, in that widowhood was associated with decreased risk for dementia and AD among the never-depressed, increased risk for AD among those with a history of antidepressant use but no depression, and with increased risk for dementia and AD among those with a history of both. In addition, a trend was found for increased risk for AD among widowed persons with two or more dependent children at the time of widowhood.

Findings from this study are consistent with investigations showing biological, physiological, and epidemiological evidence in animal and human studies that chronic stress is associated with reduced hippocampal volume (e.g., Bremner et al., 2003; Ekstrand et al., 2008), reduced brain weight (e.g., Sousa et al., 1998), memory problems (e.g., Peavy et al., 2007; Sotiropoulos et al., 2011), AD pathology (e.g., Kang et al., 2007), and increased prevalence of mild cognitive impairment (Wilson et al., 2007) and AD (Wilson et al., 2005). This evidence also indicates widowhood in particular to be associated with chronic stress (Buckley et al., 2009; Gerritsen et al., 2009); stress-related

conditions, such as anger and anxiety, sleeping fewer hours (Buckley et al., 2009), and depression (e.g., Hughes & Waite, 2009), diminished self-care (Shahar et al., 2001), and with cognitive impairment (e.g., Aartsen et al., 2005; Karlamangla et al., 2009), and dementia and AD (Hakansson et al., 2009), though some studies did not find a link between widowhood and cognitive functioning or dementia (e.g., Comijs et al., 2011; Fratiglioni et al., 2000). A discussion of each finding in the present study is provided below, in the context of the published literature.

Moderating Effect of Gender

This study found that the association between incident widowhood and dementia depended on gender, in that among women, widowhood was associated with 21% higher risk for dementia, while among men widowhood was associated with 28% lower risk for dementia. This is contrary to several previous studies that found a stronger association between life stressors and health outcomes among men rather than women. These associations included those between widowhood and depression (G. R. Lee et al., 2001), widowhood and stroke (Maselko et al., 2009), remarriage after widowhood and depression (Williams, 2003), widowhood and cognitive decline (Aartsen et al., 2005; Rosnick et al., 2010), and between widowhood and institutionalization to a nursing home (Noël-Miller, 2010). Some of these studies (G. R. Lee et al., 2001; Noël-Miller, 2010; Williams, 2003) offered a similar explanation of this moderating effect. They argued that marriage protects men from adverse health outcomes more than it does women, and consequently that men are affected more by widowhood than women. In one study (G. R.

Lee et al., 2001), this interpretation was supported by mean differences of married and widowed men and women. The authors found that among men, mean scores on the CES-D depression scale (range 0-84) for those who were married were relatively low (*M* = 11.15, *SD*s not reported) compared to those who were widowed (*M* = 17.37); whereas, among women mean CES-D scores for those who were married were relatively high (*M* = 15.29) compared to those who were widowed (*M* = 17.22). This indicates that mean depression scores among married men and widowed men were different only because depression scores among the former were relatively low, and suggests that marriage offers social, emotional, or functional support more to men than women, such that widowhood affects men more than women. In a few studies (Engström et al., 2004; Simons et al., 1998), an association between widowhood and health outcomes was found among women rather than men. However, in one of these (Engström et al., 2004), the relationship was only slightly moderated by gender, with widowed women experiencing increased risk for stroke relative to married women (*RR* = 1.13, 95% *CI*: 1.02-1.24), and widowed men experiencing an increased risk for stroke relative to married men that was similar to that found among women, but nonsignificant (*RR* = 1.13, 95% *CI*: 0.99-1.28). Simons and colleagues stated that it was unclear why an association was found among women but not men, but conjectured that it may have been due to gender differences in social support. Differences between findings from this dissertation and previous studies in the moderating effect of gender on the relationship between life stressors and adverse health outcomes may be due to population differences. These differences merit future study.

Moderating Effect of Depression

This study found the association between incident widowhood and dementia to also depend on history of depression. Among persons with no history of depression or antidepressant use, widowhood trended towards 34% and 46% decreased risk for dementia and AD, respectively, whereas among persons with a history of depression and antidepressant use, widowhood trended towards 93% and 89% increased risk for these conditions. This latter finding is consistent with previous findings that depressed persons tend to lack effective coping skills (Greenglass et al., 2006), and that declines in cognitive functioning tend to be greater among depressed widowed persons than among non-depressed widowed persons (Aartsen et al., 2005). However, models also revealed that among those with a history of depression but no antidepressant use, incident widowhood was not related dementia or AD risk, whereas among those with a history of antidepressant use but no history of depression, persons who experienced incident widowhood trended towards 80% increased risk for AD over persons who did not experienced incident widowhood. This suggest either that antidepressant use is a more useful indicator of depression than history of depression itself, or that antidepressant use itself compounds the stress associated with life stressors.

Moderating Trend of Dependent Children at Widowhood

This study found a trend towards increased risk for AD among persons with two or more children at the time of widowhood (*HR* = 1.72, 95% *CI*: 0.99-2.98). This is consistent with a previous study (Alter et al., 2007) that found that widowed women with

more dependent children are at higher risk of mortality than widowed women with fewer dependent children. This trend may imply that having dependent children at the time of widowhood exacerbates the stress of losing one's spouse. However, recent studies suggest an alternative explanation. These studies found associations between parity and risk for AD and cognitive impairment. For instance, Colucci and colleagues (2006) found that risk of AD was 80.0% higher in women who had had 1-2 pregnancies, and over three times higher in women with three or more pregnancies, than in nulliparous women, and that women with AD who had three or more pregnancies had an earlier age of onset than other women with AD. Another study (Ptok, Barkow, & Heun, 2002) found that among women, but not men, those with children experienced almost three times greater risk for AD relative to those without children. In McLay, Maki, and Lyketsos (2003), women who had given birth to a live infant at some point in their life experienced greater cognitive decline than women who had not. In addition, Beeri and colleagues (2009) found that among women, but not men, those with more children had more neuritic plaques in the amygdala and in the brain overall. Given that these studies found the association between number of children and AD or cognitive impairment to occur only among women, the biological, behavioral, or social mechanisms mechanism explaining this association are likely also to be specific to women. For instance, some theorize that this association is due to changes in endocrine regulation and activity associated with child birth. These findings suggest that among women, having children can lead to increased risk for AD regardless of life stressors.

Confounding of Age

In general, this study found the relationship between widowhood and dementia or AD to be highly confounded with age at the baseline interview. To assess how this compares with previous studies, relationships between subject and study characteristics regarding age and study outcomes in previous studies were explored. This is featured in Table 5.1. This indicates that in all previous studies, participants spanned a broad range of ages, indicating that in none of these studies was age controlled for age by using participants of the same age. Rather, in all previous studies age was controlled for statistically, with the exception of Ward and colleagues (2007), who controlled for age by matching bereaved and nonbereaved persons on age and a number of other factors, and Helmer and colleagues (1999), who did not control for age. In some previous studies (Aartsen et al., 2005; Hakansson et al., 2009; Karlamangla et al., 2009; H. B. Lee et al., 2011; Van Gelder et al., 2006) researchers found widowhood was associated with cognitive impairment or dementia even after inclusion of age as a covariate. In other studies (Rosnick et al., 2007, 2010; Sachs-Ericsson et al., 2010) it could not be determined whether inclusion of age as a covariate affected the statistical effect of widowhood because models without age as a covariate were either not conducted or not reported.

In other studies (Fratiglioni et al., 2000; Ward et al., 2007), widowhood became nonsignificant after controlling for age or mood. Fratiglioni and colleagues (2000) found that persons who were widowed or divorced experienced increased risk for dementia relative to married persons in unadjusted models (*HR* =1.6, 95% *CI*: 1.1-2.3) but not in

Table 5.1

Relationships Between Subject and Study Characteristics Regarding Age and Study Outcomes in Previous Studies

Study	Age range at baseline	Mean (SD) age at baseline[a]	Age included as covariate	Main effect nonsignificant with age added	Widowhood related to cognitive impairment?	Widowhood related to dementia or AD?
Aartsen et al. (2005)	60-85	70.3 (6.6)	yes	no	yes	
Comijs et al. (2011)	61-91	72.5 (6.6)	yes	no	no	
Fratiglioni et al. (2009)	nr	75+	yes	yes		not in adjusted models
Hakannson et al. (2009)	65-80	71.3 (4.9)	yes	no		yes
Hatch (this study)	65-105	75.9 (7.3)	yes	yes		moderated relationship only
Helmer et al. (1999)	nr	65+	no	n/a		no
Karlamanga et al. (2009)	nr[b]	74.9 (nr)	yes	no	yes	
Lee et al. (2011)	nr	65+ (nr)	yes	no	yes	
Rosnick et al. (2007)	60-85	73.0 (6.2)	yes	nr[c]	no	
Rosnick et al. (2010)	51-86	70 (6.33)	yes	nr[c]	moderated relationship only	
Sachs-Ericsson et al. (2010)	nr	71.6 (5.4)	yes	nr[c]	moderated relationship only	
Van Gelder et al. (2006)	70-89	75.2 (4.2)	yes	no	yes	
Ward et al. (2007)	65-80	71.1 (4.0)	no[d]	n/a	not in adjusted models	

[a] Minimum eligible age reported for studies that did not report mean age.
[b] nr = not reported.
[c] Model without age as covariate not reported.
[d] Widowed and non-widowed persons matched on age.

models adjusted for age and other factors (*HR* = 1.3, 95% *CI*: 0.8-2.0). Because living arrangement (living with someone or living alone) was statistically significant after inclusion of age, the authors combined this factor with marital status to form a composite variable (married and living with someone, single and living alone, widowed/divorced and living alone, married and living alone, single and living with someone, widowed/divorced and living with someone). After inclusion of age and other covariates, those who were widowed or divorced and living alone trended towards increased risk for dementia (*HR* = 1.5, 95% *CI*: 0.9-2.2). In Ward and colleagues (2007), the association between widowhood and decreased attention, information-processing speed, and verbal fluency became nonsignificant after inclusion of mood (as assessed by the Depression Anxiety Stress Scales; DASS), rather than age. This could indicate that depression mediates the link between widowhood and cognitive impairment. In Comijs and colleagues (2011), those who were widowed or divorced experienced similar risk of cognitive impairment in models without covariates. Because widowhood/divorce was not significant in this initial model, the authors did not test this factor in models with covariates. Given that this dissertation found opposite trends in dementia risk among widowed and divorced persons, it is likely that the lack of association in Comijs and colleagues and Fratiglioni and colleagues (2000) occurred because these studies combined widowhood and divorce, obscuring the opposite effects of these risk factors.

In this dissertation and in previous studies, confounding by age could have taken different forms. For instance, given that risk of both widowhood and AD increase with age, confounding by age could reflect influences associated with the process of aging

common to these conditions. Confounding by age may also reflect cohort effects, in that persons of different ages were exposed to different historical factors that may have been associated with differential risk for AD. To address this, future analyses could interact age at widowhood with baseline age.

In summary, widowhood was associated with dementia risk in this dissertation study, even though only moderated relationships were identified. This is generally consistent with findings from prior studies reviewed herein, where widowhood was found to have an independent association with cognitive decline or dementia even after inclusion of age. Taken together, the present study concludes that widowhood acts as a psychosocial stressor by exerting adverse effects on late-life cognitive health, particularly for more distress-prone individuals such as females and those with a history of depression. Further study is needed to better understand mechanisms involved.

Population Differences

Differences between this study and previous studies in the association between widowhood and dementia may stem from differences in populations used. In Cache County and Utah in general, several population characteristics are conducive to a low-stress lifestyle. For instance, seniors in Cache County have one of the highest life expectancies in the country (88.1 years and 85.7 years among females and males, compared to the national average of 78.5 and 71.5, respectively; Murray et al., 1998). This is due to low rates of tobacco use and chronic disease (Welsh-Bohmer et al., 2006) as well as low cancer rates (Merrill & Lyon, 2005). This occurs partly because a majority

of the seniors in Cache County (91%) are members of the LDS church, which proscribes alcohol and tobacco use. High life expectancy may also be a result of low poverty and high physical activity in this region (Welsh-Bohmer et al., 2006).

In addition to being high in life expectancy, Utah is characterized by other low-stress features. For instance, crime in Utah is generally low, with Utah ranking fifth lowest in violent crimes (225.6 crimes per 100,000 persons, compared to 467.2 per 100,000 in the U.S. as a whole; U.S. Census Bureau, 2012). Persons in Utah also tend to have large families, with Utah having the highest average household size in the U.S. (3.13 in Utah compared to 2.64 in U.S. overall; U.S. Census Bureau, 2011), which may improve health via social support resources. This interpretation stands in contrast to findings from this study, in which those with more adult children at the time of widowhood trended towards increased risk for dementia. However, this effect may have been due to the association between parity and AD. Together, these studies suggest that persons in Cache County and Utah in general may be less exposed to stressful experiences than persons in other locales. This low-stress environment may buffer the effects of specific life stressors such as widowhood.

Strengths and Limitations

This dissertation benefits from several strengths. Analyses for this study were conducted using 12 years of longitudinal data from a large population-based epidemiological study of dementia and AD. Dementia diagnoses were conducted in participants' homes, using a careful, multi-stage, expert-consensed diagnosis protocol.

This dissertation also benefitted from CCMS's vast array of genetic and environmental variables related to dementia and AD. Very high participation rates in the Cache County Study (90%) were also advantageous, dramatically reducing non-responder bias (Norton et al., 1994). In addition to CCMS data, this dissertation captured widowhood events objectively, utilizing data from one of the world's foremost linked genealogical databases, containing an extensive set of Utah family histories, including objective birth, marriage, divorce, and death data.

Potential limitations to this investigation can be noted. In this study, a large number of analyses were conducted, which increases the risk of Type I error. However, many of these were conducted to demonstrate the effect of each covariate entered separately. Given that final models were the most critical to findings and that a relatively small number (24) of these were conducted, risk of Type I error is reduced. Moreover, this risk of Type I error is justified in that analyses were based on a priori hypotheses grounded in extant literature. In addition to some risk for Type I error, this study did not have direct measures of stress, such as cortisol measurements taken at regular intervals, so it cannot confirm the underlying biological mechanism for observed associations. An addition limitation to this study is homogeneity in this sample in terms of race and religion, in that 90% of the sample was Caucasian and 99% were LDS. Although this homogeneity may hinder the generalizability of findings to other populations, it is also advantageous in that it reduces the number of potential confounding factors, thus increasing internal validity. Findings from this dissertation, while not dramatic in magnitude or universal across all analyses, offers sufficient evidence that the effect of

widowhood on dementia risk may be nontrivial and may look different for subgroups defined by gender, depression history, and family size.

Clinical and Scientific Implications

This study advances clinical and scientific knowledge concerning widowhood, its context, and effects on risk for dementia and AD. Findings from this study highlight links between widowhood, a pivotal life stressor, and dementia and AD, conditions that pose dramatic public health concerns. This study also identifies groups of people, including those with a history of depression and antidepressant use, and possibly women, who are more susceptible to the adverse effects of life stressors such as widowhood. Identifying more vulnerable subpopulations can help target preventive interventions for those at highest risk and potentially help to tailor interventions to meet those needs. In addition, this study underscores to the scientific community the importance of context on life stressors, and illuminates those contextual factors that alter the association between widowhood and dementia.

Future Research Directions

Future investigations can build upon the findings of this study in a number of ways. Given that this study has found widowhood and its context to be associated with risk for dementia and AD, future studies can seek to investigate how other life stressors, such as divorce, economic downturn, and child or parent death, and the unique context of stressors such as these, are related to dementia and AD. Future studies in this area would

also benefit from direct measures of stress, such as cortisol measurements, and heart rate and blood pressure readings, taken at regular intervals during the window of exposure to those various life stressors. In addition, future studies would benefit from more in-depth investigations to illuminate mechanisms explaining how contextual factors identified in this study exert their moderating influence. Such investigations could examine, for instance, gender differences in how heavily various coping strategies are used, and how those different strategies relate to dementia risk and other health outcomes. Finally, future investigations could explore ways in which persons subjectively experience widowhood, including their cognitive appraisals about the meaning of widowhood to their lives and their sense of self-efficacy in designing a continuation of life without the deceased partner, and how these relate to neurodegenerative effects and cognitive health. Studies of these and other aspects of subjective stress surrounding widowhood may further clarify ways to design preventive interventions to neutralize adverse effects on cognitive health in late-life.

Conclusions

This study of the association between widowhood, its contexts, and dementia and AD builds on previous findings linking chronic stress with AD pathology, cognitive impairment, and AD, and findings linking widowhood with chronic stress, cognitive impairment, and dementia and AD. A number of contextual factors surrounding widowhood were found to be critical. Gender was found to moderate the relationship between widowhood and AD, in that widowed men trended towards decreased risk

relative to married men, and widowed women trended towards increased risk relative to married women. This is counter to findings from previous studies, and may represent population differences between this and previous studies in how men and women deal with stress. In addition, this study found the association between widowhood and dementia and AD to be strongest among those with a history of depression and antidepressant use, and less strong among those with only a history of depression, suggesting that depression history moderates the widowhood/dementia association only at more severe levels of depression. Widowed persons with two or more dependent children at the time of widowhood, but not those with fewer or no children at widowhood, trended towards increased risk for AD. However, evidence suggests that this effect is conflated with the association between parity and AD. In general, the relationship between widowhood and dementia or AD was highly confounded with age. However, this problem with confounding was generally not found in previous studies investigating this relationship, possibly because previous studies did not include the oldest old. Differences between this and previous studies may also be due to population differences, which may include some societal differences in Utah that foster a low stress lifestyle. Findings from this dissertation will aide in the identification of segments of the population who are particularly susceptible to the adverse effects of life stressors. These findings guide the formation of interventions for these persons, and underscore the importance of the context of life stressors on dementia and AD risk.

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APPENDIX

Table A.1

Marital History Missingness by Covariates, Moderators, Dementia, and AD

Variables	Never married n= 49 (1.2%)	Missing marital Hx n=290 (7.3%)	Not missing marital Hx 3,633 (91.5%)	Statistical test	*p* value
Education, mean (*SD*)	14.3 (3.4)	13.1 (3.2)	13.3 (2.8)	$F = 3.72$	.02
Occupation of longest duration				$\chi^2 = 35.80$	< .001
Professional, technical, managerial, n (%)	24 (1.9%)	98 (7.6%)	1164 (90.5%)		
Clerical, sales, n (%)	8 (1.0%)	71 (8.5%)	755 (90.5%)		
Service, n (%)	6 (1.5%)	46 (11.5%)	347 (87.0%)		
Agricultural, n (%)	6 (1.1%)	19 (3.5%)	514 (95.4%)		
Miscellaneous[a], n (%)	4 (0.4%)	56 (6.2%)	847 (93.4%)		
Age, mean (*SD*)	75.1 (6.8)	74.6 (6.8)	74.6 (6.7)	$F = 0.14$	.87
Gender				$\chi^2 = 22.16$	< .001
Male, n (%)	13 (0.8%)	90 (5.3%)	1,580 (93.9%)		
Female, n (%)	36 (1.6%)	200 (8.7%)	2,053 (89.7%)		
Presence of APOE ε4 allele				$\chi^2 = 1.86$	.39
0 APOE ε4 alleles, n (%)	30 (1.1%)	200 (7.4%)	2,476 (91.5%)		
1+ APOE ε4 allele, n (%)	19 (1.6%)	82 (6.8%)	1,108 (91.6%)		
Number of chronic conditions, mean (*SD*)	1.1 (1.1)	1.1 (1.1)	1.2 (1.1)	$F = 0.18$	.84
DASH[b] diet score	25.0 (6.8)	26.8 (5.7)	26.3 (6.0)	$F = 1.54$	.22
Exercise				$\chi^2 = 4.23$	.12
Not physically active, n (%)	25 (1.4%)	138 (7.6%)	1,651 (91.0%)		
Physically active, n (%)	13 (0.9%)	88 (6.2%)	1,328 (92.9%)		
Alcohol consumption				$\chi^2 = 6.19$	.045
Not current drinker, n (%)	33 (1.3%)	170 (6.6%)	2,387 (92.2%)		
Current drinker, n (%)	16 (1.2%)	120 (8.7%)	1,241 (90.1%)		
Smoking				$\chi^2 = 38.37$	< .001

(*table continues*)

Variables	Never married n= 49 (1.2%)	Missing marital Hx n=290 (7.3%)	Not missing marital Hx 3,633 (91.5%)	Statistical test	*p* value
Never smoked, n (%)	40 (1.4%)	167 (5.8%)	2,685 (92.8%)		
Ever smoked, n (%)	9 (0.8%)	123 (11.4%)	945 (87.7%)		
Death during observation period				$\chi^2 = 1.78$	.41
Didn't die during observation period, n (%)	29 (1.1%)	198 (7.3%)	2,474 (91.6%)		
Died during observation period, n (%)	20 (1.6%)	92 (7.2%)	1,159 (91.2%)		
History of depression				$\chi^2 = 5.40$	.49
No depression hx/no antidepressant hx[c], n (%)	26 (1.0%)	196 (7.8%)	2,277 (91.1%)		
Depression hx/no antidepressant hx[d], n (%)	8 (1.6%)	34 (6.8%)	457 (91.6%)		
No depression hx/antidepressant hx[e], n (%)	9 (1.7%)	32 (6.2%)	477 (92.1%)		
Depression hx/antidepressant hx[f], n (%)	6 (1.3%)	28 (6.2%)	421 (92.5%)		
Dementia, n (%)				$\chi^2 = 5.78$	.06
Not diagnosed with dementia, n (%)	43 (1.3%)	261 (7.7%)	3,085 (91.0%)		
Diagnosed with dementia, n (%)	6 (1.0%)	29 (5.0%)	548 (94.0%)		
Diagnosed with AD, n (%)				$\chi^2 = 2.36$	.31
Not diagnosed with AD, n (%)	43 (1.3%)	261 (7.7%)	3,085 (91.0%)		
Diagnosed with AD, n (%)	5 (1.3%)	22 (5.6%)	369 (93.2%)		

[a] Miscellaneous: blue collar (processing, machine work, benchwork, structural), miscellaneous, never worked outside of home.
[b] Dietary approaches to stopping hypertension
[c] No history of depression or antidepressant use
[d] History of depression but no history of antidepressant use.
[e] No history of depression but history of antidepressant use.
[f] History of depression and antidepressant use

Table A.2

Drop Out or Death, by Widowhood, Covariates, Moderators, and Cognitive Decline

Variables	Uncensored dementia cases *n* = 548 (15.1%)	Right truncated cases: Death *n* = 1,159 (31.9%)	Right truncated cases: Drop out *n* = 667 (18.4%)	Right censored cases *n* = 1,259 (34.7%)	Statistical test	*p* value
Prevalent widowhood					$\chi^2 = 95.74$	< .001
No widowhood, n (%)	331 (13.8%)	669 (27.9%)	468 (19.5%)	927 (38.7%)		
1+ prevalent divorce, no widowhood, n (%)	13 (8.7%)	54 (36.0%)	28 (18.7%)	55 (36.7%)		
1+ widowhood, n (%)	204 (18.8%)	436 (40.1%)	171 (15.7%)	277 (25.5%)		
Incident widowhood[a]					$\chi^2 = 51.85$	< .001
No widowhood, n (%)	151 (11.4%)	318 (24.1%)	265 (20.1%)	587 (44.4%)		
1+ widowhood, n (%)	193 (15.8%)	405 (33.1%)	231 (18.9%)	395 (32.3%)		
Education, in years, mean (SD)	13.2 (3.0)	12.9 (2.9)	13.1 (2.6)	13.8 (2.8)	F = 20.60	< .001
Occupation of longest duration					$\chi^2 = 92.89$	< .001
Professional, technical, managerial, n (%)	172 (14.8%)	333 (28.6%)	188 (16.2%)	471 (40.5%)		
Clerical, sales, n (%)	95 (12.6%)	212 (28.1%)	158 (20.9%)	290 (38.4%)		
Service, n (%)	68 (19.6%)	115 (33.1%)	72 (20.7%)	92 (26.5%)		
Agricultural, n (%)	93 (18.1%)	195 (37.9%)	80 (15.6%)	146 (28.4%)		
Processing, n (%)	11 (17.5%)	26 (41.3%)	12 (19.0%)	14 (22.2%)		
Machine work, n (%)	15 (14.6%)	38 (36.9%)	18 (17.5%)	32 (31.1%)		
Benchwork, n (%)	12 (12.2%)	32 (32.7%)	17 (17.3%)	37 (37.8%)		
Structural, n (%)	20 (11.3%)	79 (44.6%)	32 (18.1%)	46 (26.0%)		
Miscellaneous, n (%)	10 (10.6%)	40 (42.6%)	17 (18.1%)	27 (28.7%)		
Never worked outside home, n (%)	51 (16.3%)	86 (27.6%)	71 (22.8%)	104 (33.3%)		
Age, mean (*SD*)	77.5 (6.7)	77.7 (7.1)	72.9 (5.5)	71.3 (4.7)	*F* = 299.03	< .001
Gender					$\chi^2 = 27.39$	< .001
Male, *n* (%)	227 (14.4%)	573 (36.3%)	253 (16.0%)	527 (33.4%)		
Female, *n* (%)	321 (15.6%)	586 (28.5%)	414 (20.2%)	732 (35.7%)		

(*table continues*)

Variables	Uncensored dementia cases *n* = 548 (15.1%)	Right truncated cases: Death *n* = 1,159 (31.9%)	Right truncated cases: Drop out *n* = 667 (18.4%)	Right censored cases *n* = 1,259 (34.7%)	Statistical test	*p* value
Presence of APOE ε4 allele					$\chi^2 = 45.78$	< .001
0 APOE ε4 alleles, n (%)	311 (12.6%)	825 (33.3%)	457 (18.5%)	883 (35.7%)		
1+ APOE ε4 allele, n (%)	233 (21.0%)	303 (27.3%)	198 (17.9%)	374 (33.8%)		
Number of chronic conditions, mean (SD)	1.1 (1.1)	1.4 (1.2)	1.1 (1.0)	1.0 (1.0)	$F = 26.70$	< .001
DASH[b] diet score	26.2 (6.2)	25.2 (5.7)	26.8 (6.0)	27.0 (6.1)	$F = 15.87$	< .001
Exercise					$\chi^2 = 73.70$	< .001
Not physically active, n (%)	249 (15.1%)	601 (36.4%)	255 (15.4%)	546 (33.1%)		
Physically active, n (%)	181 (13.6%)	306 (23.0%)	276 (20.8%)	565 (42.5%)		
Alcohol consumption					$\chi^2 = 6.47$	.09
Not current drinker, n (%)	354 (14.8%)	733 (30.7%)	447 (18.7%)	853 (35.7%)		
Current drinker, n (%)	192 (15.5%)	426 (34.3%)	219 (17.6%)	404 (32.6%)		
Smoking					$\chi^2 = 35.13$	< .001
Never smoked, n (%)	422 (15.7%)	785 (29.2%)	504 (18.8%)	974 (36.3%)		
Ever smoked, n (%)	126 (13.3%)	374 (39.6%)	162 (17.1%)	283 (29.9%)		
History of depression					$\chi^2 = 70.44$	< .001
No depression hx/no antidepressant hx[c], *n* (%)	305 (13.4%)	758 (33.3%)	443 (19.5%)	771 (33.9%)		
Depression hx/no antidepressant hx[d], *n* (%)	51 (11.2%)	132 (28.9%)	89 (19.5%)	185 (40.5%)		
No depression hx/antidepressant hx[e], *n* (%)	123 (25.8%)	150 (31.4%)	57 (11.9%)	147 (30.8%)		
Depression hx/antidepressant hx[f], *n* (%)	69 (16.4%)	118 (28.0%)	78 (18.5%)	156 (37.1%)		
3MS cognitive decline[g], mean (*SD*)	2.3 (2.4)	0.47 (2.2)	0.12 (1.4)	.014 (0.57)	$F = 126.26$	< .001

[a] Incident widowhood [Uncensored dementia cases: *n* = 344 (13.5%), Right truncated cases, death: *n* = 723 (28.4%), Right truncated cases, Not Death: *n= 496 (19.5%), Right Censored Cases: n = 982 (38.6%)]*

[b] Dietary Approaches to Stop Hypertension

[c] No history of depression or antidepressant use.

[d] History of depression but no history of antidepressant use.

[e] No history of depression but history of antidepressant use.

[f] History of depression and antidepressant use.

[g] Average decline on Modified Mini-Mental State Examination (3MS) per year.

Table A.3

Prevalent Exposure by Covariates and Moderators

Variables	No prevalent widowhood *n* = 2,395 (65.9%)	1+ prevalent divorce, no prevalent widowhood *n* = 150 (4.1%)	1+ prevalent widowhood *n* = 1,088 (29.9%)	Statistical test	*p* value
Education, mean (*SD*)	13.6 (2.9)	13.4 (3.0)	12.6 (2.5)	$F = 54.57$	< .001
Occupation of longest duration				$\chi^2 = 175.75$	< .001
Professional, technical, managerial, *n* (%)	843 (72.4%)	51 (4.4%)	270 (23.2%)		
Clerical, sales, *n* (%)	471 (62.4%)	30 (4.0%)	254 (33.6%)		
Service, *n* (%)	183 (52.7%)	12 (3.5%)	152 (43.8%)		
Agricultural, *n* (%)	380 (73.9%)	13 (2.5%)	121 (23.5%)		
Processing, *n* (%)	34 (54.0%)	2 (3.2%)	27 (42.9%)		
Machine work, *n* (%)	63 (61.2%)	12 (11.7%)	28 (27.2%)		
Benchwork, *n* (%)	47 (48.0%)	2 (2.0%)	49 (50.0%)		
Structural, *n* (%)	138 (78.0%)	12 (6.8%)	27 (15.3%)		
Miscellaneous, *n* (%)	55 (58.5%)	12 (2.8%)	27 (28.7%)		
Never worked outside home, *n* (%)	180 (57.7%)	4 (1.3%)	128 (41.0%)		
Age, mean (*SD*)	72.9 (5.8)	71.9 (5.0)	78.5 (6.9)	$F = 321.02$	< .001
Gender				$\chi^2 = 329.16$	< .001
Male, *n* (%)	1,264 (80.0%)	90 (5.7%)	226 (14.3%)		
Female, *n* (%)	1,131 (55.1%)	60 (2.9%)	862 (42.0%)		
Presence of APOE ε4 allele				$\chi^2 = 13.87$	< .001
0 APOE ε4 alleles, *n* (%)	1,604 (64.8%)	89 (3.6%)	783 (31.6%)		
1+ APOE ε4 allele, *n* (%)	761 (68.7%)	57 (5.1%)	290 (26.2%)		
Number of chronic conditions, mean (*SD*)	1.2 (1.1)	1.3 (1.1)	1.2 (1.1)	$F = 0.56$	.57
DASH[a] diet score	26.3 (6.1)	26.2 (6.2)	26.3 (5.9)	$F = 0.02$	.98
Exercise				$\chi^2 = 26.39$	< .001
Not physically active, *n* (%)	1,050 (63.6%)	66 (4.0%)	535 (32.4%)		
Physically active, *n* (%)	955 (71.9%)	56 (4.2%)	317 (23.9%)		

(*table continues*)

Variables	No prevalent widowhood *n* = 2,395 (65.9%)	1+ prevalent divorce, no prevalent widowhood *n* = 150 (4.1%)	1+ prevalent widowhood *n* = 1,088 (29.9%)	Statistical test	*p* value
Alcohol consumption				$\chi^2 = 4.98$	.08
Not current drinker, *n* (%)	1,558 (65.3%)	90 (3.8%)	739 (31.0%)		
Current drinker, *n* (%)	833 (67.1%)	60 (4.8%)	348 (28.0%)		
Smoking				$\chi^2 = 58.85$	< .001
Never smoked, *n* (%)	1,705 (63.5%)	90 (3.4%)	890 (33.1%)		
Ever smoked, *n* (%)	687 (72.7%)	60 (6.3%)	198 (21.0%)		
Death during observation period				$\chi^2 = 51.97$	< .001
Didn't die during observation period, *n* (%)	1,726 (69.8%)	96 (3.9%)	652 (26.4%)		
Died during observation period, *n* (%)	669 (57.7%)	54 (4.7%)	436 (37.6%)		
History of depression				$\chi^2 = 27.48$	< .001
No depression hx/no antidepressant hx[b], *n* (%)	1,556 (68.3%)	84 (3.7%)	637 (28.0%)		
Depression hx/no antidepressant hx[c], *n* (%)	262 (57.3%)	30 (6.6%)	165 (36.1%)		
No depression hx/antidepressant hx[d], *n* (%)	317 (66.5%)	18 (3.8%)	142 (29.8%)		
Depression hx/antidepressant hx[e], *n* (%)	259 (61.5%)	18 (4.3%)	144 (34.2%)		

[a] Dietary Approaches to Stopping Hypertension.
[b] No history of depression or antidepressant use.
[c] History of depression but no history of antidepressant use.
[d] No history of depression but history of antidepressant use.
[e] History of depression and antidepressant use.

Table A.4

Incident Exposure by Covariates and Moderators

Variables	No incident widowhood n = 1,321 (51.9%)	1+ incident widowhood n = 1,224 (48.1%)	Statistical test	p value
Education, mean (*SD*)	13.9 (3.0)	13.3 (2.8)	t = 5.80	<.001
Occupation of longest duration			χ^2 = 62.17	<.001
Professional, technical, managerial, *n* (%)	501 (56.0%)	393 (44.05)		
Clerical, sales, *n* (%)	240 (47.0%)	261 (52.1%)		
Service, *n* (%)	75 (38.5%)	120 (61.5%)		
Agricultural, *n* (%)	226 (57.5%)	167 (42.5%)		
Processing, *n* (%)	14 (38.9%)	22 (68.1%)		
Machine work, *n* (%)	50 (66.7%)	25 (33.3%)		
Benchwork, *n* (%)	21 (42.9%)	28 (57.1%)		
Structural, *n* (%)	90 (60.0%)	60 (40%)		
Miscellaneous, *n* (%)	37 (55.2%)	30 (44.8%)		
Never worked outside home, *n* (%)	66 (35.9%)	118 (64.1%)		
Age, mean (*SD*)	71.0 (4.8)	74.9 (6.0)	t = -18.0	< .001
Gender			χ^2 = 185.29	< .001
Male, *n* (%)	874 (64.5%)	480 (35.5%)		
Female, *n* (%)	447 (37.5%)	744 (62.5%)		
Presence of APOE ε4 allele			χ^2 = 0.03	.87
0 APOE ε4 alleles, *n* (%)	878 (51.9%)	815 (48.1%)		
1+ APOE ε4 allele, *n* (%)	427 (52.2%)	391 (47.8%)		
Number of chronic conditions, mean (*SD*)	1.2 (1.1)	1.2 (1.1)	t = -0.15	.88
DASH[a] diet score	26.1 (6.1)	26.5 (6.0)	t = -1.38	.17
Exercise			χ^2 = 0.10	.76
Not physically active, *n* (%)	582 (52.2%)	534 (47.8%)		
Physically active, *n* (%)	534 (52.8%)	477 (74.2%)		
Alcohol consumption			χ^2 = 0.14	.71
Not current drinker, *n* (%)	851 (51.6%)	797 (48.4%)		
Current drinker, *n* (%)	468 (52.4%)	425 (47.6%)		
Smoking			χ^2 = 25.90	< .001
Never smoked, *n* (%)	873 (48.6%)	922 (51.4%)		
Ever smoked, *n* (%)	446 (59.7%)	301 (40.3%)		
Death during observation period			χ^2 = 25.39	< .001
Didn't die during observation period, *n* (%)	1,003 (55.0%)	819 (45.0%)		
Died during observation period, *n* (%)	318 (44.0%)	405 (56.0%)		
History of depression			χ^2 = 19.0	< .001
No depression hx/no antidepressant hx[a], *n* (%)	902 (55.0%)	738 (45.0%)		
Depression hx/no antidepressant hx[b], *n* (%)	142 (48.6%)	150 (51.4%)		
No depression hx/antidepressant hx[c], *n* (%)	153 (45.7%)	182 (54.3%)		
Depression hx/antidepressant hx[d], *n* (%)	123 (44.4%)	154 (55.6%)		

[a] No history of depression or antidepressant use.
[b] History of depression but no history of antidepressant use.
[c] No history of depression but history of antidepressant use.
[d] History of depression and antidepressant use.

Table A.5

Dementia by Exposure Variables, Covariates, and Moderators

Variable	No dementia *n* = 3,085 (84.9%)	Dementia *n* = 548 (15.1%)	Statistical test	*p* value
Prevalent widowhood			χ^2= 19.22	<.001
No widowhood, *n* (%)	2,064 (86.2%)	331 (13.8%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (91.3%)	13 (8.7%)		
1+ widowhood, *n* (%)	884 (81.2%)	204 (18.8%)		
Prevalent widowhood, Age at first widowhood			χ^2= 26.72	<.001
No widowhood, *n* (%)	2,064 (86.2%)	331 (13.8%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (91.3%)	13 (8.7%)		
45 or younger, *n* (%)	82 (86.3%)	13 (13.7%)		
46-64, *n* (%)	305 (84.3%)	57 (15.7%)		
65 or older, *n* (%)	497 (78.8%)	134 (21.2%)		
Prevalent widowhood, with remarriage			χ^2= 20.61	<.001
No widowhood, *n* (%)	2,064 (86.2%)	331 (13.8%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (91.3%)	13 (8.7%)		
1+ widowhood, no remarriage, *n* (%)	740 (80.7%)	177 (19.3%)		
1+ widowhood, with remarriage, *n* (%)	144 (84.2%)	27 (15.8%)		
Prevalent widowhood, with manner of death			χ^2= 20.36	<.001
No widowhood, *n* (%)	2,064 (86.2%)	331 (13.8%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (91.3%)	13 (8.7%)		
Natural Causes, *n* (%)	306 (82.0%)	67 (18.0%)		
Accident or suicide, *n* (%)	21 (87.5%)	3 (12.5%)		
Missing manner of death, *n* (%)	557 (80.6%)	134 (19.4%)		
Prevalent widowhood, with number of dependents[a]			χ^2= 21.94	<.001
No widowhood, *n* (%)	2,064 (86.2%)	331 (13.8%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (91.3%)	13 (8.7%)		
No dependents, *n* (%)	750 (80.8%)	178 (19.2%)		
1 dependent, *n* (%)	65 (87.8%)	9 (12.2%)		
2+ dependents, *n* (%)	69 (80.2%)	17 (19.8%)		
Prevalent widowhood, with number of adult children[b]			χ^2= 23.81	<.001
No widowhood, *n* (%)	2,064 (86.2%)	331 (13.8%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (91.3%)	13 (8.7%)		
No adult children, *n* (%)	127 (85.8%)	21 (14.2%)		
1-2 adult children, *n* (%)	271 (81.9%)	60 (18.1%)		
3-4 adult children, *n* (%)	295 (81.0%)	69 (19.0%)		
5+ adult children, *n* (%)	191 (78.0%)	54 (22.0%)		
Incident widowhood[c]			χ^2= 10.22	.001
No widowhood, *n* (%)	1,170 (88.6%)	151 (11.4%)		
1+ widowhood, *n* (%)	1,031 (84.2%)	193 (15.8%)		
Education, mean (*SD*)	13.3 (2.8)	13.2 (3.0)	*t*= 0.51	.61
Occupation of longest duration			χ^2= 17.66	.04
Professional, technical, managerial, *n* (%)	992 (85.2%)	172 (14.8%)		
Clerical, sales, *n* (%)	660 (87.4%)	95 (12.6%)		
Service, *n* (%)	279 (80.4%)	68 (19.6%)		
Agricultural, *n* (%)	421 (81.9%)	93 (18.1%)		

(*table continues*)

Variable	No dementia *n* = 3,085 (84.9%)	Dementia *n* = 548 (15.1%)	Statistical test	*p* value
Processing, *n* (%)	52 (82.5%)	11 (17.5%)		
Machine work, *n* (%)	88 (85.4%)	15 (14.6%)		
Benchwork, *n* (%)	86 (87.8%)	12 (12.2%)		
Structural, *n* (%)	157 (88.7%)	20 (11.3%)		
Miscellaneous, *n* (%)	84 (89.4%)	10 (10.6%)		
Never worked outside home, *n* (%)	261 (83.7%)	51 (16.3%)		
Age, mean (*SD*)	74.0 (6.5)	77.5 (6.7)	t= -11.45	<.001
Gender			χ^2= 1.12	.29
Male, *n* (%)	1,353 (85.6%)	227 (14.4%)		
Female, *n* (%)	1,732 (84.4%)	321 (15.6%)		
Presence of APOE ε4 allele			χ^2= 42.64	<.001
0 APOE ε4 alleles, *n* (%)	2,165 (87.4%)	311 (12.6%)		
1+ APOE ε4 allele, *n* (%)	875 (79.0%)	233 (21.0%)		
Number of chronic conditions, mean (*SD*)	1.2 (1.1)	1.1 (1.1)	t= 1.17	.24
DASH[d] diet score	26.3 (6.0)	26.2 (6.2)	t= 0.51	.61
Exercise			χ^2= 1.26	.26
Not physically active, *n* (%)	1,402 (84.9%)	249 (15.1%)		
Physically active, *n* (%)	1,147 (86.4%)	181 (13.6%)		
Alcohol consumption			χ^2= 0.26	.61
Not current drinker, *n* (%)	2,033 (85.2%)	354 (14.8%)		
Current drinker, *n* (%)	1,049 (84.5%)	192 (15.5%)		
Smoking			χ^2= 3.10	.08
Never smoked, *n* (%)	2,263 (84.3%)	422 (15.7%)		
Ever smoked, *n* (%)	819 (86.7%)	126 (13.3%)		
History of depression			χ^2= 53.77	<.001
No depression hx/no antidepressant hx[e], *n* (%)	1,972 (86.6%)	305 (13.4%)		
Depression hx/no antidepressant hx[f], *n* (%)	406 (88.8%)	51 (11.2%)		
No depression hx/antidepressant hx[g], *n* (%)	354 (74.2%)	123 (25.8%)		
Depression hx/antidepressant hx[h], *n* (%)	352 (83.6%)	69 (16.4%)		

[a] Number of dependent children at first prevalent widowhood.
[b] Number of adult children at first prevalent widowhood.
[c] Incident widowhood [no dementia: *n* = 2,201 (86.5%); dementia: *n* = 344 (13.5%)].
[d] Dietary Approaches to Stopping Hypertension
[e] no history or depression or antidepressant use.
[f] History of depression but no history of antidepressant use.
[g] No history of depression but history of antidepressant use.
[h] History of depression and antidepressant use.

Table A.6

AD by Exposure Variables, Covariates, and Moderators

Variables	No dementia *n* = 3,085 (89.3%)	AD *n* = 369 (10.7%)	Statistical test	*p* value
Prevalent widowhood			χ^2= 25.61	<.001
No widowhood, *n* (%)	2,064 (90.8%)	210 (9.2%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (94.5%)	8 (5.5%)		
1+ widowhood, *n* (%)	884 (85.4%)	151 (14.6%)		
Prevalent widowhood, Age at first widowhood			χ^2= 32.66	<.001
No widowhood, *n* (%)	2,064 (90.8%)	210 (9.2%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (94.5%)	8 (5.5%)		
45 or younger, *n* (%)	82 (91.1%)	8 (8.9%)		
46-64, *n* (%)	305 (87.4%)	44 (12.6%)		
65 or older, *n* (%)	497 (83.4%)	99 (16.6%)		
Prevalent widowhood, with remarriage			χ^2= 29.78	<.001
No widowhood, *n* (%)	2,064 (90.8%)	210 (9.2%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (94.5%)	8 (5.5%)		
1+ widowhood, no remarriage, *n* (%)	740 (84.6%)	135 (15.4%)		
1+ widowhood, with remarriage, *n* (%)	144 (90.0%)	16 (10.0%)		
Prevalent widowhood, with manner of death			χ^2=26.79	<.001
No widowhood, *n* (%)	2,064 (90.8%)	210 (9.2%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (94.5%)	8 (5.5%)		
Natural Causes, *n* (%)	306 (84.5%)	56 (15.5%)		
Accident or suicide, *n* (%)	21 (91.3%)	2 (8.7%)		
Missing manner of death, n (%)	557 (85.7%)	93 (14.3%)		
Prevalent widowhood, wtih number of dependents[a]			χ^2= 28.93	<.001
No widowhood, *n* (%)	2,064 (90.8%)	210 (9.2%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (94.5%)	8 (5.5%)		
No dependents, *n* (%)	750 (85.1%)	131 (14.9%)		
1 dependent, *n* (%)	65 (91.5%)	6 (8.5%)		
2+ dependents, *n* (%)	69 (83.1%)	14 (16.9%)		
Prevalent widowhood, with number of adult children[b]			χ^2=31.80	<.001
No widowhood, *n* (%)	2,064 (90.8%)	210 (9.2%)		
1+ prevalent divorce, no widowhood, *n* (%)	137 (94.5%)	8 (5.5%)		
No adult children, *n* (%)	127 (89.4%)	15 (10.6%)		
1-2 adult children, *n* (%)	271 (86.3%)	43 (13.7%)		
3-4 adult children, *n* (%)	295 (85.5%)	50 (14.5%)		
5+ adult children, *n* (%)	191 (81.6%)	43 (18.4%)		
Incident widowhood[c]			χ^2= 19.19	<.001
No widowhood, *n* (%)	1,170 (93.5%)	82 (6.5%)		
1+ widowhood, *n* (%)	1,031 (88.3%)	136 (11.7%)		
Education, mean (*SD*)	13.3 (2.8)	13.2 (3.0)	*t*= 0.78	.44
Occupation of longest duration			χ^2= 13.02	.16
Professional, technical, managerial, *n* (%)	992 (89.7%)	114 (10.3%)		
Clerical, sales, *n* (%)	660 (91.4%)	62 (8.6%)		
Service, *n* (%)	279 (86.4%)	44 (13.6%)		
Agricultural, *n* (%)	421 (87.3%)	61 (12.7%)		

(*table continues*)

Variables	No dementia n = 3,085 (89.3%)	AD n = 369 (10.7%)	Statistical test	p value
Processing, n (%)	52 (83.9%)	10 (16.1%)		
Machine work, n (%)	88 (88.0%)	12 (12.0%)		
Benchwork, n (%)	86 (90.5%)	9 (9.5%)		
Structural, n (%)	157 (91.8%)	14 (8.2%)		
Miscellaneous, n (%)	84 (92.3%)	7 (7.7%)		
Never worked outside home, n (%)	261 (88.2%)	35 (11.8%)		
Age, mean (SD)	74.0 (6.5)	78.0 (6.6)	t= -11.15	<.001
Gender			χ^2= 5.60	.02
Male, n (%)	1,353 (90.7%)	138 (9.3%)		
Female, n (%)	1,732 (88.2%)	231 (11.8%)		
Presence of APOE ε4 allele			χ^2= 47.37	<.001
0 APOE ε4 alleles, n (%)	2,165 (91.7%)	197 (8.3%)		
1+ APOE ε4 allele, n (%)	875 (83.7%)	170 (16.3%)		
Number of chronic conditions, mean (SD)	1.2 (1.1)	1.0 (1.0)	t= 3.77	<.001
DASH[d] diet score	26.3 (6.0)	26.5 (6.4)	t= -0.40	.69
Exercise			χ^2= 0.79	.38
Not physically active, n (%)	1,402 (89.3%)	168 (10.7%)		
Physically active, n (%)	1,147 (90.3%)	123 (9.7%)		
Alcohol consumption			χ^2= 0.09	.76
Not current drinker, n (%)	2,033 (89.2%)	245 (10.8%)		
Current drinker, n (%)	1,049 (89.6%)	122 (10.4%)		
Smoking			χ^2= 2.84	.09
Never smoked, n (%)	2,263 (88.8%)	286 (11.2%)		
Ever smoked, n (%)	819 (90.8%)	83 (9.2%)		
History of depression			χ^2= 25.51	<.001
No depression hx/no antidepressant hx[e], n (%)	1,972 (90.0%)	218 (10.0%)		
Depression hx/no antidepressant hx[f], n (%)	406 (92.1%)	35 (7.9%)		
No depression hx/antidepressant hx[g], n (%)	354 (82.5%)	75 (17.5%)		
Depression hx/antidepressant hx[h], n (%)	352 (89.6%)	41 (10.4%)		

[a] Number of dependent children at first prevalent widowhood.
[b] Number of adult children at first prevalent widowhood.
[c] Incident widowhood [no dementia: n = 2,201 (91.0%); AD: n = 218 (9.0%)].
[d] Dietary Approaches to Stopping Hypertension.
[e] No history of depression or antidepressant use.
[f] History of depression but no history of antidepressant use.
[g] No history of depression but history of antidepressant use.
[h] History of depression and antidepressant use.

CURRICULUM VITAE

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Education

PhD. in Experimental and Applied Psychological Science
Research and Evaluation Methodology (REM) emphasis
Utah State University (USU), Logan, Utah
Dissertation: The Influence of Widowhood and Sociodemographic Moderators on Dementia and Alzheimer's Disease Risk
Chair: Maria Norton, PhD.
May 2013

Master of Science in Psychology
USU, Logan, Utah
Thesis: Factors Moderating the Association between Multiple Rating Sources of Geriatric Depression: Self, Informant, and Physician
May 2011

Bachelor of Arts in Psychology
Minor in Spanish
USU, Logan, Utah
May 2004

Publications

Higginbotham, B., Hatch, D., Parry, T. (2013). *Religiosity and marital outcomes in remarried couples*. Manuscript in preparation.

Hatch, D. J., DeHart, W.B., Norton, M.C. (2013). *Contextual factors moderate effectiveness of a multi-component, multi-site intervention on caregiver depression and burden*. Manuscript submitted for publication.

Higginbotham, B., Hatch, D., Albertson, M., Brower, N., Perryman, C. (2012). *Smart child care: caregiver education for parents, family, friends, and neighbors*. Manuscript submitted for publication.

Reither, E.N., Fedor, T.M., Abel, K.M., Hatch, D.J. (2009). Associations between educational attainment and diabetes in Utah: The Behavioral Risk Factor Surveillance System, 1996-2007. *Utah's Health: An Annual Review 19,* 42-51.

Presentations

Hatch, D.J., Taylor, K.A., Peterson, R. (April, 2012). *Perils and pitfalls: Community-Based Participatory Research*. Panel discussion presented at the annual meeting of the Intermountain Graduate Research Symposium, Logan, UT.

Tschanz, J., Hatch, D.J., Croasdell, S., Wanzek, J., Kauwe, J., Corcoran, C., Norton, M., Green, R., Munger, R., Breitner, J., Welsh-Bohmer, K., Lyketsos, C. (July, 2011). *Family history of memory problems that are not Alzheimer's Disease predicts rate of cognitive decline in ApoE4 non-carriers: The Cache County Dementia Progression Study*. Poster presented at the meeting of the International Conference on Alzheimer's Disease, Paris, France.

Hatch, D.J., Smith, K.R., Tschanz, J.T., Corcoran, C., Østbye, T., Norton, M.C. (March, 2011). *Marriage, widowhood and divorce: Effects on dementia risk*. Poster session presented at the meeting of the American Association of Geriatric Psychiatry, San Antonio, Texas.

Reither, E.N., Fedor, T.M., Abel, K.M., Hatch, D.J. (March, 2009). *Associations between educational attainment and diabetes in Utah: The Behavioral Risk Factor Surveillance System, 1996-2007*. Poster session presented at the Graduate Student Symposium, Logan, Utah.

Hatch, D.J., Behl, D., Roberts, R. (July, 2007). *Evidence-based care coordination*. Poster session presented at the meeting of the American Association of Indian Psychologists, Logan, Utah.

Hatch, D.J. (March, 2004). *Using stimulus equivalence to teach reading and spelling to individuals with developmental disabilities and academic deficits: A review*. Poster session presented at the meeting of the Undergraduate Psychology Research Conference.

Additional Research Experience

Research Assistant for Brian Higginbotham, PhD, and Kay Bradford, PhD (8/2012-present)

Analyzed outcome data regarding Smart Child Care, a caregiver education program for parents, and caregivers who were family, friends, and neighbors of parents. Prepared manuscript based on findings.

Examined data regarding married couples with partners in second marriages, in which I assessed how membership in the Church of Jesus Christ of Latter-day Saints, and public and private religious behaviors related to marital satisfaction, adjustment, and instability, and to positive and negative marital behaviors.

Internship in Program Evaluation for Bach-Harrison, LLC, Salt Lake City, Utah (5/2011-9/2011)

Analyzed data from the Prevention Needs Assessment, a survey administered biannually to roughly 45,000 6^{th}, 8^{th}, 10^{th}, and 12^{th} graders in 37 of Utah's 40 school districts. Analyses involved preparing descriptive statistics and charts describing substance use patterns and risk and protection profiles among adolescents stratified by letter grade and 30-day alcohol use.

Managed data used in epidemiological reports of substance abuse, and of qualitative data from interviews with key informants regarding how they select prevention programs.

Research Assistant for the Cache County Memory Study, USU, Logan, Utah (8/2009-5/2011)

Wrote extensive SPSS program to combine interview data concerning multiple first degree relatives, across multiple time points, reconciling discrepancies and deriving an aggregate variable capturing family history of Alzheimer's disease.

Provided detailed documentation within SPSS program (Dr. Maria Norton, principal investigator)

Research Assistant for the Lifespan Stressors and Alzheimer's disease study, USU, Logan, Utah (8/2009-5/2011)

Participated in weekly teleconferences which discussed new variable derivation from a large-scale genealogical and medical database, and which discussed statistical analyses to meet study's specific aims. (Dr. Maria Norton, principal investigator).

Research Assistant at the Early Intervention Research Institute, USU, Logan, Utah, (10/2006-8/2007). Assisted in conducting a literature review on care coordination.

Grants

Grant awarded from the Utah Agricultural Experiment Station, 2011-2012 ($12,000) to fund dissertation work on widowhood and sociodemographic moderators increasing risk for AD and other dementias.

College Teaching Experience

Teaching Assistant: Psychology 6570 Research Methods in Psychology and Education, USU, Logan, Utah, Fall 2011, Spring 2012, Fall 2012, Spring 2013

Instructor: Psychology 3500 Research Methods in Psychology, USU branch campus, Brigham City, Utah, Spring 2011

Presentation for Psychology 3500 Research Methods in Psychology, on longitudinal designs, USU, Logan, Utah, Spring 2011

Instructor: Psychology 2800 Psychological Statistics, USU branch campus, Brigham City, Utah, Fall 2010

Teaching Assistant: Psychology 6570 Research Methods in Psychology and Education, USU, Logan, Utah, Spring 2009

Teaching Assistant: Psychology 6570 Research Methods in Psychology and Education, USU, Logan, Utah, Fall 2008

Teaching Assistant: Psychology 6010 Introduction to Evaluation, USU, Logan, Utah, Fall 2008

Teaching Assistant: Psychology 1010 Introduction to Psychology, USU, Logan, Utah, Spring 2008

Teaching Assistant: Psychology 5100 History and Systems, USU, Logan, Utah, Spring 2008

Teaching Assistant: Psychology 1010 Introduction to Psychology, USU, Logan, Utah, Fall 2007

Teaching Assistant: Psychology 5330 Psychometrics, USU, Logan, Utah, Fall 2007

Graduate Courses in Research Methodology and Statistics

Introduction to Educational and Psychological Research
Introduction to Evaluation
REM program seminar
Research Design and Analysis I
College Teaching Seminar
Professional Ethics and Standards
Research Design and Analysis II
Qualitative Methods
Advanced Psychometric Models
Categorical Data Analysis
Biostatistics Methods
Literature Reviews in Education and Psychology
Grant Writing
University Teaching Apprenticeship

Advanced Evaluation	Sociobehavioral Epidemiology
Multivariate Methods	Seminar
Seminar in Epidemiology	Design of Experiments (Stats)
Seminar in Sociology: Population & Health	Multivariate II

Professional Development

Software Programs

SPSS (including SPSS syntax)
SAS
Mplus
R statistical environment
Microsoft Word, Power Point, Excel

Affiliations

American Association of Geriatric Psychiatry (AAGP)
Society for Epidemiologic Research (SER)

Service

REM Seminar planning committee, Logan, Utah, 9/2007-12/2007. Chose topics and arranged guest speakers for REM seminars.

Volunteer for Spanish Ambassadors, Logan, Utah, 2/2003-5/2004
- Translated for Latino parents at parent teacher conferences.
- Translated documents from English into Spanish for various organizations, such as the Community Abuse Prevention Services Agency (CAPSA).

Volunteer, Volunteers Involved in Development Abroad (VIDA), Logan, Utah, 1/2003-5/2003
- Organized benefit marathon that raised $500.
- Organized Neighbor to Neighbor program, in which members of the Latino community spoke on their native countries and their experiences in immigrating to the United States.

Volunteer Advocate, Community Abuse Prevention Services Agency (CAPSA), Logan, Utah, 2/2002-7/2002
- Counseled victims of domestic violence.
- Educated community about domestic violence.

Volunteer Representative for The Church of Jesus Christ of Latter-day Saints, Quito, Ecuador, 11/1998-11/2000

Learned to speak and read Spanish.
Taught English classes.

Previous Employment

Intensive Behavioral Intervention (IBI) Specialist, The Children's Center, Idaho Falls, Idaho, 7/2004-7/2006

Conducted behavior modification with developmentally disabled youth with significant behavioral impairments.
Trained parents on use of behavior modification.