ABSTRACT

The Role of Medical Comorbidities on the Risk for Severe Dementia, Institutionalization, and Death in Alzheimer’s Disease: A Population Study in Cache County, Utah

by

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Alzheimer’s disease is a progressive disease that impairs cognitive and functional abilities. Currently, there is no cure and it is estimated there will be 81 million cases of Alzheimer’s disease by 2040. Life for the individual with Alzheimer’s disease, and their family, changes drastically when the affected individual experiences significant impairments in cognitive or functional ability (severe dementia), is placed in a skilled nursing home facility (institutionalization), or passes away (death). Until a cure is discovered, it will be important to identify modifiable factors that influence progression to severe dementia, institutionalization, and death. Three hundred thirty-five participants who were living in the community were followed after the onset of Alzheimer’s disease and continued until they left the study or the study period ended. Participants completed neuropsychological assessments at each visit. Visits occurred as close to every 6 months as possible and the mean number of visits was 5.32 (SD = 3.46). Outcomes of interest
were severe dementia, institutionalization, and death. Predictor variables were hypertension, stroke, congestive heart failure, number of prescription medications being taken, General Medical Health Rating (GMHR) score, and Charlson Comorbidity Index score. Cox Regression was utilized to identify associations with progression to the specified outcomes. GMHR score, congestive heart failure, and number of prescription medications were associated with progression to severe dementia. The number of prescription medications was also associated with nursing home placement. GMHR score, stroke, and number of prescription medications were associated with death. These findings are important because they contribute to a better understanding of how measures of medical health, certain medical conditions, and potentially their prevention or treatment may help those with Alzheimer’s disease sustain a higher quality of life.
PUBLIC ABSTRACT

The Role of Medical Comorbidities on the Risk for Severe Dementia, Institutionalization, and Death in Alzheimer’s Disease: A Population Study in Cache County, Utah

Mac J. Gilbert

Alzheimer’s disease is a progressive disease that impairs cognitive and functional abilities. Without a cure, it is estimated there will be 81 million cases of Alzheimer’s disease by 2040. Life for the individual with Alzheimer’s disease, and their family, changes drastically when the affected individual experiences significant problems with memory, thinking, and ability to complete daily tasks. Some become so debilitated that they need to be placed in a nursing home for supportive care. Until a cure is discovered, it will be important to identify what can be done to help those with Alzheimer’s disease minimize time spent experiencing severe disability and maximize their quality of life. Medical conditions are of interest because they have been shown to impact the possibility of getting Alzheimer’s disease and it is thought they may influence how quickly an individual progresses to a state of severe disability.

The participants in this study were enrolled into the Cache County Dementia Progression Study within a few years of the onset of Alzheimer’s disease. Along with their caregivers, the participants were followed for several years until they either decided they wanted to stop participating, they moved away, passed away, or the study was completed in 2013. Each participant was seen as close to every 6 months as possible. At
each visit the participants completed tests that would measure how well their memory and thinking abilities were and how well they could complete everyday tasks. The medical conditions of hypertension, congestive heart failure, stroke, the number of prescription medications being used, and scores from two rating scales of physical health status (General Medical Health Rating [GMHR] and the Charlson Comorbidity Index), were studied to see if they predicted how fast a participant would be classified as having severe dementia, be placed in a nursing home, or pass away. Worse ratings on the GMHR, history of congestive heart failure, and number of prescription medications were associated with progression to severe dementia. Number of prescription medications was also associated with nursing home placement. Worse ratings on the GMHR, stroke, and number of prescription medications were also associated with death.

These findings are important because they contribute to a better understanding of how certain medical conditions and general medical wellness can potentially help slow the progression of Alzheimer’s disease. Knowing this information may inform research directed to discover the important factors in understanding how medical conditions and overall medical wellness can help maximize the overall functioning of persons with Alzheimer’s disease and potentially delay the onset of severe disability and institutionalization.
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CHAPTER I
INTRODUCTION

Alzheimer’s disease (AD) is a progressive disease and is most commonly associated with severe memory and cognitive impairment (Small et al., 1997). It is a type of dementia that is most frequently diagnosed in late life and has received increased attention because of the high prevalence (Small et al., 1997). It was estimated that in 2005, there were 24 million cases of dementia worldwide (Ferri et al., 2005) and a recent estimate of 5.3 million cases of AD in the U.S. alone (Alzheimer’s Association, 2015). This number is estimated to increase to 81 million by the year 2040 (Ferri et al., 2005).

Because of the significant and progressive cognitive and functional impairment associated with the condition, persons with AD lose their independence (Galasko et al., 1995; Sano & Weber, 2003), which results in family caregivers expending substantial amounts of time, money, and emotional resources to care for those with the condition (Coduras et al., 2010).

AD is believed to be a result of both genetic and environmental factors (Profenno, Porsteinsson, & Faraone, 2010). Despite multiple hypotheses regarding the biological and environmental factors that are thought to contribute to the development and progression of AD, no interventions have been identified to prevent the development of the condition, or reverse its effects after onset. Although some of the symptoms of AD may be temporarily slowed through pharmacological treatment (Corbett, Smith, & Ballard, 2012), disease progression cannot be stopped and ultimately may lead to severe disability, institutionalization, and premature death. These are important clinical
outcomes as they are often associated with greater patient suffering and higher caregiver emotional and financial burden (Herrmann, Gauthier, & Lysy, 2007; Rountree, Chan, Pavlik, Darby, & Doody, 2012; Sloane et al., 2005). Identifying risk factors that hasten the onset of severe dementia, institutionalization, and death is important for predicting patient prognosis, planning for care, and potentially identifying modifiable factors for intervention.

The level of dementia severity has been determined via various measures that identify impairment in cognitive and functional abilities (Arrighi, Neumann, Lieberburg, & Townsend, 2010; Ferris & Yan, 2003; Galasko et al., 1995). Two common methods that indicate a rating of “severe dementia” include either a score of 10 or fewer points out of 30 on the Mini-Mental State Exam (MMSE) or a rating of 3 (severe), 4 (profound), or 5 (terminal) on the Clinical Dementia Rating scale (CDR; Folstein, Folstein, & McHugh, 1975; Rabins et al., 2013).

In the AD literature, institutionalization generally refers to residence in a skilled nursing facility, and excludes residence in an assisted-living facility. This is because individuals placed in a nursing home are more of a homogeneous group with regards to the significant inability to care for oneself due to both cognitive and physical impairments while individuals placed in assisted living setting are more varied with regards to need (Spillman et al., 2002). Despite this difference, both places of residence are associated with need for an increased level of care. Severe dementia and residential placement in a skilled nursing or assisted living facility have been associated with lower patient quality of life and higher costs (Herrmann et al., 2007; Sloane et al., 2005).
Death occurs earlier among persons with AD than those without (F. Li, Wang, & Jia, 2013). In addition, increased severity of AD is correlated with a decrease in time from dementia onset to death (F. Li. et al., 2013). Understanding when an individual will pass away is important for patient planning and care (Rountree et al., 2012).

Few modifiable risk factors have been studied with respect to the rate of progression of AD, in particular with respect to the clinical outcomes of severe dementia, institutionalization and death. While one area of focus has been on medical comorbidities and their influence on the development of AD (de Toledo Ferraz Alves, Ferriera, Waingarten, & Busatto, 2010; Luchsinger & Mayeux, 2004; Polidori, Mariani, Mecocci, & Nelles, 2006), there has been relatively little research on medical comorbidities and their association with the progression of AD. This is an important area of investigation given the often higher occurrence of medical comorbidities in AD compared to age matched controls without AD or persons with other forms of dementia (Malone et al., 2009). Additionally, overall health and specific medical conditions are associated with rate of cognitive and functional impairment (Leoutsakos et al., 2012; Mielke et al., 2007). In addition, medical comorbidities, to some degree, may be preventable or treatment may lessen their severity and effect on cognitive and functional outcomes in AD.

Much of the current literature consists of studies of samples that are comprised of individuals who have various types of dementia. This can make application of findings to a single cause of dementia more challenging. Study designs also alternate between utilizing prevalence (onset of AD occurred before the study began) and incident (the study began before the onset of AD) cases that are often from a clinical setting instead of
the broader community. This can affect the type of data that is collected (e.g., prevalent cases likely consist of more severely impaired persons) and complicate the interpretation of results and their generalizability to less severe, community-dwelling individuals.

There are several approaches to examining medical comorbidities. One frequently used approach is to obtain an indicator of overall health by factoring in the total number of medical conditions, their severity, their stability, and the medications used for treatment. A commonly used index in general health studies is the Charlson Comorbidity Index (CCI; Charlson, Pompei, Ales, & MacKenzie, 1987). The CCI was developed by identifying medical conditions that had high relative risk values for mortality and then deriving weighted values, which were determined by the seriousness of the condition, for the included conditions (Charlson et al., 1987). The CCI has been used in studies of older individuals with AD to predict hospitalization (Rudolph et al., 2010) and cost of medical care (Hill et al., 2002). It has also been used in a study that predicted the development of AD (Scarmeas et al., 2009). Two studies have looked into associations between the CCI and progression of functional abilities among persons with AD, one reporting no association (Gill, Koepsell, Hubbard, & Kukull, 2011) and another reporting an increase in CCI score being associated with greater rate of progression to functional impairment (Slaughter & Hayduk, 2012).

The General Medical Health Rating (GMHR; Lyketsos et al., 1999) is an overall rating of health that was developed specifically for use in dementia. The GMHR takes into account current results from a physical exam, physical appearance (as an indicator of frailty), medications being taken (excluding those being taken for psychological
conditions) and the presence of any stable or unstable medical conditions (Lyketsos et al., 1999). Using this information, the individual is given a rating, of Excellent (4), Good (3), Fair (2), or Poor (1). Because of the nature of its components, the GMHR rating is likely to fluctuate over time.

The GMHR has been utilized frequently among individuals with dementia (Buckley et al., 2012; Lyketsos et al., 1999; Tighe et al., 2008; Treiber et al., 2008), and has been reported to be associated with greater risk for mortality (Lyketsos et al., 1999), functional impairment (Leoutsakos et al., 2012; Lyketsos et al., 1999; Samus et al., 2009), and cognitive impairment (Leoutsakos et al., 2012) in dementia.

Some investigators have examined the number of medical comorbidities in relation to the rate of dementia progression in AD. One study reported the number of comorbidities is significantly associated with faster cognitive and functional decline and shorter time to death (e.g., J. Li et al., 2010). While no research was contradictory to these findings with regards to rate of progression, one study did report no associations between the number of comorbidities and scores on neuropsychological assessments in individuals with possible and probable AD (Reitz et al., 2007).

Other studies have grouped similar medical conditions together and identify the presence of a summary variable such as “vascular conditions.” This is problematic because it is not possible to identify associations with specific conditions. Other approaches to studying medical comorbidities and dementia progression have examined associations between AD outcomes and specific medical comorbidities, although the number of studies examining outcomes of severe dementia, institutionalization and death
in AD are limited. According to the literature, hypertension (HTN), congestive heart failure (CHF), and stroke (CVA) have been significantly associated with faster rates of progression to cognitive and functional impairment and death (e.g., J. Li et al., 2010; Singer, 2005). However, there are also studies reporting no associations (e.g., Bhargava, Weiner, Hynan, Diaz-Arrastia, & Lipton, 2006). History of stroke has been associated with a slower rate of progression of cognitive impairment in one study (Reitz et al., 2007). Also, there has been a report of no association between hypertension and congestive heart failure with risk for institutionalization in AD (Yaffe et al., 2002). No studies were found reporting on the association between stroke and risk of institutionalization.

In reviewing the available literature on comorbidities and dementia progression, there is evidence that the presence of stroke (J. Li et al., 2010), heart disease (Helzner et al., 2009), or hypertension (J. Li et al., 2010) are each individually associated with greater rates of progression in the severity of dementia. Hypertension (Helzner et al., 2008), stroke (Singer, 2005), and congestive heart failure (Singer, 2005) are each individually associated with greater rates of mortality. Research on stroke, hypertension, and congestive heart failure and their association with institutionalization is limited with a couple of studies reporting no association between heart disease and institutionalization (Andel, Hyer, & Stack, 2007; Yaffe et al., 2002). However, there are significant limitations to the existing literature. First, there have been very few investigations examining the association of medical comorbidity and dementia progression. The emphasis in existing studies has been on rates of cognitive or functional decline, rather
than other perhaps more important (and costly) clinical endpoints of severe dementia and institutionalization. Second, the vast majority of studies used prevalent cases rather than incident cases of dementia. The use of prevalent cases of dementia often does not provide information about milder stages of the disease and necessarily may be biased as those with a shorter (more rapid disease course are often excluded. Third, several studies have used samples consisting of different forms of dementia. Rates of progression may vary widely and medical comorbidities may not exert the same effects across all forms of dementia. Fourth, several studies have limited their examination of medical comorbidities to that of baseline status, and studies have also grouped multiple medical comorbidities into a single summary variable, for example, “vascular factors” representing the presence of diverse conditions such as hypertension, congestive heart failure, heart attack and other health issues. Finally, many studies have been conducted in a clinical setting, which may be unrepresentative of the broader population of persons with AD (Kokmen, Ozsarfati, Beard, O’Brien, & Rocca, 1996; Massoud et al., 1999).

The goal of this project is to examine the relationship between medical comorbidities and the progression to significant clinical dementia outcomes of severe dementia, institutionalization and mortality in a population-based, incidence sample of persons with AD. The project will propose to fill some of the gaps in the existing literature by using several methods to examine comorbidities namely, a total number of prescriptions, the CCI which has rarely been used in examining the clinical endpoints in AD, the GMHR, and three medical conditions (hypertension, congestive heart failure, and stroke) that will each be examined independently, as supported by the literature.
CHAPTER II
LITERATURE REVIEW

Overview of Alzheimer’s disease

Dementia is most commonly diagnosed in individuals over the age of 65 (Jellinger & Attems, 2010); thus, older adults are at greatest risk for this condition. In addition, those over age 65 constitute one of the fastest growing segments of the population (U. S. Census Bureau, 1996), and as a result, it can be assumed that rates of dementia will increase in the future (Taylor, Sloan, & Doraiswamy, 2004; Eaker, Vierkant, & Mickel, 2002). AD is the most common form of dementia in late life and is characterized by a progressive loss of memory and other cognitive abilities (Small et al., 1997). It is estimated that worldwide, 24 million individuals currently suffer from AD and that by the year 2040, this total will reach 81 million (Ferri et al., 2005). In the U.S., the current prevalence of AD is estimated at roughly 5.4 million, with projections reaching 13.8 million by the year 2050 (Hebert, Weuve, Scherr, & Evans, 2013). If these projections hold, the burden of formal and informal care costs will also increase (Coduras et al., 2010). It has been estimated that total cost of care, by all payers, for individuals with AD will increase from $203 billion in 2013 to over $1 trillion in the year 2050 (Alzheimer’s Association, 2013). Because the cost of AD increases with disease severity, it follows that delaying the onset or progression of AD can result in lower health care costs (Herrmann et al., 2010). For example, it has been suggested that if in the year 2015, the onset of dementia were delayed by 5 years, the costs related to dementia care would
decline from $1 trillion to $630 billion in the year 2050 (Alzheimer’s Association, 2013).

**Etiology of Alzheimer’s Disease**

Research into the etiology of AD has associated cell death in the brain with the accumulation of amyloid plaques and the presence of neurofibrillary tangles in specific regions of the brain (Anand, Gill, & Mahdi, 2014). The resulting regional cell death is believed to be a major cause of symptoms experienced in the majority of sporadic, cases of AD when there is no family history. Rare genetic mutations have been associated with genetically transmitted forms of AD through “deterministic genes” (Smith & Bondi, 2008), which are responsible for less than 5% of all cases (Smith & Bondi, 2008). Multiple genetic and environmental factors are likely the cause of sporadic AD (Profenno et al., 2010), sometimes called “late-onset AD,” the most commonly occurring form.

**Diagnosis and Symptom Progression**

According to the *Diagnostic and Statistical Manual* (DSM-IV-TR; American Psychiatric Association [APA], 2000), a diagnosis of AD requires memory impairment and the presence of one of the following: aphasia, apraxia, agnosia, or a disturbance in executive functioning of sufficient severity to cause significant impairment in social and/or occupational functioning. Exclusionary criteria include other central nervous systems diseases, systemic, or substance induced conditions, delirium, or a psychological condition that causes similar symptoms (APA, 2000). The diagnosis of AD also has two sets of specifies that can be applied. One is early or late onset, with age 65 or younger
being early onset and the other being with or without behavioral disturbances (APA, 2000). The cognitive impairment in AD is characterized by a gradual onset, decline from previous levels of functioning, and progression over time. Cognitive impairment in AD typically involves declines in memory, executive function, attention, language, visual-spatial abilities, and psychomotor and other learned motor acts. As a general rule with AD, the decline in cognitive function is gradual over time (Sano & Weber, 2003).

Diagnosis of AD in this study was made using criteria from the Diagnostic and Statistical Manual of Mental Disorders 3rd Edition-Revised (DSM-III-R; APA, 1987). These criteria are slightly different from the DSM-IV-TR in that it requires impairment in memory and impairment in one of the following: abstract thinking, judgment, higher cortical functions such as aphasia, apraxia, agnosia, constructional ability, or personality change (APA, 1987).

Another fundamental feature of AD is impairment in functional ability. These abilities are often referred to as activities of daily living (ADLs). ADL's can be conceptualized as “instrumental” and “basic.” Instrumental ADLs (IADLs) are complex, higher-level skills that include such activities as cooking, shopping, calculating change, using the telephone, or managing medications (Suchy, Kraybill, & Franchow, 2011). Basic ADLs (BADLs) or personal ADLs (PADLs) include self-care tasks such as grooming, bathing, dressing, toileting, feeding, and ambulation (Y. Li, Glance, Yin, & Mukamel, 2011). A decrease in ability to perform IADLs and BADLs is associated with an increase in cognitive impairment (Galasko et al., 1995). Among individuals with AD, those above the age of 85 have a faster rate of progression regarding decline in functional
ability (Nourhashemi et al., 2009). Functional impairment associated with AD often impacts IADLs first and then progresses to the point where BADLs are impaired (Desai, Grossberg, & Sheth, 2004). Impairment in functional and cognitive ability factors into the determination of the level of severity of dementia.

Severe Dementia

With the progression of AD, a person may have deficits in cognitive or functional ability that are so impaired they are considered severely demented. At this point, persons with AD may experience severe disability as evidenced by a greater dependence and burden to caregivers, higher risk of institutionalization, greater financial requirements (Herrmann et al., 2007) and a shortened lifespan. Severe dementia is also associated with greater likelihood of placement in an assisted living or structured nursing facility as indicated by increased impairment in BADLs and IADLs (Miller & Rosenheck, 2006; Miller, Schneider, & Rosenheck, 2011). Additionally, the disability experienced in severe dementia is not solely due to a medical condition. Severe dementia has been identified using cognitive measures. Folstein et al. (1975) suggested that Mini-Mental State Exam (MMSE) scores of 3-9 represent severe AD and scores less than 3 represent very severe AD. A MMSE score of 10 or less have also been used in more recent research to indicate severe impairment (Feldman & Woodward, 2005; Ferris & Yan, 2003; Herrmann & Gauthier, 2008). In a widely used instrument to rate the level of dementia severity, the Clinical Dementia Rating scale (CDR) classifies severe dementia (i.e., a global score of 3) when the individual lacks the ability to eat without assistance, walk or sit upright, recognize others or their surroundings, speak in a comprehensible manner and have full
control of their body (Arrighi et al., 2010).

**Institutionalization**

It is understood that severe dementia is one of the best predictors of institutionalization due to the substantial burden on family caregivers (Liebermann & Kramer, 1991; Wetzels, Zuidema, de Jonghe, Verhey, & Koopmans, 2010). Institutionalization and factors associated with its occurrence are important topics of study due to the higher economic burden to state and federal health care programs and to the personal savings of the individual and families (Alzheimer’s Association, 2013). Additionally, there is greater emotional stress on individuals with dementia who are institutionalized as indicated by self-reported lower quality of life ratings compared to persons with dementia living in the community (Sloane et al., 2005).

A large percentage of individuals with AD will reportedly spend time in a skilled nursing facility (Smith, Kokmen, & O’Brien, 2000). It has been suggested that within 5 years of diagnosis, close to 50% of those diagnosed with AD will have spent some time in an assisted living or skilled nursing home facility (Luppa, Luck, Brahler, König, & Riedel-Heller, 2008). Assisted living facilities generally provide higher levels of care than in a private home, and residents require less supervision than persons in a skilled nursing facility and receive varying levels of help with ADLs in a homelike environment (Spillman, Liu, & McGilliard, 2002). A skilled nursing facility, or nursing home, provides care for those who can no longer care for themselves, provides supervision, helps with ADLs, and focuses on medical or health conditions that require nursing care (Spillman et al., 2002). The term “institutionalization” refers to only skilled nursing
facilities and not assisted living facilities, though placement in either facility is generally an indication of greater impairment and need for higher levels of care.

**Mortality**

The overall time course of dementia from onset to death is another indicator of severity. Generally, associated with more rapid rate of decline in cognitive and functional abilities is a shortened time of survival. Having a better understanding of the time to death in AD (and the factors associated with it) can aid prognosis and impact planning for end of life medical care (Rountree et al., 2012). The life expectancy of someone with AD is generally shorter than an age-matched individual without cognitive impairment (Rountree et al., 2012). Average time from an AD diagnosis until death varies depending upon age at diagnosis and can be summarized as an average of 6.0, 5.0, and 3.5 years until death for those with a diagnosis before age 75 years, from age 75 years to 84 years, and at age 85 years or later, respectively (Brookmeyer, Corrada, Curriero, & Kawas, 2002). AD is also one of the leading causes of death for those who are 65 years of age or older (Minino, Xu, Kochanek, & Tejada-Vera, 2010).

As noted above, the three clinical endpoints of severe dementia, institutionalization, and death are correlated and are generally affected by the rate of progression of cognitive and functional decline. Increasing our understanding of factors that affect the rate of the progression of dementia to these endpoints may have significant implications for patients and family members with respect to quality of life, caregiver burden and the personal and societal costs of care. Decreasing the rate of the progression of dementia in AD may allow individuals with AD and their caregivers to experience
higher quality of life and significantly reduce the financial burden associated with severe dementia. In the next section, I will discuss risk factors associated with the progression of AD, and focus in particular on factors associated with the onset of severe dementia, institutionalization and mortality.

**Risk Factors for Progression of Alzheimer’s Disease**

Much of the research into risk factors on the rate of dementia progression has focused on demographic risk factors, such as gender, age and years of education, and medical comorbidities. These two categories have been extensively studied with regard to the risk for developing AD. Research regarding medical comorbidities and risk for developing AD has sparked interest into how medical comorbidities impact progression of AD. Investigation into these associations is warranted because advances in medicine and medical care may produce effective treatment strategies and lessen the impact of these conditions on dementia. In the next several sections, I will discuss the literature on risk factors that have been studied in relation to dementia progression, in particular those related to the development of severe dementia, increasing risk of institutionalization or hastening mortality. I will begin with a brief summary of literature related to demographic factors followed by a lengthier discussion of studies on medical comorbidities.
Demographic Factors and Severe Dementia, Institutionalization and Mortality

Current literature that reported on associations between dementia severity and education, age, and sex were evaluated. In general, having completed more years of formal education was significantly associated with less severe dementia at baseline, in prevalent AD cases (Nourhashemi et al., 2008). However, this was not the case when dementia severity was examined longitudinally in a mix of prevalent (Nourhashemi et al., 2008) or incident cases (Rabins et al., 2013). It has also been reported that less education was associated with greater rates of institutionalization in incident and prevalent AD cases (Giley et al., 2004; Smith et al., 2000). With respect to mortality, contradictory findings are reported. Specifically, greater education has been associated with faster rate of progression to mortality, in incident cases of AD (Helzner et al., 2008), but slower rates of progression to mortality in prevalent cases of AD (Steenland, MacNeil, Vega, & Levey, 2009; Suh, Yeon, Shah, & Lee, 2005).

With respect to age, older age has been associated with greater dementia severity at baseline among a prevalent AD sample (Nourhashemi et al., 2008) and greater cognitive and functional impairment at baseline among an incident sample of AD (Leoutsakos, 2012). Others reported that in prevalent AD cases, younger age was associated with faster rates of cognitive decline (Bernick, Cummings, Raman, Sun, & Atsen, 2012; Lopez et al., 2010). Older age of AD patients was associated with greater rates of institutionalization, as reported in a meta-analysis (Luppa et al., 2008). However, two studies of AD cases reported no association between age and institutionalization.
(McCann et al., 2005; Miller et al., 2011). All studies are consistent in reporting older age and higher rates of mortality in AD (Gambassi et al., 1999; Paradise et al., 2009; Xie, Brayne, & Matthews, 2008; Zanetti, Solerte, & Cantoni, 2009).

Research looking at onset age, or age of dementia diagnosis, and its association with clinical outcomes is scarce. One of the few studies to look at onset age included 435 participants who were identified as having dementia onset before 65 years and 435 participants with onset of 65 years or greater (Park et al., 2015). These participants were from hospitals across Korea and diagnosed with AD (Park et al., 2015). Park et al. reported that those who had an onset age less than 65 performed worse on cognitive assessments. Another study included 132 participants with prevalent dementia that were diagnosed with probable or possible AD (Rasmusson, Carson, Brookmeyer, Kawas, & Brandt 1996). These participants were identified from a medical center and given the MMSE every 6 months (Rasmusson et al., 1996). The researchers reported that the average change in MMSE score, of -1.61 points, for those who had a younger onset age was significantly larger than the average change in score of -1.37 points, for those who had an older onset age (Rasmusson et al., 1996).

When considering sex, it was reported that among AD cases, females declined faster in cognitive and functional abilities (Sinforniani et al., 2010; Tschanz et al., 2011) and also had higher rates of institutionalization (Smith et al., 2000). However, a majority of articles reported no association between sex and institutionalization (Eaker et al., 2002; Miller et al., 2011; Rozzini et al., 2006; Severson et al., 1994). With respect to mortality, a consistent finding is that males with AD show faster progression to death than females.
with AD (Ganguli, Dodge, Shen, Pandav, & DeKosky, 2005; Helzner et al., 2008; Moritz, Fox, Luscombe, & Kraemer, 1997; Rountree et al., 2012; Russ, Batty, & Starr, 2011; Sinforiani et al., 2010; Waring, Doody, Pavlik, Massman, & Chan, 2005).

In summary, there is empirical evidence that demographic variables such as education, age and sex, affect progression of dementia severity, risk for institutionalization and death. Additional predictors that have been studied are medical comorbidities. According to a recent study, the majority of elderly individuals will experience at least one chronic health condition, while more than half will experience multiple chronic conditions (Wolff, Starfield, & Anderson, 2002). Medical comorbidity is an important issue in AD because AD patients reportedly experience a similar (Zekry et al., 2008), or greater number of comorbidities (Malone et al., 2009) than elderly persons without dementia. In addition, persons with dementia may experience worse functional outcomes despite having similar levels of medical comorbidities as non-demented patients (Zekry et al., 2008). This is a potentially important risk factor since the prevention and treatment of health conditions may impact rates of dementia progression in AD. In this next section, I will review the literature on medical comorbidities and their association with severe dementia, institutionalization, and mortality in AD.

**Alzheimer’s and Medical Comorbidities**

It is important to consider the impact that medical comorbidities has on events or constructs such as mortality, quality of life, admission to a hospital or nursing home, and cognitive and functional abilities in persons with AD. According to the literature, the
The occurrence of multiple medical conditions is associated with increased mortality, hospitalization, and physical disability (Fried, McGraw, Agostini, & Tinetti, 2008) and a decrease in functional ability (Colon-Emeric, Whitson, Pavon, & Hoenig, 2013).

**Charlson Comorbidity Index**

There are various ways that researchers have assessed medical comorbidities as predictors of death and other outcomes, some of which rely on differential weighting to improve prediction (Huntley, Johnson, Purdy, Valderas, & Salisbury, 2012). One measure, the Charlson Comorbidity Index (CCI), has been validated as a predictor of death in elderly individuals in hospitals, specialty settings, primary care, and community populations, and has been used more than any other measure for this purpose (Huntley et al., 2012). The CCI takes into account multiple conditions and assigns a specific weight for each (Charlson et al., 1987). Conditions that receive a weight of 1 are myocardial infarction (heart attack), congestive heart failure, peripheral vascular disease, cerebrovascular accident (stroke), dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer, mild liver disease, and diabetes. Conditions receiving a weight of 2 are paraplegia, moderate or severe renal disease, diabetes with end organ damage, or any non-metastatic cancer. Those with a weight of 3 are metastatic solid tumor and severe liver disease, and a weight of 6 is for AIDS (Charlson et al., 1987). The CCI does not currently have cut-off points reported for probabilities of death.

The CCI is a measure that uses information about a person’s medical comorbidities to help determine a score that represents their risk of death. The CCI has seldom been utilized in populations of individuals suffering from dementia, but it has
frequently been utilized with elderly individuals who have medical conditions. Research involving individuals with dementia has reported on the associations between CCI score and hospitalization, cost of medical care, seizures, medication use, functional decline, onset of disability, and differences between demented and nondemented individuals with regards to medical comorbidities (Gill et al., 2011; Hill et al., 2002; Rudolph et al., 2010; Scarmeas et al., 2009; Slaughter & Hayduk, 2012). The CCI has been used in studies of the elderly as a covariate, to help examine whether physical activity (Scarmeas et al., 2009) or diet (Gu, Nieves, Stern, Luchsinger, & Scarmeas, 2010) predicts the development of AD. In both studies, there was no significant difference in CCI score between those who developed AD and those who did not develop AD (Gu et al., 2010; Scarmeas et al., 2009). In studies of individuals with AD, significant positive associations were reported between the CCI and hospitalization. Rudolph et al. reported that participants with AD who have a CCI score of 1 or more were 87% more likely to be hospitalized for a medical condition compared to those with a CCI score of zero. Nuttall, van der Meulen, and Emberton (2006) found that significantly more individuals had emergency room admissions when there CCI score was 1 or greater compared to those who had scores of 0 (11.9% vs. 8.4%, respectively). The CCI has also been used to compare individuals with AD to nondemented individuals. Zekry et al. (2008) reported that CCI score was not significantly different between those with dementia of mixed types, mild cognitive impairment, and controls. Contradicting this, Malone et al. (2009) reported that when individuals with AD were compared with non-AD matched controls, those with AD had significantly higher scores on a variation of the CCI, the Deyo-
Charlson Comorbidity Index (DCI; \( p < .0001 \)), suggesting greater health concerns in persons with AD. Two articles were identified that utilized the CCI in a population of individuals with AD, and had outcome variables related to the progression of dementia. A sample of 1,880 community-dwelling individuals with dementia (1,761 with AD) from 32 AD centers across the U.S. were studied. There was no association between score on the CCI and functional decline, as measured by the Functional Activities Questionnaire (FAQ; Gill et al., 2011). Possible limitations to this study include a skewed distribution on the CCI where 84.4% of those with AD and 86.1% with dementia of the Lewy body type had CCI scores of zero (Gill et al., 2011). Additionally, the follow-up period was 1 year and the majority of individuals (over 75%) had very mild or mild dementia severity (Gill et al., 2011). Another study of 120 individuals with AD with moderately severe dementia from 15 nursing homes across western Canada found that a higher score on the CCI was significantly associated with earlier disability onset as measured by walking (i.e., being able to walk to meals versus use of a wheelchair or inability to leave one’s room) and eating (i.e., independently feeding without physical help (Slaughter & Hayduk, 2012). Thus, the CCI may have limited association with functional abilities among persons with mild AD, but may show some predictive associations for those with greater severity.

**General Health Medical Rating**

One of the benefits of the CCI over a simple count of medical comorbidities is that it applies differential weights to each condition to improve prediction of mortality. However, the CCI does not account for the current status of whether a medical condition
is acute/chronic or stable/unstable. The GMHR is one index that considers the relative stability of health conditions. The rater selects which of the four categories that best describes the individual: Excellent (4), Good (3), Fair (2), or Poor (1). Ratings are generally based on the results of a physical exam, how the individual appears physically (e.g., degree of physical frailty), and the caregiver’s report of the number of current stable and unstable medical conditions and the number of medications being used (Lyketsos et al., 1999). Additionally, any impairment or inability demonstrated that is a result of a cognitive issue (not being able to open a jar because of turning the lid in the wrong direction) is not factored into the rating. This allows for a more pure rating of medical health. The GMHR has had limited use in studies of dementia progression. In one of the original articles written about the GMHR, the score on the GMHR was significantly associated with impairment in ADL’s in a sample of 819 community-dwelling individuals with dementia (Lyketsos et al., 1999). With each level of decrease in GMHR score (worse health), scores on the Psychogeriatric Dependency Rating Scale (PGDRS-P) increased (more impairment in ADL’s) by 4.1 \( (p = .001) \) points for those with MMSE scores of 10-29 points and by 5.3 \( (p = .001) \) points for those with MMSE scores less than 10 (Lyketsos et al., 1999). The authors also reported that as the GMHR score decreased, the rate of mortality increased significantly. There was a 1.7 times increase for each unit decrease on the GMHR in models controlling for MMSE and age (Lyketsos et al., 1999).

In a study that examined functional dependence among 155 persons with dementia recently admitted to an assisted living facility, Samus et al. (2009) reported that a higher score on GMHR was significantly associated with greater functional
independence as measured by the PGDRS-P physical dependency subscale. They reported that for every point decrease on the GMHR, that the PGDRS-P increased by 3.54 points (Samus et al., 2009).

In studies examining rate of cognitive or functional decline, Leoutsakos et al. (2012) reported that among 335 incident cases of AD from the Cache County Memory Study (CCMS), GMHR score fluctuated in both directions over the follow-up period, which ranged from 0.65 to 11.18 years (median years = 3.07). While GMHR was not significantly associated with rate of change in measures of dementia progression on the MMSE and CDR (Leoutsakos et al., 2012), a GMHR score of 1 or 2 was significantly associated with worse cognitive and functional abilities (MMSE: $\beta = -1.07, p = 0.01$; CDR-SB: $\beta = 1.79, p < 0.001$; Leoutsakos et al., 2012). Leoutsakos et al. also looked at the number of comorbidities identified and reported that the more comorbidities that were present at baseline, the greater the decline in MMSE score across time ($\beta = -0.02, p = 0.04$). In a subset of the Cache County Study population that included 149 nursing home and other community-dwelling residents with dementia, 255 persons with cognitive impairment (no dementia), and 321 persons with no cognitive impairment, the three groups did not differ significantly in number of medical comorbidities (Lyketsos et al., 2005). However, when considering the severity of medical conditions with the GMHR, those with dementia and CIND had significantly worse GMHR ratings than those with no cognitive impairment (Lyketsos et al., 2005). In addition, persons with dementia were more likely to be rated as having moderate to severe comorbidity than little to no comorbidity. Moreover, a lower GMHR score was significantly associated with more
severe functional and cognitive impairment as measured by the Dementia Severity Rating Scale (DSRS; $F = 47.993, p < 0.001$) and MMSE ($F = 6.94, p < 0.001$; Lyketsos et al., 2005).

Overall, the GMHR has mostly been utilized in populations suffering from dementia. It has been used to provide a picture of overall medical health that incorporates whether the medical condition is well-controlled (stable) or not well-controlled (unstable). Research has reported the GMHR to be significantly associated with length of stay in an assisted living facility, impairment in ADL’s, rate of mortality, functional independence, and cognitive and functional abilities in dementia.

Medical indices are useful because they allow health care providers to account for multiple medical comorbidities at once. However, individual single health conditions have been examined with respect to their impact on the progression of AD. In conducting my literature search on medical comorbidities and dementia progression to the clinical endpoints of interest here, I found a limited number of studies. Some of the search terms that were used were “rate of progression,” “medical comorbidities,” “medical conditions,” and “comorbidity index.” The most common medical conditions listed during searches were vascular conditions (hypertension, stroke, diabetes, heart disease, congestive heart failure, and high cholesterol). It is likely that these conditions are the most frequently reported on because there is a wealth of literature regarding the known associations between vascular factors and the risk for developing AD and a logical extension of this research moves towards dementia progression.

There were three conditions (hypertension, stroke, and congestive heart failure)
that had some evidence supporting an association with one more of the clinical outcomes of severe dementia, institutionalization and death, although the number of studies was quite limited. Below, I will discuss the literature for these three conditions and their associations with the above outcomes.

**Severe Dementia**

Literature regarding dementia severity is one of the more frequently reported on outcomes that will be reviewed here. One cross-sectional study by Goldstein et al. (2008) looked at 74 individuals with AD who were identified from a memory clinic. They reported that individuals who had a history of hypertension (at baseline) performed significantly worse on a design copy ($\beta = -2.20, p < 0.001$) and recall task ($\beta = -1.6, p < 0.01$) compared to those without a history of hypertension (Goldstein et al., 2008). In addition, it was reported that as the severity of hypertension increased (measured by either systolic or diastolic pressure), scores on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) design copy task decreased ($r = -0.26, p <0.05$; Goldstein et al., 2008). However, this finding was no longer significant after controlling for age, education, race, sex, MMSE score, and diabetes or a cardiac disease (Goldstein et al., 2008). Sakuri et al. (2011) followed 150 individuals with AD from a memory clinic for a mean of 39 months. The authors reported that individuals with a history of hypertension at baseline progressed towards greater cognitive impairment, as measured by the MMSE, at significantly faster rates ($\beta = -0.173, p = 0.032$) than those with no history of hypertension (Sakuri et al., 2011).

Another study followed 243 individuals with incident (newly diagnosed) cases of
AD for a mean of 5.5 years (Reitz et al., 2007). Those with a history of hypertension (at baseline or follow-up) performed significantly worse on a category fluency test at follow-up than did those without a history of hypertension (Reitz et al., 2007). Another finding from Reitz et al. was that history of stroke at baseline was protective, such that those with a history of stroke performed better on a measure of delayed recall and abstract verbal reasoning, at follow-up, than those with no history of stroke. In this analysis, Reitz et al. controlled for age, sex, education, ethnicity, and E4 genotype of Apolipoprotein E (APOE). Another longitudinal study followed individuals living in urban cities in China for five years (J. Li et al., 2010). Among the 415 individuals who developed AD during follow-up (incident cases) those with a history of hypertension at baseline had significantly worse scores on assessments of cognitive (MMSE; $\beta = -0.483 \pm 0.093, p < 0.001$) and functional ability (modified Activities of Daily Living; $\beta = -0.377 \pm 0.171, p = 0.028$; J. Li et al., 2010). J. Li et al. also reported on strokes and transient ischemic attacks (TIAs), however, their results contradicted those of Reitz et al. They reported that history of a TIA prior to baseline was significantly associated with a faster progression of cognitive (MMSE; $\beta = -0.609 \pm 0.105, p < 0.001$) and functional decline (ADL: $\beta = -0.555 \pm 0.150, p < 0.001$; J. Li et al., 2010). The authors (J. Li et al., 2010) also reported that the occurrence of a new stroke, during the follow-up period, was also associated with faster cognitive (MMSE: $\beta = -0.836 \pm 0.089, p < 0.001$) and functional decline (ADL: $\beta = -0.827 \pm 0.140, p < 0.001$). This study differed from Reitz et al. in its inclusion of TIAs and incident strokes during follow-up, which along with population differences may help account for differences in results. Mielke et al. (2007) also reported
on both stroke and hypertension. They followed 135 individuals with incident AD from the CCMS for a mean follow-up of 3 years (Mielke et al., 2007). The authors found that when compared to individuals who did not have high blood pressure (systolic BP < 160 vs. ≥ 160), those with high blood pressure, at baseline, had significantly faster rates of cognitive decline, as measured by the MMSE ($\beta = -2.38$, 95% C.I. = -3.23 to -1.53, $p < .001$), and functional decline, as measured by the CDR sum-of-boxes score ($\beta = 1.78$, 95% C.I. = 1.20 to 2.36, $p < .001$; Mielke et al., 2007). They also reported an interaction with age where those who were 86 or older, and had HTN, declined faster on both cognitive and functional measures than those who were younger than 86 with HTN (Mielke et al., 2007). The authors also reported no significant association between stroke at baseline and rate of cognitive and functional decline.

However, in a different article that utilized data from the same population, CCMS ($n = 216$), Mielke et al. (2011) reported an interaction between history of stroke at baseline and APOE genotype with progression of cognitive and functional decline. Specifically, those who had a history of stroke and an APOE E4 allele had a greater initial decline on MMSE score than did those with history of stroke and no APOE E4 allele; however, after approximately 5 years, the rate of progression in the APOE4 carriers slowed whereas the rate of progression in the non-carriers increased (and resulted in a quicker decline in cognitive ability than the other group) over time (Mielke et al., 2011). The trajectories of these two groups were significantly different ($x^2 = 10.32$, 2 df, $p = 0.006$; Mielke et al., 2011). A similar trend was observed in functional ability (Mielke et al., 2011). Similar to Mielke et al. (2007), stroke was not significantly associated with
rate of progression when individuals were not stratified by APOE E4 status (Mielke et al., 2011). Thus APOE E4 may be an important moderator of the effects of stroke and cognitive and functional decline.

Helzner et al. (2009) reported on 156 community-dwelling individuals with incident dementia who were followed for an average of 3.5 years. The authors found that when stratified by APOE E4 status, those with an APOE E4 allele and either a history of heart disease at baseline ($\beta = -0.187, p = 0.001$) or stroke at baseline ($\beta = -0.178, p = 0.02$) had significantly faster rates of cognitive decline (Helzner et al., 2009). Cognitive impairment was measured by parts of the Selective Reminding Test, Benton Visual Retention Test, WAIS-R, Dementia Rating Scale, Rosen Drawing Test, Boston Naming Test, Boston Diagnostic Aphasia Examination, and the Controlled Oral Word Association Test (Helzner et al., 2009). Regarding the heart disease variable, it is important to note that congestive heart failure was one of three conditions that categorized persons as having a history of heart disease; the other two conditions were history of myocardial infarction or angina (Helzner et al., 2009). Thus, it is uncertain whether the results hold for congestive heart failure alone. In addition, these reported associations were not significant when participants were not stratified by APOE E4 status. The authors also reported that hypertension was not significantly associated with rate of progression for cognitive impairment, regardless of APOE genotype (Helzner et al., 2009).

Musicco et al. (2009) reported that among 154 individuals with AD, that were followed for a mean of 23 months, hypertension was not significantly associated with fast (change of five or more points on MMSE) or slow (change of less than five points on
MMSE) decline in cognition. Another study utilized three years of retrospective data for 247 individuals with AD, from an AD Center (Bhargava et al., 2006) and found that individuals categorized as “fast progressors” (CDR score increased from 1 to 2 or greater after three years) and “slow progressors” (CDR score remained at 1 after three years) did not significantly differ based on history of hypertension, stroke, or heart problems (Bhargava et al., 2006).

**Institutionalization**

Much of the literature pertaining to dementia and institutionalization focuses on behavioral disturbances. Gaugler, Yu, Krichbaum, and Wyman (2009) completed a meta-analysis that reported factors associated with nursing home placement among individuals with dementia. It is important to note that this meta-analysis included studies that looked at individuals with any type of dementia. Of the 13 studies that addressed behavioral symptoms and were classified as “high quality,” seven, or 53.8%, reported significant associations between the presence of behavioral symptoms and placement in a nursing home (Gaugler et al., 2009). The remaining 6 studies reported no significant associations (Gaulger et al., 2009). This same meta-analysis also identified seven studies that reported on the presence of psychotic symptoms and their association with nursing home placement (Gaulger et al., 2009). When all seven studies were included, three (42.9%) had significant associations between the presence of psychotic symptoms and institutionalization while the remaining 4 had no significant associations (Gaulger et al., 2009). However, when only “high-quality” studies were included, the number of studies decreased to two and one reported the presence of psychotic symptoms was significantly
associated with institutionalization while the other reported no association (Gaulger et al., 2009).

One study not included in the meta-analysis followed 24 men and 24 women, who all had dementia of various types, for up to 2 years to track admission to a skilled nursing facility (Kenny et al., 2008). The authors reported 23 of the 48 individuals were admitted to a nursing home and that the presence of depression was significantly associated with nursing home placement (odds ratio of 1.19; Kenny et al., 2008).

There are few studies that have examined individual medical comorbidities and risk for institutionalization in AD. Many of the studies examining this issue have relied on comorbidity indices instead of a single medical condition. In an article reporting a single medical comorbidity and institutionalization, the Medicare Alzheimer’s Disease Demonstration and Evaluation study examined 3,859 prevalent AD cases from eight memory clinics, during a 3-year period (Yaffe et al., 2002). The investigators reported that individuals with a history of heart disease at baseline did not differ from those without a history of heart disease in risk of institutionalization. Andel et al. (2007) studied 587 individuals who were diagnosed with prevalent dementia. These individuals were identified from a data set of persons age 65 or older who were registered for Medicare or Medicaid in Florida from 1998 to 1999 (Andel et al., 2007). The authors reported that history of heart disease was not significantly associated with risk of becoming institutionalized over a maximum follow-up period of 4 years. Additionally, the sample in this study consisted of individuals with dementia from any etiology, and not solely those with AD (frequency of AD was not reported). Across many of the studies
looking at congestive heart failure, there is a consistent limitation. The authors often only identified “heart disease” or some other term that incorporated multiple heart conditions. The authors discussed how their model may have some variability because nursing home placement is partially dependent upon social circumstances, preferences, and values and medical variables do not capture this.

Mortality

While the outcome of death has more established literature related to medical comorbidities than institutionalization, there were still a limited number of studies on the topic. Singer (2005) followed 521 individuals who were identified from a health organization in the western U.S., had prevalent AD cases, and were followed for a mean of 5.2 years. Among individuals who died, those who had a history of stroke or congestive heart failure prior to baseline had a significantly shorter median survival time than those lacking those conditions (Singer 2005). Singer reported that the 5-year survival rate of individuals with a history of congestive heart failure was 30% while those with no history had a 5-year survival rate of 52%. In contradiction, time to death was similar for those who had a history of hypertension and those that did not (Singer, 2005).

In a study of community-dwelling individuals from the northeast United States, 323 individuals with incident cases of AD were followed for a mean of 4.1 years (Helzner et al., 2008). The authors found that individuals who were reported to have hypertension at baseline were significantly more likely to die during the follow-up period (HR = 2.57, 95% C. I. = 1.04-6.37) than those without such a history (Helzner et al., 2008). They also reported no significant association between a history (or lack of history) of stroke at
baseline and time to death (Helzner et al., 2008). Regarding the lack of findings for stroke, the authors (Helzner et al., 2008) suggested the large proportion of non-Caucasian individuals in this study (55% Latino and 33% African-American) may be one reason for differing results from the study conducted by Singer (2005).

Another study reported on data from the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database. This study involved 9,264 individuals (who were followed for a mean of 23 months) with prevalent cases of AD who were registered with Medicare and living in a nursing home in one of five U.S. states (Gambassi et al., 1999). The authors reported that individuals with a history of congestive heart failure did not have a significantly higher risk of death during follow-up compared to those without the condition (Gambassi et al., 1999). Rountree et al. (2012) followed 641 individuals, who had prevalent cases of AD, from a U.S. medical center and evaluated them for a mean of 3.0 years and 2.4 visits. The authors reported that both individuals with or without a history of coronary disease or hypertension were not significantly different with regards to time to death during study follow-up (Rountree et al., 2012). This article, along with many of the above reported articles, has the limitation that congestive heart failure was not examined individually as a predictor. It is also important to keep in mind that some of the articles use predictor variables that specifically include congestive heart failure while some only include comorbidities included in heart disease, which often exclude this condition. Additionally, there are differences in results between studies that utilize data from incident cases of AD compared to those that utilize data from prevalent cases. There is a trend where studies that use data from incident cases reported more
significant associations between the presence of medical comorbidities (hypertension, stroke, and heart failure) and measures of dementia progression (severe dementia, institutionalization, and death). Studying incident cases of dementia longitudinally has advantages in studying a broader range of persons with AD and have less survival bias (to enter the study) than prevalent cases.

**Number of Prescriptions**

Rather than examining individual medical conditions or a summary index, many studies have examined number of various medical comorbidities. For example, Lechowski et al. (2009) followed 687 community-dwelling French individuals who had been identified as having AD. These individuals were evaluated every 6 months for 4 years (Lechowski et al., 2009). The authors reported that there was a trend among both males and females where those with two or more medical comorbidities had more impairment in BADL score than those with one or zero comorbidities (Male: 0 or 1 comorbidity—mean BADL score = 4.6 vs. 2+ comorbidities—mean BADL score = 3.8; Female: 0 or 1 comorbidity—mean BADL score = 4.6 vs. 2+ comorbidities—mean BADL score = 4.0; Lechowski et al., 2009). Among the medical comorbidities included were congestive heart failure and cardiac disease (Lechowski et al., 2009). J. Li and colleagues (2010) also dichotomized their sample of 324 individuals with incident AD who were living in urban Chinese cities and followed them for 5 years. The authors reported that those with one or more vascular factors (i.e., hypertension, TIA, stroke, hypercholesterolemia) had significantly greater rates of cognitive (MMSE: $\beta = -1.059 \pm 0.109, p < 0.001$) and functional decline (ADL: $\beta = -1.954 \pm 0.099, p < 0.001$) when
compared to individuals with no comorbidities (J. Li et al., 2010). Boksay, Boksay, Reisberg, Torossian, and Krishnamurthy (2005) reported on 40 individuals who had been diagnosed with probable AD and also progressed to the end stages of the disease as determined by a global deterioration scale (GDS) score of 7. These participants were followed longitudinally at intervals of 3 to 4 years. At each visit, their medical conditions were recorded and classified into the following groups: cardiovascular, endocrine, respiratory, nervous system, hematological, neoplastic, gastrointestinal, dermatological and connective tissue disorders, allergic, history of surgeries, injuries and fractures, eye and ear, genitourinary and gynecological, and musculoskeletal disorders. The authors reported that individuals that progressed to severe dementia (GDS = 7) in less than 4 years (mean of 3.2 years) had a mean of 6.0 condition groups while those who progressed in over 4 years (mean of 6.9 years) had a mean of 3.9 condition groups (Boksay et al., 2005).

Mortality has also been studied using predictor variables that include a long list of comorbidities. Rizzuto et al. (2012) followed 371 individuals, with incident AD, from the Kungsholmen project for 7.4 years. They performed a log-rank test and found that individuals with AD and a history of cardiovascular disease (chronic rheumatic heart disease, hypertension, angina, myocardial infarction, chronic pulmonary heart disease, acute pericarditis, cardiac dysrhythmias, or cerebrovascular disease) had significantly shorter length of survival \( p < 0.001 \) during follow-up than did individuals with AD and no cardiovascular disease. A different study that looked at survival was completed by Suh et al. (2005) and followed 252 individuals for 1 year. These individuals with prevalent
AD cases and were living in a private residence or nursing home (Suh et al., 2005). The authors reported that among those living in a nursing home, that history of one or more vascular factor (hypertension, heart disease, diabetes mellitus, or Hypercholesterolemia) was significantly associated with an increased risk for death during the 1-year follow-up (RR = 4.07, 95% C.I. = 1.77 – 9.37, \( p < 0.05 \); Suh et al., 2005). Risk of death was not higher for those in a nursing home lacking the above health conditions or for those living outside of nursing homes. Another study by Gambassi et al. (1999) followed, for a mean of 23 months, 9,264 individuals with prevalent AD. These individuals were Medicare recipients and living in a nursing home in one of five U.S. states. Individuals with a history of cardiovascular disease (i.e., congestive heart failure, hypertension, ischemic heart disease, or arrhythmia) had a significantly greater risk of dying during the follow-up compared to AD patients without a history of cardiovascular disease: RR = 1.22, 95% C.I. = 1.14-1.30; Gambassi et al., 1999).

**Summary**

As it stands, the literature on AD and the medical comorbidities that influence its progression provide important information to individuals in many different settings. However, a number of limitations are noted. First, there have been very few investigations even examining the issue of comorbidity and dementia progression. Of these, the emphasis has been on rates of cognitive or functional decline, while significant, does not speak to some important (and costly) clinical endpoints of severe dementia and institutionalization. Second, the vast majority of studies used prevalent cases rather than
incident cases of dementia. The use of prevalent cases of dementia often does not provide information about milder stages of the disease and necessarily is biased towards those who have survived. This may limit generalizability to a subgroup of persons with dementia. To address this, only incident cases of AD will be used in this study. Another limitation is that some studies have samples that consist of individuals with all types of dementia and do not limit to only AD. This is problematic because different types of dementia have different etiologies and the effects of medical comorbidities may differ for the different types of dementia. This study addresses this by using data from individuals with a diagnosis of AD. The other limitations are relevant to the type of data collected and how often it was collected. Specifically, some studies only collected data on medical comorbidities at baseline, and did not include new medical conditions that arose during follow-up. This study, where possible, will examine history of medical comorbidities up to baseline as well as those that developed during follow-up. Additionally, many other studies have only examined a summary variable, grouping multiple medical comorbidities into a single variable, such as a vascular risk factor or condition representing the presence of diverse conditions such as hypertension, congestive heart failure, heart attack and other health issues. This study will address this limitation by representing medical comorbidities a number of ways, including total number, two indexes, and specific conditions guided by past research. Finally, many studies have been conducted in a clinical setting, which may be unrepresentative of the broader population of persons with AD. This project proposes to examine the role of medical comorbidities and time to progression to the three clinical endpoints in a population-based sample. By
addressing some of the past limitations of previous studies and gaps in the literature, this study will contribute to a better understanding of how medical comorbidities are associated with the progression of AD.

**Research Questions**

Guided by previous research and its limitations, longitudinal data from individuals with incident AD from an extant data set was analyzed. Specific focus was placed on the associations between medical comorbidities and the progression to specific clinical dementia outcomes. The aims of this study were to address the following research questions.

1. What is the association between two separate global measures of medical comorbidity (the Charlson Index and the GMHR) and the time to reach the outcomes of severe dementia, institutionalization and death? It was hypothesized that higher scores on the Charlson Comorbidity Index would be associated with shorter survival time to all three outcomes. It was also hypothesized that poorer ratings on the GMHR would predict shorter survival time to each dementia outcome. Because the GMHR and CCI may measure similar constructs, it was also of interest to examine whether the GMHR and CCI were redundant measures for each of the three clinical endpoints.

2. What was the association between a history of specific medical comorbidities and the time to the outcomes of severe dementia, institutionalization, and death? Past research indicated that hypertension, congestive heart failure, and stroke were associated with dementia progression, and these conditions were examined separately as well as
together (in a multivariate model) for associations with severe dementia, institutionalization, and death. The presence of each of these medical comorbidities was hypothesized to decrease survival time to each of the three outcomes. It was also of interest to examine whether these three medical comorbidities were redundant measures for each of the three clinical endpoints.

3. What was the association between a simple count of (nonpsychotropic) prescription medications and survival time to the outcomes of severe dementia, institutionalization and death? Informed from previous literature, it was hypothesized that a higher number of comorbidities would be associated with shorter survival time to each of the three clinical outcomes.

In view of other factors that influence dementia progression, I tested a number of covariates and examined potential for confounding for each outcome by including participant age, sex, education, APOE E4 status, and dementia duration in all models.
CHAPTER III

METHOD

Research Design and Methodology

This project used extant data collected from the Cache County Study on Memory in Aging (CCSMA) and the Dementia Progression Study. The Cache Country Dementia Progression Study (DPS) was a longitudinal study of persons with dementia that studied factors associated with varying rates of dementia progression as a major aim. Participants in the DPS were recruited from individuals with newly diagnosed dementia from the CCSMA. An overview of the CCSMA procedures for dementia ascertainment are described elsewhere (Breitner et al., 1999) and will be described here briefly. In 1994, all individuals who were 65 years or older, and were living in Cache County, Utah, were asked to be in the CCSMA. Of the 5,657 individuals who were asked, 5,092 agreed to participate (90%) in the first stage of screening with the Modified Mini-Mental State Exam–Revised (3MS-R), revised for epidemiologic studies (Tschanz et al., 2002). Those unable to complete the 3MS-R had a proxy informant complete the Information Questionnaire of Cognitive Decline (IQCODE; Jorm, 2004). Those who screened positive or who were members of a subsample of individuals (randomly selected based on an age, gender, and APOE genotype match to each case of AD) were asked to complete the second stage of screening with the Dementia Questionnaire (DQ; Kawas, Segal, Stewart, Corrada, & Thai, 1994), which involved a knowledgeable informant. The informant was asked to complete a telephone interview about the CCSMA participant
regarding the presence of any cognitive or functional impairment common to dementia. Participants whose DQs suggested the presence of dementia or significant cognitive impairment, along with the selected subsample, were asked to participate in a more extensive clinical assessment (CA). This was conducted by a trained neuropsychological technician and research nurse who completed neuropsychological testing and a structured physical and neurological examination, respectively with the participant.

Questions about the participant’s cognitive and functional impairment, medical history, and psychiatric symptoms were asked of a knowledgeable informant. Results of the CA were reviewed by a geropsychiatrist and neuropsychologist who assigned preliminary diagnoses of dementia or other cognitive disorders. Diagnoses of dementia followed the criteria from the DSM-III-R. Participants who were diagnosed with dementia, or were suspected to be in the prodromal stages of dementia, were asked to complete an MRI scan and standard laboratory tests for a dementia evaluation. They were also asked to participate in an 18-month follow-up CA. A final determination of dementia, and dementia type were made by a panel of experts in neurology, geropsychiatry and neuropsychology. Age of dementia onset was assigned as the age at which the participant met DSM-III-R criteria for dementia. Three other waves of dementia screening and assessment occurred in 1998, 2002, and 2005 with a similar protocol (Miech et al., 2002). Participants with “incident” dementia (those identified through waves 2-4) and their caregivers were then invited to participate in the DPS. Once in the DPS, participants and their caregivers completed follow-up visits as close to every six months as possible.
Procedure

In addition to the 18-month follow-up completed by the CCSMA, the DPS evaluated participants and their caregivers approximately every 6 months and followed them until refusal, relocation outside of the study area, death, or the end of data collection. Follow-up evaluations were conducted by a trained team of research technicians and consisted of a test battery developed by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). This battery, which includes the MMSE, was developed to help clinicians identify symptoms of AD, track progress of changes in cognition, and to help discriminate between memory and cognitive impairment associated with normal aging and that associated with dementia (Morris et al., 1989). In addition, the informant was questioned regarding the participant through a semistructured interview. They provided information relevant to the participant’s cognitive and functional abilities, their health, and their living circumstances from the previous visit to the current visit.

After the completion of each visit, the two research technicians, the principal investigator (PI), and if needed, a consulting geropsychiatrist or research nurse would meet to review each case and assign the participant a score on the CDR and GMHR. Ratings for the CDR considered the report of the caregiver as well as neuropsychological test data to assign scores for each of the six CDR subcategories (see Appendix A). The scores from all six subcategories were then used in an algorithm, designed by the authors of the CDR, to derive the global CDR score (Morris, 1994; Washington University Alzheimer’s Disease Research Center, n.d.). Cases that were unclear or where disagreements between the PI and a research technician occurred were reviewed with a
consulting study geropsychiatrist.

The GMHR score for the participant was also determined in the same meeting through a consensus. The research technician presented the medical history for the participant, considering current and past chronic health conditions, making note of those that were not well-controlled, acute conditions, and total number of medications used for health problems (see below for rating categories). Again, ambiguous cases or those with disagreements between were referred to a consulting study geropsychiatrist for adjudication.

**Measures**

**Predictor Variables**

**General Medical Health Rating.** The GMHR (Lyketsos et al., 1999) is a measure that is designed to identify medical comorbidity and medical instability (i.e. uncontrolled diabetes) among individuals with dementia while also excluding any impairment resulting from cognitive deficits. The GMHR was developed to be utilized in a quick manner. It involves a trained technician collecting an individual’s non-dementia related medical information. In doing this, the GMHR provides a rating that is independent of functional impairment that is rooted in cognitive deficits and strictly related to medical health. Such an example would be inability to eat due to a loss in understanding of how to use a fork (not included) versus the inability to pick up a fork due to paralysis in the hand (included). There are four possible ratings on the GMHR and they range from 1 to 4, with higher ratings representing fewer, more stable, and less
severe medical comorbidities. A rating of a 4 represents excellent health, 3 represents good health, 2 represents fair health, and 1 represents poor health. In a study that compared ratings on the GMHR that were given by psychiatrists and nurses, the GMHR was found to be a reliable instrument with regards to inter-rater reliability (94% agreement, weighted kappa = .93; Lyketsos et al., 1999). The GMHR has also been reported to be a valid measure and is correlated with the number of medical conditions across all stages of AD ($p < .001$) and the number of medications across all stages of AD ($p < .008$; Lyketsos et al., 1999). Because of the GMHR’s correlation with a measurement of impairment in ADL’s, it is also thought that the GMHR captures an aspect of the severity of comorbid medical conditions (Lyketsos et al., 1999). An example of the GMHR can be found in Appendix B.

**Charlson Comorbidity Index.** The Charlson Comorbidity Index (Charlson et al., 1987) is a measure that identifies the number of comorbid medical conditions an individual has, that was validated to predict 1-year patient mortality (Needham, Scales, Laupacis, & Pronovost, 2005). The CCI involves 17 medical conditions, with each condition having a weighted value of 1, 2, 3, or 6. Medical conditions with a weight of 1 include: acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, dementia (excluded here since all subjects meet this criteria), chronic pulmonary disease, connective tissue disorder (e.g., Sjogren’s, Systemic Lupus Erythematosus), peptic ulcer, mild liver disease (alcoholic cirrhosis, cirrhosis without mention of alcohol, biliary cirrhosis, and chronic hepatitis), and diabetes without end-organ damage (Charlson et al., 1987). Medical conditions with a weighted value of 2 are:
diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes), paraplegia, renal disease, and non-metastatic cancer (Charlson et al., 1987). Those with a weighted value of 3 are metastatic cancer and severe liver disease (hepatic coma, portal hypertension, esophageal varices; Charlson et al., 1987). The only condition with a weighted value of 6 is AIDS (Charlson et al., 1987). Adaptations to the original CCI have been created where the above listed medical conditions have been associated with ICD-9-CM diagnostic codes to facilitate scoring and enhance reliability (Sundararajan et al., 2004). For this study, the CCI was modified by removing the comorbidity of dementia, because all individuals have dementia, and AIDS status due to no individuals in the sample with AIDS. The score was computed by summing the weighted value of all 15 comorbidities with a maximum score of 24 possible.

Data to score the CCI came from a medical health history that was completed for participants, a medical conditions checklist, and a case staffing report that contained a medical history obtained by a research nurse. Data were checked by running a macro to search each specific Microsoft Word file for specific words. This data were then entered into a statistical program. The macro searched for the following words: “MI” (myocardial infarct), “myocardial,” “infarct,” “attack,” “CHF,” “congestive,” “heart,” “failure,” “PVD” (peripheral vascular disease), “peripheral,” “vascular,” “CVA,” “cerebral,” “stroke,” “COPD” (chronic obstructive pulmonary disease), “chronic,” “obstructive,” “pulmonary,” “connective tissue,” “connective,” “tissue,” “Sjogren,” “systemic,” “lupus,” “erythematous,” “peptic ulcer,” “mild,” “liver,” “alcohol,” “ETOH” (ethanol), “cirrhosis,” “biliary,” “hepatitis,” “diabetes,” “end organ,” “retinopathy,” “neuropathy,”
“nephropathy,” “brittle,” “paraplegia,” “para” “renal,” “non-metastic,” “cancer,”
“metastic,” “severe liver,” “hepatic,” “coma,” “portal,” “hypertension,” “esophageal,”
“varices,” “AIDS” (acquired immune deficiency syndrome), “acquired,” “immune,”
“deficiency,” and “syndrome.” The results of this search were reviewed to eliminate
erroneously identified conditions. During follow-up visits, CVA, MI, and diabetes were
specifically asked about in closed-ended questions while other medical conditions were
identified through an open-ended question. During follow-up visits, there were fewer
closed-ended questions that specifically asked about conditions on the CCI. Because of
this, the CCI score was only calculated as a baseline score.

Multiple research studies have validated the CCI and reported its capacity to
predict mortality (Sundararajan et al., 2004). Data from the Australian Department of
Veterans Affairs showed that the CCI, which had a median score of zero, predicted
mortality in a population of elderly individuals that had been hospitalized during the
previous year (Lu, Barratt, Vitry, & Roughead, 2011). This was true for prediction of
mortality at 1 year (c statistic = 0.766, AIC = 55630.76) and 3 years (c statistic = 0.750,
AIC = 98012.30; Lu et al., 2011). A study that involved stroke patients from the United
States Department of Veteran Affairs reported that every 1-point increase on the CCI was
associated with a 29% increase in the chance for mortality at 1 year follow-up after
discharge from the hospital (Goldstein, Samsa, Matchar, & Horner, 2004). The English
National Health Service reported that both the Charlson Deyo version and Charlson
Dartmouth-Manitoba version predicted mortality (AIC = .71 and .73, respectively) from
records of 20,138 patient who had urological cancer surgery between 1998 and 2002
Of the various adaptations of the CCI, little to no difference has been found with regards to predictive ability of mortality (Cleaves, Sanchez, & Draheim, 1997; Ghali, Hall, Rosen, Ash, & Moskowitz, 1996). These adaptations consist of modifying the CCI so that it can be used with codes from the International Statistical Classification of Diseases and Related Health Problems manual (Cleves et al., 1997). The CCI Deyo adaptation renamed “connective tissue disorder” as “rheumatological disease” (Deyo, Cherkin, & Ciol, 1992). The Romano adaptation was similar to the Deyo adaptation except it included more diseases for the categories of peripheral vascular disease, complicated diabetes, and cancer (Romano, Roos, & Jollis, 1993).

**Medical conditions.** The presence or history of hypertension, stroke and congestive heart failure were identified through medical history information collected from the subject via self-report within the CCSMA before the onset of dementia and from the informant within the DPS thereafter. Medical conditions not specifically queried (e.g., cancer) were identified at each visit through review of medications recorded and the use of an open-ended question.

**Number of prescription medications.** The number of nonpsychotropic prescription medications will be based on the number identified through data collected in the CCSMA and DPS follow-up visits. During data collection, all medications were recorded along with its indication, if it was prescription or over the counter, how much was being taken and how often the medication was supposed to be taken. Psychotropic medications and medications prescribed to slow the progression of dementia
(antidementia) were excluded from the final count. Only prescription medications were included in the final count.

**Covariates.** The covariates of age of dementia onset, education, APOE4 genotype, and duration of dementia were identified through data collected in the CCSMA.

**Outcome Variables**

**Severe dementia.** The determination of severe dementia was made using the MMSE and CDR (see below for descriptions). The participant was categorized as having severe dementia when they either scored 10 or fewer points on the MMSE or they were given a global CDR rating of 3 (severe), 4 (profound), or 5 (terminal) according to previous work (Rabins et al., 2013). The date of severe dementia is the date of the visit at which the participant first meet the above criteria. This assumed that once the participant achieved that stage, he/she would not revert back to a milder stage. Information is provided below on both the MMSE and CDR as they are used to determine severe dementia.

**Mini-Mental State Examination.** The Mini-Mental State Examination (MMSE) is a brief, global cognitive test that has been used extensively in studies of dementia to estimate cognitive impairment and track cognitive change (Folstein et al., 1975; Rabins et al., 2013; Tschanz et al., 2011). The MMSE consists of 11 items and assesses five areas of cognition: orientation, registration, attention and calculation, recall, and language. Scores range from 0 to 30, with lower scores identifying more severe cognitive impairment. The MMSE score can be adjusted for motor and sensory impairments.
Studies have identified the MMSE as being reliable and valid with elderly persons with and without dementia (Busch & Chapin, 2008; Ismail, Rajji, & Shulman, 2010). Test-retest reliability has been established in clinically stable geriatric patients over 28 days ($r = .99$; Folstein et al., 1975) and with geriatric individuals diagnosed with dementia over 24 hours ($r = .90$; Anthony, Le Resche, Niaz, Von Korff, & Folsterin, 1982). Several studies have used a score of 10 or less on the MMSE as indicative of SD (Feldman & Woodward, 2005; Ferris & Yan, 2003; Folstein et al., 1975; Herrmann & Gauthier, 2008). An example can be found in Appendix C.

**Clinical Dementia Rating scale (CDR).** The Clinical Dementia Rating scale (Morris, 1993) is used to rate the severity of AD. The CDR requires that the individual be rated in six domains and that each domain, which accounts for both ADLs and physical function, is rated independent of the others. The six domains are: (1) memory, (2) orientation, (3) judgment and problem solving, (4) community affairs, (5) home and hobbies, and (6) personal care. Each domain is rated on a 5-point scale that ranges from 0 to 3 with higher scores representing greater severity of AD. A score of 0 represents no cognitive impairment, 0.5 represents very mild dementia, 1 represents mild dementia, 2 represents moderate dementia, and 3 represents severe dementia. Additional scores of 4 and 5, which are used in the older version of the CDR, were used in the CCSMA and DPS, representing, profound impairment and a terminal stage of dementia, respectively. Scores from each domain can also be entered into an algorithm (Morris, 1993) which provides the CDR global score which is the score that is widely used for staging of dementia severity (Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993). In
the current project, severe dementia was designated as a global CDR >2.

Multiple studies have demonstrated good interrater reliability among physicians ($r = 0.62$; Rockwood, Strang, MacKnight, Downer, & Morris, 2000) and researchers (87% agreement of ratings, kappa = 0.83; Schafer et al., 2004). Internal consistency has been calculated using Cronbach’s alpha (Coley et al., 2011). In a sample of 667 individuals diagnosed with mild to moderate AD, Coley et al. reported a Cronbach’s alpha of 0.88. Validity has been assessed in multiple ways. One study identified that of the individuals rated as having severe AD by the CDR, 92% were identified as having severe AD through neuropathological diagnosis (Berg, McKeel, Miller, Baty, & Morris 1993). An additional study utilized data collected by the National Alzheimer’s Coordinating Center (NACC) database on 12,462 individuals (O’Bryant et al., 2010). They reported that when the CDR was applied to the whole data set, that it correctly identified the level of dementia for 94% of the database (O’Bryant et al., 2010). O’Bryant et al. reported a Kappa value of 0.91, indicating a high level of rater agreement. Convergent validity has been demonstrated between the CDR and the Alzheimer’s Disease Assessment Scale-cognitive (ADAS-cog; larger score indicates greater impairment), MMSE, and Katz Index of Independence in Activities of Daily Living (Katz ADL; larger score indicates less impairment; Coley et al., 2011). The correlations were 0.650, -0.662, and -0.463, respectively (Coley et al., 2011). An example can be found in Appendix A (as previously referenced).

**Institutionalization.** Information regarding the participant’s residence was obtained from the informant at each visit. The informant was asked to account for the
current place of residence for the participant as well as any other locations the participant may have lived in since the last visit. Institutionalization was defined as living in a skilled nursing facility with no subsequent evidence of discharge. Additionally, movement to assisted living facilities was tracked and will be used as a secondary variable if there are sufficient numbers. Date of institutionalization was recorded.

**Death.** Information regarding the participant’s death was obtained in two ways. One was from daily surveillance of obituaries in the local newspaper. The other was from caregiver report that was obtained when the caregiver was contacted in order to schedule a follow-up visit. Thus vital status was not dependent upon the manner or cause of death. Dates of death were collected from each source.

**Statistical Analyses**

**Exploratory Analysis**

An initial exploratory analysis was completed where descriptive statistics (means, standard deviations for continuous variables; percentages for categorical variables) were calculated for all independent and dependent variables. Descriptive statistics on the survival time for each of the predictors were examined through Kaplan-Meier plots, means and medians. A log rank test was used to show areas of significant differences in survival time in the independent variables, disregarding covariates.

**Cox Regression**

Separate Cox regression models were used to address each research question for the outcomes of severe dementia, institutionalization and death. A key component of the
data being analyzed was that the outcome variables were dichotomous and indicated whether or not an event occurred. For example, the outcome variable for severe dementia has two conditions; severe dementia or not. Being classified as reaching severe dementia illustrates the occurrence of an event. When a participant had not yet been observed reaching the event they were considered “censored.” In addition, the outcomes were mutually exclusive at each observation because criteria for severe dementia had either been met or not.

Along with providing information about how many participants, for each of the predictors experienced a specific event, Cox regression also analyzed survival time, which is the length of time it took for the event to occur (Le, 1997). For survival time to be analyzed, three pieces of information need to be obtained. They are: (a) a starting point or time when the participant began being observed, (b) when the event of interest occurred (if it occurred), and (c) a scale of measurement for the time between the starting point and event (Le, 1997). Survival time is expressed by either a survival function or hazard function (Le, 1997). A survival function, or survival rate, provides information about the probability of a participant surviving until a specific time (Le, 1997). A hazard function, or risk function, provides information about the proportion of participants that have experienced the event in question at a specific time (Le, 1997).

Survival and hazard functions can be calculated for participants in each condition of the predictor variable. Once this information is calculated, the relative risk ratio, which compares hazard ratios for two conditions of the predictor variable, can be calculated. This is a ratio of the hazard function of participants from one of the conditions of the
predictor variable (condition present) compared to the hazard function of participants from the other condition of the predictor variable (condition not present; Le, 1997.

The events which were analyzed and that were mentioned in the research questions are: being classified as severely demented (vs. not severely demented), being institutionalized (vs. being community-dwelling), and death (vs. still living). The predictor variables included: presence or absence of HTN, CHF, and CVA, CCI score, GMHR score, and the number of medical comorbidities (as measured by the number of prescription medications). The starting point for observation was from the year of the first examination identifying the person with dementia.

Cox-regression models can also account for competing risk between different events. In this study, the occurrence of death represented a competing risk in the models that looked at the events of severe dementia and institutionalization. This is because if a participant died, they were no longer able to experience the event of severe dementia or institutionalization. To account for this competing risk, any participant that experiences death was censored at their time of death, in all models that were concerned with the clinical outcomes of severe dementia or institutionalization (Allison, 2010). This essentially allowed the model to identify that this individual could no longer reach the event of severe dementia or institutionalization because they reached the event of death first. It is important to understand that when a participant is censored due to competing risk that it is non-informative and does not provide any information about what may have occurred later with regards to reaching the events of severe dementia or institutionalization (Allison, 2010). However, using right-censoring at death allows each
such participant to contribute information to the modeling of effect of medical
morbidity on the other two outcomes, all the way up to death.

Before Cox regression was utilized, the data were checked to verify that the
assumptions of the procedure were met. The assumptions were: (a) among the different
conditions of a variable, that the base hazard functions are proportional at all observation
points (proportional hazard assumption) and (b) no outliers are present in the data for any
of the variables (Le, 1997. The proportional hazards assumptions was checked through
two methods. One was a crude visual inspection of the survival function. Because some
conditions had small sizes, the survival functions overlapped or displayed irregularities
which complicated visual inspection. A more exact method to evaluate the proportional
hazards assumptions was to include a term in each model that accounted for the
interaction between time and the predictor variable (Allison, 2010). If this term was
significant, it indicated the assumption was not met. In this case, the correction was to
leave the term in the model (Allison, 2010). Outliers were checked for among the
predictor variables by visual inspection of a frequency distribution.

Variables were considered significant if they had a $p$ value that is less than or
equal to a value of 0.008. This value was derived using the common level of significance
of 0.05 and a Bonferroni correction to account for multiple comparisons. There were six
tests completed for each outcome. When entered into the Bonferroni correction equation,
which is the general alpha level of 0.05 divided by the number of tests (six), a resulting
value of 0.008 was obtained (Bonferroni, 1935). This is the value that was used to
determine statistical significance in all of the Cox regression models.
Time-Varying Variables

The primary predictor variables of interest, except CCI, were considered as time-varying. This is the case when the condition a participant is categorized as changes over observations. To address this problem, SPSS was used to develop time-varying variables which utilized data from each observation.
CHAPTER IV

RESULTS

Sample

The initial sample of the DPS consisted of 335 individuals who were diagnosed with AD and excluded anyone with other types of dementia. Basic descriptive information is available in Tables 1 and 2. Not all participants completed the same number of visits during the study. Two hundred and thirty participants had two or more visits with 16, being the maximum number of visits (see Table 3). The numbers of subjects who met the outcomes of severe dementia, institutionalization, and death are discussed below.

Table 1

Descriptive Information for Categorical Demographic Variables

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Number of participants</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>220</td>
<td>65.7</td>
</tr>
<tr>
<td>Genotype (E4 absent)</td>
<td>184</td>
<td>54.9</td>
</tr>
</tbody>
</table>

Table 2

Descriptive Information for Continuous Demographic Variables

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length in study(^a)</td>
<td>4.07</td>
<td>2.75</td>
<td>0.70</td>
<td>13.29</td>
</tr>
<tr>
<td>Onset age of AD(^a)</td>
<td>84.27</td>
<td>6.39</td>
<td>68.00</td>
<td>104.00</td>
</tr>
<tr>
<td>Duration of dementia(^a)</td>
<td>1.63</td>
<td>1.25</td>
<td>0.01</td>
<td>7.21</td>
</tr>
<tr>
<td>Education(^a)</td>
<td>13.24</td>
<td>3.00</td>
<td>3.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Number of visits</td>
<td>5.32</td>
<td>3.46</td>
<td>1.00</td>
<td>16.00</td>
</tr>
</tbody>
</table>

\(^a\) Measured in years.
Table 3

**Study Retention**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Participants</th>
<th>Percent of participants</th>
<th>Mean years from initial visit</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>335</td>
<td>100.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>230</td>
<td>68.66</td>
<td>1.49</td>
<td>0.78</td>
</tr>
<tr>
<td>3</td>
<td>160</td>
<td>47.76</td>
<td>2.60</td>
<td>1.19</td>
</tr>
<tr>
<td>4</td>
<td>135</td>
<td>40.30</td>
<td>3.34</td>
<td>1.27</td>
</tr>
<tr>
<td>5</td>
<td>111</td>
<td>33.13</td>
<td>3.94</td>
<td>1.32</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>26.27</td>
<td>4.67</td>
<td>1.43</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>22.09</td>
<td>5.44</td>
<td>1.53</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>18.21</td>
<td>6.02</td>
<td>1.14</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>14.03</td>
<td>6.56</td>
<td>1.11</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>9.55</td>
<td>7.18</td>
<td>1.54</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>5.97</td>
<td>7.97</td>
<td>1.39</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>3.88</td>
<td>8.84</td>
<td>1.49</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>2.99</td>
<td>9.65</td>
<td>1.59</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>2.09</td>
<td>11.16</td>
<td>0.42</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>1.19</td>
<td>11.73</td>
<td>0.62</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>0.06</td>
<td>12.51</td>
<td>1.10</td>
</tr>
</tbody>
</table>

There were 69 (21.29%) individuals who met criteria for severe dementia, in a mean of 4.25 years (Table 4), over the course of the study. These individuals had a significantly longer duration of dementia at baseline and a significantly lower mean age of dementia onset compared to those who never met criteria for severe dementia. There were no significant differences between the two groups regarding percentage of males and females, presence of APOE E4 allele or mean years of education (Tables 5 and 6).

There were 45 (14.24%) individuals who, at a mean of 3.19 years from baseline, were placed in a nursing home over the course of the study (see Table 4). Those who had been placed in a nursing home had a significantly longer duration of dementia at baseline, younger onset age of dementia, and were more likely to be female (see Tables 5 and 6).
Table 4

**Descriptive Information for Clinical Outcomes**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean years</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe dementia</td>
<td>4.25</td>
<td>2.19</td>
<td>1.08</td>
<td>11.73</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>3.19</td>
<td>2.53</td>
<td>0.06</td>
<td>10.11</td>
</tr>
<tr>
<td>Death</td>
<td>3.79</td>
<td>2.55</td>
<td>0.03</td>
<td>13.46</td>
</tr>
</tbody>
</table>

Table 5

**Chi-Square Tests of Categorical Variables by Clinical Outcomes**

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Severe dementia</th>
<th>Institutionalization</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>(\chi^2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>94</td>
<td>19</td>
<td>2.08</td>
</tr>
<tr>
<td>Female</td>
<td>161</td>
<td>50</td>
<td>1.64</td>
</tr>
<tr>
<td>E4 genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>111</td>
<td>36</td>
<td>1.64</td>
</tr>
<tr>
<td>Absent</td>
<td>144</td>
<td>33</td>
<td>1.26</td>
</tr>
</tbody>
</table>

*Note.* Severe dementia incorporates cognitive and functional measures. Institutionalization incorporates nursing home placement only.

* *p < .05. ** *p < .01. *** *p < .001.

Table 6

**t Test of Continuous Variables (in Years) by Clinical Outcomes**

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Severe dementia</th>
<th>Institutionalization</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>p</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13.26</td>
<td>13.23</td>
<td>0.95</td>
</tr>
<tr>
<td>SD</td>
<td>2.93</td>
<td>3.03</td>
<td>2.99</td>
</tr>
<tr>
<td>Dementia duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.47</td>
<td>1.93</td>
<td>&lt; 0.01***</td>
</tr>
<tr>
<td>SD</td>
<td>1.15</td>
<td>1.26</td>
<td>1.18</td>
</tr>
<tr>
<td>Onset age of dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>85.18</td>
<td>81.94</td>
<td>&lt; 0.01***</td>
</tr>
<tr>
<td>SD</td>
<td>5.81</td>
<td>6.46</td>
<td>6.10</td>
</tr>
</tbody>
</table>

*Note.* Severe dementia incorporates cognitive and functional measures. Institutionalization incorporates nursing home placement only.

* *p < .05. ** *p < .01. *** *p < .001.
There were no significant differences with regards to presence of APOE E4 allele and mean years of education for those who were versus those who were not placed in a nursing home.

There were 287 (85.67%) individuals who died over the course of the study at a mean of 3.79 years from the initial visit (see Table 4). Those who died had a significantly older age of dementia onset. There were no significant differences in the mean years of education or duration of dementia at baseline, presence of APOE E4 allele, or percentage of males and females who had died vs. remained living at the end of the study (see Tables 5 and 6). Each of the predictor health variables and relation to clinical outcomes is discussed by research question in the sections that follow.

**Research Question 1: Overall Health Status (GMHR and CCI) and Association with Clinical Outcomes of Dementia**

**GMHR Exploratory Findings**

At baseline, there were two participants with a GMHR rating of “poor” and 44 with a rating of “excellent,” while 100 and 189 participants had ratings of “fair” and “good,” respectively. Because of the small sample sizes for the categories of “poor” and “excellent,” the “poor” and “fair” categories were collapsed as were “good” and “excellent.” At baseline, 30.4% of participants received ratings of “poor” or “fair.” Although the sample decreased at each follow-up, the percentages of GMHR ratings remained relatively consistent until the 14th visit. Frequencies of GMHR scores at each visit are listed in Table 7. A distribution of baseline frequencies is in Appendix D.
Table 7

**GMHR Score and Number of Medications Across Visits**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Total n</th>
<th>GMHR of poor/fair</th>
<th></th>
<th>GMHR of good/excellent</th>
<th></th>
<th>No. of medications at each visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Participants</td>
<td>Percent</td>
<td>Participants</td>
<td>Percent</td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>335</td>
<td>102</td>
<td>30.4</td>
<td>233</td>
<td>69.6</td>
<td>5.47</td>
</tr>
<tr>
<td>2</td>
<td>230</td>
<td>42</td>
<td>18.3</td>
<td>188</td>
<td>81.7</td>
<td>7.63</td>
</tr>
<tr>
<td>3</td>
<td>160</td>
<td>40</td>
<td>25.0</td>
<td>120</td>
<td>75.0</td>
<td>8.30</td>
</tr>
<tr>
<td>4</td>
<td>135</td>
<td>26</td>
<td>19.3</td>
<td>109</td>
<td>80.7</td>
<td>8.69</td>
</tr>
<tr>
<td>5</td>
<td>111</td>
<td>20</td>
<td>18.0</td>
<td>91</td>
<td>80.0</td>
<td>8.40</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>13</td>
<td>14.8</td>
<td>75</td>
<td>85.2</td>
<td>8.32</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>9</td>
<td>12.2</td>
<td>65</td>
<td>87.8</td>
<td>8.41</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>6</td>
<td>9.8</td>
<td>55</td>
<td>90.2</td>
<td>7.72</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>7</td>
<td>14.9</td>
<td>40</td>
<td>85.1</td>
<td>7.33</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>5</td>
<td>15.6</td>
<td>27</td>
<td>84.4</td>
<td>7.55</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>2</td>
<td>10.0</td>
<td>18</td>
<td>90.0</td>
<td>7.58</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>1</td>
<td>7.7</td>
<td>12</td>
<td>92.3</td>
<td>7.97</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>3</td>
<td>30.0</td>
<td>7</td>
<td>70.0</td>
<td>7.20</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>5</td>
<td>71.4</td>
<td>2</td>
<td>28.6</td>
<td>9.29</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>4</td>
<td>100.0</td>
<td>0</td>
<td>0.0</td>
<td>9.50</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>1</td>
<td>50.0</td>
<td>1</td>
<td>50.0</td>
<td>13.00</td>
</tr>
</tbody>
</table>

Bivariate exploration of baseline health condition, as measured by the GMHR, and survival time to each of the three clinical outcomes of severe dementia, institutionalization and death were examined using Kaplan-Meier (K-M) plots. Having a GMHR score of “fair” or “poor,” was associated with shorter survival time to death. See Appendix E for K-M plots.

**GMHR Cox Regression**

To check the proportional hazards assumption for each of the three outcomes (severe dementia, nursing home placement and death), Log Minus Log (LML) plots were
examined for divergence in the hazard for each outcome (see Appendix F). Crude inspection of the plots (when there was separation) suggested that the proportional hazard assumption was met. The assumption was also checked by incorporating a variable that represented an interaction between time and GMHR into the final model. This term, which was nonsignificant and excluded from the final model, provided support that the proportional hazard assumption was met (Allison, 2010).

GMHR score was entered into a Cox Regression as a time-varying variable for each of the outcomes (severe dementia, nursing home placement and death). With severe dementia as the outcome variable, 324 individuals were included; 11 were excluded as they met criteria for severe dementia at baseline and an additional 114 individuals were excluded because they were censored before the earliest occurrence of severe dementia in the sample. Of the 210 individuals included in the final model, 69 (32.86%) met criteria for severe dementia and 141 did not over the course of the study. GMHR score was significantly associated with occurrence of severe dementia. Individuals with a GMHR score of “fair or poor” had a hazard of reaching severe dementia that was 59.2% greater than those who had a GMHR score of “good or excellent” (see Table 8). This association remained significant after correction for multiple comparisons. The covariate of onset age was also significantly associated with severe dementia at the conventional level of $p < .05$. For every 1-year increase in onset age, there was a 4.6% decrease in occurrence of severe dementia. However, this result was not significant with the more stringent $p$ value correction for multiple comparisons.

With nursing home placement as the outcome variable, 316 individuals were
### Cox Regression for the General Medical Health Rating and Clinical Outcomes

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia 95% C.I.</th>
<th>Institutionalization 95% C.I.</th>
<th>Death 95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR Lower Upper p</td>
<td>HR Lower Upper p</td>
<td>HR Lower Upper p</td>
</tr>
<tr>
<td>GMHR</td>
<td>1.592 1.205 2.103 0.001</td>
<td>1.213 0.834 1.765 0.313</td>
<td>1.433 1.257 1.633 &lt;.001</td>
</tr>
<tr>
<td>Onset age</td>
<td>0.954 0.912 0.997 0.038</td>
<td>1.005 0.954 1.059 0.839</td>
<td>1.093 1.069 1.118 &lt;.001</td>
</tr>
<tr>
<td>Duration</td>
<td>1.138 0.953 1.359 0.154</td>
<td>1.212 0.955 1.537 0.114</td>
<td>1.096 0.990 1.213 0.077</td>
</tr>
<tr>
<td>Education</td>
<td>0.909 0.825 1.003 0.057</td>
<td>0.827 0.723 0.945 0.005</td>
<td>1.002 0.962 1.043 0.931</td>
</tr>
<tr>
<td>Gender</td>
<td>0.713 0.406 1.251 0.238</td>
<td>0.361 0.158 0.823 0.015</td>
<td>1.309 1.013 1.691 0.040</td>
</tr>
<tr>
<td>APOE</td>
<td>0.817 0.492 1.358 0.436</td>
<td>0.607 0.321 1.147 0.124</td>
<td>0.937 0.733 1.196 0.601</td>
</tr>
</tbody>
</table>

*Note: Reference groups are: GMHR – “poor” or “fair,” Gender – male, APOE - present.*

included in the model. Nineteen individuals were excluded because of nursing home placement prior to the baseline visit and an additional 96 individuals were excluded because they were censored before the time of first nursing home placement in the sample. Of the 220 included in the final model, 45 (20.45%) were placed in a nursing home and 175 were not. GMHR was not significantly associated with nursing home placement (HR = 1.213; p = 0.313). Of the significant covariates, males had a hazard that was 63.95 lower than females and education was associated with a lower hazard. Thus, for every one-unit increase in education, the hazard of being placed in a nursing home decreased by 17.3% (see Table 8). Education remained significant after correction for multiple comparisons while gender did not.

With mortality as the outcome, seven of the 335 individuals were excluded because they were censored prior to the first occurrence of death in the sample. The final model included 328 individuals, of which, 287 (87.50%) died during follow-up visits and
41 lived past their last visit. GMHR significantly predicted mortality before and after correction for multiple comparisons. For those with a GMHR score of “fair or poor,” their hazard of dying was 43.3% greater than those with a GMHR score of “good or excellent.” Age of dementia onset was also significantly associated with death such that with each additional year of age, a person’s hazard increased by 9.3%. Also, being male was associated with a 30.9% increase in the occurrence of death. Onset age remained significant after correction for multiple comparisons while gender did not (see Table 8).

**CCI Exploratory Findings**

For the CCI, only baseline scores were available as information on the majority of health conditions were obtained at the diagnosis visit only. The overall CCI score at baseline ranged from 0 to 5 out of a maximum possible of 24 points. Due to the small numbers of persons with scores of above 2, the CCI was trichotomized into those with scores of zero, 1, or 2 or greater. Table 9 shows the frequencies of the CCI scores and each of the medical conditions that contributed to the total score. A distribution of raw CCI score is shown in Appendix D.

Bivariate exploration of *baseline* health condition, as measured by the CCI, and survival time to each of the three clinical outcomes of severe dementia, institutionalization, and death were examined using Kaplan-Meier (K-M) plots (see Appendix G). There were no differences in survival time between scores of 0, 1, or 2+.

**CCI Cox Regression**

For each of the clinical outcomes, the assumption of proportional hazards was
Table 9

*Charlson Comorbidity Index Scores and Distribution of Conditions*

<table>
<thead>
<tr>
<th>Charlson Comorbidity Index</th>
<th>Score</th>
<th>Weighted value</th>
<th>Frequency</th>
<th>% of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCI score at baseline</td>
<td>0</td>
<td>178</td>
<td>53.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>73</td>
<td>21.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>84</td>
<td>25.07</td>
<td></td>
</tr>
</tbody>
</table>

CCI components

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
<th>Weighted value</th>
<th>Frequency</th>
<th>% of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>1</td>
<td>56</td>
<td>16.72</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>1</td>
<td>11</td>
<td>3.28</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>1</td>
<td>3</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>1</td>
<td>13</td>
<td>3.88</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
<td>4</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>1</td>
<td>7</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>1</td>
<td>13</td>
<td>3.88</td>
<td></td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1</td>
<td>2</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Diabetes w/o end organ</td>
<td>1</td>
<td>63</td>
<td>18.81</td>
<td></td>
</tr>
<tr>
<td>Diabetes w/ end organ</td>
<td>2</td>
<td>7</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Paraplegia</td>
<td>2</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>2</td>
<td>4</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Nonmetastic cancer</td>
<td>2</td>
<td>50</td>
<td>14.93</td>
<td></td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>3</td>
<td>1</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>3</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>6</td>
<td>0</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

checked through LML plot (see Appendix H). Crude inspection of the plots (when there was separation) suggested that the proportional hazard assumption was met. This assumption was also checked by including a variable that incorporated the interaction of time and CCI score in the final model for each outcome. This interaction variable was not significant in any of the three models and further indicates that the proportional hazard assumption was met.

With severe dementia as the outcome, the original sample of 335 individuals was
reduced by 11 who met criteria for severe dementia at baseline and an additional 114 were excluded because they were censored prior to the first occurrence of severe dementia in the sample. The CCI ($HR = 1.109; p = 0.507$) was not significantly associated with the hazard of severe dementia (Table 10). The only covariate that was significant was education. Each additional unit of education was associated with a 9.8% decrease in severe dementia. This did not remain significant after correction for multiple comparisons.

With nursing home placement as the outcome variable, 19 individuals were excluded from the model because they were placed in a nursing home at baseline and an additional 96 were excluded because they were censored before the first occurrence of placement in a nursing home in the sample, leaving 220 individuals that were included in the model. CCI was not significantly associated with the hazard of nursing home placement ($HR = 1.048; p = 0.812$). Among the covariates, males were associated with a

Table 10

Cox Regression for the Charlson Comorbidity Index and Clinical Outcomes

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia</th>
<th>Institutionalization</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% C.I.</td>
<td>p</td>
</tr>
<tr>
<td>CCI</td>
<td>1.109</td>
<td>0.817</td>
<td>1.503</td>
</tr>
<tr>
<td>Onset age</td>
<td>0.959</td>
<td>0.918</td>
<td>1.003</td>
</tr>
<tr>
<td>Duration</td>
<td>1.152</td>
<td>0.961</td>
<td>1.380</td>
</tr>
<tr>
<td>Education</td>
<td>0.902</td>
<td>0.818</td>
<td>0.993</td>
</tr>
<tr>
<td>Gender</td>
<td>0.732</td>
<td>0.408</td>
<td>1.314</td>
</tr>
<tr>
<td>APOE</td>
<td>0.472</td>
<td>0.727</td>
<td>1.989</td>
</tr>
</tbody>
</table>

Note. Reference groups are: GMHR – “poor” or “fair,” Gender – male, APOE - present.
63.6% lower hazard of nursing home placement than females, and each additional year of education was associated with a 17.3% reduction in hazard of nursing home placement (Table 10). Only education remained significant after correction for multiple comparisons.

With death as the outcome, seven individuals were excluded from the model because they were censored before the first event occurred. As a result, statistical modeling included 328 individuals. CCI was not significantly associated with mortality (HR = 1.009; p = 0.906). There was a significant association with onset age where each increase of one year in onset age was associated with a 9.7% increase in chance of death (Table 10). Additionally, each increase of one year in dementia duration at baseline was associated with a 13.5% increase in chance of death and being male was associated with a 34.6% increase in chance of death. Only onset age remained significant after correction for multiple comparisons.

Pearson Product-Moment Correlations between the GMHR and CCI was significant at baseline ($r = -0.255, p = < .001$). GMHR and CCI were also entered, at the same time, into Cox Regression models. When severe dementia was the outcome, only GMHR was significant ($HR = 1.499, p = 0.005$). When the outcome was institutionalization, education ($HR = 0.884, p = 0.026$), and gender ($HR = 0.356, p = 0.016$) were significant. When the model looked at death, GMHR ($HR = 1.438, p = < .001$), onset age ($HR = 1.094, p = < .001$), and gender ($HR = 1.326, p = 0.036$) were significant.
Research Question 2: Independent Medical Conditions (Hypertension, Cerebral Vascular Accident, Congestive Heart Failure) and Association with Clinical Outcomes of Dementia

HTN Exploratory Findings

An exploratory analysis was conducted on the predictor variable of HTN. At baseline, 45.70% of participants had a history of HTN (see Table 11). This percentage remained relatively consistent until visit 13. A bivariate exploration of HTN at baseline for each of the three clinical outcomes was done using KM plots. Visual inspection shows that the survival time did not differ for any of the three clinical outcomes.

Table 11

*Frequency of Hypertension, Congestive Heart Failure, and Cerebrovascular Accident Across Visits*

<table>
<thead>
<tr>
<th>Visit</th>
<th>Participants</th>
<th>HTN present</th>
<th>CHF present</th>
<th>CVA present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>335</td>
<td>153</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>230</td>
<td>106</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>160</td>
<td>82</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>135</td>
<td>65</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>111</td>
<td>57</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>41</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>36</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>20</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
The plot for the outcome of nursing home placement displayed two lines, representing survival time for a presence and absence of HTN, that were roughly parallel until around 7 years after baseline. At this time the lines crossed. The plots for severe dementia and death were overlapping at multiple points indicating no difference in survival time.

**HTN Cox Regression**

The assumption of proportional hazards was checked through crude visual inspection of LML plots (see Appendix J). Inspection of the plots (when there was separation) suggested that the proportional hazard assumption was met. This assumption was also checked by including a variable that incorporated the interaction of time and HTN in the final model for each clinical outcome. This variable was not significant in any of the three models.

When the outcome was severe dementia, 324 individuals were included in the model. Eleven were removed because they met criteria for severe dementia at baseline visit and one hundred and fourteen individuals were dropped because they were censored before the earliest occurrence of severe dementia. Of the 210 included in the model, 69 (32.86%) met criteria for severe dementia during their follow-up and 141 did not. While HTN (HR = 1.068; \(p = 0.794\)) was not significantly associated with time to severe dementia (Table 12), education was. Each one year increase in education was associated with a 10% decrease in risk of severe dementia. However, this association did not remain significant after correction for multiple comparisons.
Table 12

Cox Regression for Hypertension and Clinical Outcomes

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia (HR)</th>
<th>Institutionalization (HR)</th>
<th>Death (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% C.I.</td>
<td>95% C.I.</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>HTN</td>
<td>1.068 (0.653, 1.747)</td>
<td>1.538 (0.842, 2.813)</td>
<td>1.215 (0.960, 1.537)</td>
</tr>
<tr>
<td>Onset age</td>
<td>0.961 (0.921, 1.004)</td>
<td>1.007 (0.956, 1.061)</td>
<td>1.098 (1.074, 1.122)</td>
</tr>
<tr>
<td>Duration</td>
<td>1.163 (0.974, 1.389)</td>
<td>1.212 (0.960, 1.531)</td>
<td>1.137 (1.028, 1.258)</td>
</tr>
<tr>
<td>Education</td>
<td>0.900 (0.817, 0.991)</td>
<td>0.823 (0.719, 0.942)</td>
<td>0.996 (0.957, 1.037)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.767 (0.437, 1.347)</td>
<td>0.358 (0.157, 0.815)</td>
<td>1.367 (1.057, 1.768)</td>
</tr>
<tr>
<td>APOE</td>
<td>0.836 (0.505, 1.382)</td>
<td>0.593 (0.314, 1.119)</td>
<td>0.945 (0.740, 1.207)</td>
</tr>
</tbody>
</table>

Note: Reference groups are: GMHR – “poor” or “fair,” Gender – male, APOE - present.

A model using nursing home placement as the outcome included 220 individuals after 19 were excluded due to nursing home residency at their baseline visits and 96 more were excluded because they were censored prior to the first occurrence of nursing home placement in the sample. The final model included 220 individuals. Forty-five (20.45%) of these individuals were placed in a nursing home during the follow-up visits and 175 were not. HTN was not significantly associated with time to nursing home placement ($HR = 1.538; p = 162$). Among the covariates, education was significant and the hazard decreased by 17.7% with each one year increase in education. Males had a hazard of nursing home placement that was 63.6% less than female (see Table 12). Education remained significant after correction for multiple comparisons while gender did not.

With death as the outcome, seven were excluded because they were censored prior to the first occurrence of death. Of the 328 individuals, 287 (87.50%) died during the follow-up visits and 41 did not. HTN was not a significant predictor of time to death ($HR = 1.215; p = 0.105$). Onset age of dementia was significant such that with every one
year increase, there was a 9.8% increase in hazard of dying. Duration of dementia was significant such that for every one year increase in duration, there was a 13.5% increase in hazard of dying. Also, males were associated with a 36.7% increase in hazard of dying (Table 12). Only onset age remained significant after correction for multiple comparisons.

**CVA Exploratory Findings**

An exploratory analysis conducted on the predictor variable of CVA identified a small number of participants who had experienced a CVA. At baseline, 3.88% of participants had a history of CVA (see Table 11). Frequency of participants with CVA remained small, across all visits. A bivariate exploration of CVA at baseline for each of the three clinical outcomes was done using KM plots. The survival times did not appear to differ, though the data were limited by the low number of individuals with CVA (see Appendix K). Contingency tables were created to identify any trends in clinical outcomes when individuals were grouped by having prevalent CVA (occurred prior to the study), incident CVA (occurred during the study), or no CVA. There were no significant trends between groups (see Appendix L). CVA was also treated as a dichotomous variable (“ever” or “never”). When this dichotomous variable was included in Cox regression models, there were no significant associations with any of the clinical outcomes.

**CVA Cox Regression**

The assumption of proportional hazards was checked through crude visual inspection of LML plots (see Appendix M). Because of the small number of persons with
CVA, there was overlap in the survival times. The proportional hazards assumption was also checked by including a variable that incorporated the interaction of time and CVA in the final model for each clinical outcome. This variable was not significant in any of the three models.

A Cox regression model was run despite the low number of CVAs. When severe dementia was an outcome, 11 individuals were excluded because they met criteria for severe dementia at baseline and 114 more were dropped because they were censored before the first occurrence of severe dementia. In the final model of 210 individuals, 69 (32.86%) individuals met criteria for severe dementia while 141 did not. A history of CVA was not associated with severe dementia ($HR = 1.000; p = 0.273$; Table 13). The only covariate that was associated with severe dementia was education. Each one year increase in education was associated with a 9.6% decrease in hazard of severe dementia. This did not remain significant after correction for multiple comparisons.

With the outcome of nursing home placement, 316 individuals were available for analyses. Nineteen individuals were excluded because they resided in a nursing home at the baseline visit and 96 more were excluded because they were censored prior to the first occurrence of nursing home placement in the sample. Of the 220 individuals included in the final model, 45 (20.45%) were placed in a nursing home during the follow-up visits and 175 were not. A history of CVA was not significantly associated with severe dementia ($HR = 0.999; p = 0.234$). However, males had a 63.3% lower hazard of nursing home placement than females and each additional one year of education was associated with an 18.1% lower hazard of nursing home placement (Table 13). Education was the
Table 13

*Cox Regression for Cerebrovascular Accident and Clinical Outcomes*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Severe dementia</th>
<th>Institutionalization</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% C.I.</td>
<td>HR</td>
</tr>
<tr>
<td>CVA</td>
<td>1.000</td>
<td>1.000 1.001</td>
<td>0.273</td>
</tr>
<tr>
<td>Onset age</td>
<td>0.959</td>
<td>0.918 1.002</td>
<td>0.062</td>
</tr>
<tr>
<td>Duration</td>
<td>1.168</td>
<td>0.977 1.396</td>
<td>0.089</td>
</tr>
<tr>
<td>Education</td>
<td>0.904</td>
<td>0.822 0.995</td>
<td>0.038</td>
</tr>
<tr>
<td>Gender</td>
<td>0.773</td>
<td>0.442 1.349</td>
<td>0.364</td>
</tr>
<tr>
<td>APOE</td>
<td>0.794</td>
<td>0.473 1.331</td>
<td>0.381</td>
</tr>
</tbody>
</table>

*Note.* Reference groups are: GMHR – “poor” or “fair,” Gender – male, APOE - present.

only association that remained significant after correction for multiple comparisons.

With death as the outcome of interest, 328 individuals were included as seven were censored prior to the first person dying. There were 287 (87.50%) individuals who died during the study period and 41 who did not. CVA was significantly associated with death as was onset age of dementia (Table 13). A positive history for CVA was associated with a 0.1% increase in hazard of dying. This remained significant after correction for multiple comparisons. For each additional one year increase in onset age the hazard increase by 9.3%. Males had a 38.5% increase in hazard of dying and for every one year increase in dementia duration there was an 11.7% increase in hazard. Onset age remained significant after correction for multiple comparisons while dementia duration and gender did not.

**CHF Exploratory Findings**

An exploratory analysis conducted on the predictor variable of CHF identified a small number of participants who endorsed CHF. At baseline, 3.28% of participants had a history of CHF (see Table 11). A bivariate exploration of CHF at baseline for each of the
three clinical outcomes was done using KM plots. The survival times did not appear to differ, though the data were limited by the small number of individuals with CHF (Appendix N). Contingency tables were also created for the CHF variable. As with CVA, there were no significant associations between groups (see Appendix L). The variable of CHF was also dichotomized as “ever” or “never” and then included in Cox regression models. In these models, severe dementia and institutionalization were not significantly associated with CHF while Death was ($HR = 2.416; p = 0.003$).

**CHF Cox Regression**

Similar to CVA, the LML (see Appendix O) plots for CHF were examined, but again, there were a small number of cases, and there were overlapping plots. The interaction term was not significant in any of the three models. When predicting severe dementia as the outcome, 210 individuals were in the final model. This is after 11 were excluded because they met criteria for severe dementia at baseline and 114 were dropped because they were censored before the first occurrence of severe dementia. Of the 210 individuals in the final model, 69 (32.86%) met criteria for severe dementia during follow-up and 141 did not. The presence of CHF was associated with a 0.1% increase in hazard of severe dementia (see Table 14). This remained significant after correction for multiple comparisons. The covariates of onset age and education were significant also. For every one year increase in onset age, there was a 4.8% decrease in the hazard of meeting criteria for severe dementia. For every one year increase in education, there was a 10.5% decrease in the hazard of severe dementia. Neither of these associations remained significant after correction for multiple comparisons.
Table 14

*Cox Regression for Congestive Heart Failure and Clinical Outcomes*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia (95% C.I.)</th>
<th>Institutionalization (95% C.I.)</th>
<th>Death (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>CHF</td>
<td>1.001</td>
<td>1.000</td>
<td>1.002</td>
</tr>
<tr>
<td>Onset age</td>
<td>0.952</td>
<td>0.910</td>
<td>0.996</td>
</tr>
<tr>
<td>Duration</td>
<td>1.151</td>
<td>0.963</td>
<td>1.377</td>
</tr>
<tr>
<td>Education</td>
<td>0.895</td>
<td>0.813</td>
<td>0.984</td>
</tr>
<tr>
<td>Gender</td>
<td>0.670</td>
<td>0.381</td>
<td>1.177</td>
</tr>
<tr>
<td>APOE</td>
<td>0.773</td>
<td>0.467</td>
<td>1.281</td>
</tr>
</tbody>
</table>

*Note.* Reference groups are: GMHR – “poor” or “fair,” Gender – male, APOE - present.

With nursing home placement as the outcome, 19 were excluded because they resided in a nursing home at the baseline visit and 96 others were dropped because they were censored prior to the first occurrence of nursing home placement in the sample. Of the 220 individuals in the model, 45 (20.45%) were placed in a nursing home during the follow-up visits and 175 were not. CHF was not significantly associated with nursing home placement ($HR = 1.000; p = 0.494$). Among the covariates, the hazard of nursing home placement was 64.0% lower for males than for females. For every 1 year increase in education, there was a 14.8% lower hazard of nursing home placement (Table 14). After multiple comparisons, education remained significant, whereas Gender did not.

With death as the outcome variable, 328 individuals were included in the model after seven were excluded because they were censored before the first occurrence of death in the sample. Two hundred eighty-seven (87.50%) individuals died during the follow-up visits and 41 did not. CHF was not significantly associated with death ($HR = 1.000; p = 0.123$). Onset age of dementia was associated with death such that for every
increase of one year, there was a 9.7% increase in chance of death. For every 1 year
increase in duration of dementia there was a 13.3% increase in chance of death. Also,
males had a 32.1% increase in chance of dying (Table 14). Only the association with
onset age remained significant after correction for multiple comparisons.

Pearson product-moment correlations between each of the three medical
conditions were calculated. At baseline, HTN was significantly correlated with CHF ($r =
0.134, p = 0.014$) and CHF was significantly correlated with CVA ($r = 0.419, p = <.001$).
All three predictors were entered into Cox regression models, along with other covariates.
When severe dementia was the outcome, only CVA was significant ($HR = 1.004, p =
<.001$). When the outcome was institutionalization, CVA ($HR = 0.003, p = 0.016$),
education ($HR = 0.882, p = 0.028$), and gender ($HR = 0.380, p = 0.022$) were significant.
When the model looked at death, HTN ($HR = 1.307, p = 0.029$), CVA ($HR = 1.001, p =
<.001$), onset age ($HR = 1.094, p = <.001$), dementia duration ($HR = 1.117, p = 0.037$),
and gender ($HR = 1.422, p = 0.009$) were significant.

**Research Question 3: Number of Prescription Medications and
Association with Clinical Outcomes of Dementia**

An exploratory analysis was conducted on the number of medications at baseline.
Table 7 showed the mean ($SD$) number of prescription medications at each follow-up
visit and Appendix D shows the distribution. At baseline, the mean number of
prescription medications being taken was 5.47, with a standard deviation of 3.42 and a
range of 0 to 18). The mean number of medications increased across all visits. An
exploratory bivariate analysis at baseline was done for each of the clinical outcomes. Visual inspection shows some deviations in lines suggesting the differences in survival rates may exist (see Appendix P)

**Prescription Medication Cox Regression**

A LML plot was examined for divergence in the hazard for each outcome. Crude inspection of the plots suggested that the proportional hazard assumption was met (see Appendix Q). This assumption was also tested by including a variable in the final model that represented an interaction between the predictor and time. This was not significant and provides evidence that the assumption was met.

This predictor was entered into a Cox regression, as a time-varying variable, for each of the clinical outcomes (severe dementia, nursing home placement and death). With severe dementia as the outcome variable, 324 individuals were included; 11 were excluded as they met criteria for severe dementia at baseline and an additional 114 individuals were dropped because they were censored before the earliest occurrence of severe dementia. Of the 210 individuals included in the final model, 69 (32.86%) met criteria for severe dementia while 141 did not. Number of prescription medications was significantly associated with occurrence of severe dementia. For each additional prescription medication, there was a 10.4 greater hazard of meeting criteria for severe dementia (Table 15). Education was also significant. For every increase of 1 year of education, there was a 10% decrease in hazard of meeting criteria for severe dementia. Number of medications remained significant after a correction for multiple comparisons while education did not.
### Cox Regression for the Number of Prescriptions and Clinical Outcomes

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia</th>
<th></th>
<th>Institutionalization</th>
<th></th>
<th>Death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% C.I.</td>
<td>95% C.I.</td>
<td>95% C.I.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of medications</td>
<td>1.104 1.052 1.159 0.000</td>
<td>1.089 1.017 1.166 0.014</td>
<td>1.031 1.003 1.059 0.028</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset age</td>
<td>0.960 0.918 1.004 0.076</td>
<td>1.015 0.963 1.071 0.578</td>
<td>1.100 1.076 1.125 &lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>1.080 0.905 1.288 0.395</td>
<td>1.184 0.939 1.493 0.153</td>
<td>1.126 1.018 1.246 0.021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.900 0.814 0.944 0.038</td>
<td>0.830 0.725 0.949 0.007</td>
<td>0.996 0.956 1.037 0.846</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.717 0.407 1.261 0.248</td>
<td>0.354 0.156 .806 0.013</td>
<td>1.354 1.047 1.752 0.021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE</td>
<td>0.828 0.500 1.369 0.461</td>
<td>0.549 0.289 1.041 0.066</td>
<td>0.951 0.745 1.215 0.688</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Reference groups are: GMHR – “poor” or “fair,” Gender – male, APOE - present.

With nursing home placement as the outcome variable, 316 individuals were included in the model. Nineteen individuals were excluded because of nursing home placement prior to the baseline visit and an additional 96 individuals were excluded because they were censored prior to the first nursing home placement in the sample. Of the 220 included in the final model, 45 (20.45%) were placed in a nursing home and 175 were not. Number of medications was significantly associated with nursing home placement such that with every increase of one medication, there was an 8.9% increase in chance of nursing home placement. Significant covariates were gender and education. Males had a hazard that was 64.6% lower than females. For every increase of 1 year in education, the hazard of being placed in a nursing home decreased by 17.0% (see Table 15). Education remained significant after correction for multiple comparisons while gender did not.

Of the 335 individuals included in the model for mortality, seven were dropped because they were censored prior to the first occurrence of death in the sample. The final
model included 328 individuals, of which 287 (87.50%) died during follow-up visits and 41 did not. The number of prescription medications was a significant predictor of mortality. For each additional prescription medication, there was a 3.1% increase in the hazard of death. The age of onset also predicted mortality in that for every 1 year increase in age, there was a 10.0% increase in the hazard. Duration of dementia at baseline was also a significant predictor, such that, with an increase of 1 year, the hazard for death increased by 12.6%. In addition, males had a 35.4% increase in the hazard for mortality compared to females (Table 15). Of these associations, only onset age remained significant after correction for multiple comparisons.

**Supplementary Analysis**

Additional analyses were conducted using different operational definitions for severe dementia and institutionalization. Severe dementia was originally defined as having a score of 3 or greater on the CDR or a score of 10 or less on the MMSE. This supplementary analysis was conducted to identify discrepancies when using a definition of severe dementia that was based on either cognitive (MMSE) or functional (CDR) ability, instead of both (see Table 16). Criteria for severe dementia, which was cognitively based, was considered met when a participant’s MMSE score was 10 or less. Using this outcome, there were no differences in results when compared to results that defined severe dementia using both the MMSE and CDR. When defining severe dementia based only on the CDR, one result differed from the original models. HTN became a significant predictor of severe dementia, with a 47.8% decrease in hazard ($p = 0.033$, HR = 0.522; 0.288-0.948 95% CI). The original severe dementia definition was
Table 16

*Frequencies for Supplementary Analyses Compared to Original Analyses*

<table>
<thead>
<tr>
<th>Various operational definitions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe dementia (MMSE and CDR)</td>
<td>69</td>
</tr>
<tr>
<td>Severe dementia (CDR)</td>
<td>64</td>
</tr>
<tr>
<td>Severe dementia (MMSE)</td>
<td>56</td>
</tr>
<tr>
<td>Nursing home placement</td>
<td>45</td>
</tr>
<tr>
<td>Nursing home or assisted living placement</td>
<td>92</td>
</tr>
</tbody>
</table>

not significantly associated with HTN ($p = 0.794$). This change reflects a decrease in the hazard of functional impairment and is in line with past research that reported antihypertensive use is associated with slower functional decline.

Institutionalization was also measured in a separate way (see Table 16). It was originally operationally defined as the occurrence of being placed in a nursing home. In supplementary analyses, I defined “institutionalization as *either* residing in a nursing home or assisted living facility.” There were no changes with regards to which associations were significant when using this definition.

Additionally, there were no changes in significant associations between covariates and clinical outcomes when the definition of severe dementia was changed to using either the MMSE or the CDR, but not both. When the definition of institutionalization was changed to assisted living placement or nursing home placement, there were differences. When nursing home placement was used, onset age was either not significant or it was approaching significance, in all of the models. When assisted living or nursing home placement was used, onset age became significant in all models that looked at
institutionalization. The $p$ values for all models were < .001; the hazard ratios were as follows: GMHR = 1.096, CCI = 1.090, HTN = 1.110, CVA = 1.098, CHF = 1.097 and number of prescriptions = 1.097. All of these reflect that as onset age increases, there is a greater hazard of institutionalization. A summary of the models is provided in Table 17.

Table 17

Summary of Predictor by Outcome Variables

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia</th>
<th>Institutionalization</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>$p$</td>
<td>HR</td>
</tr>
<tr>
<td>GMHR</td>
<td>1.592</td>
<td>0.001</td>
<td>1.213</td>
</tr>
<tr>
<td>CCI (Baseline)</td>
<td>1.109</td>
<td>0.507</td>
<td>1.048</td>
</tr>
<tr>
<td>Number of prescriptions</td>
<td>1.104</td>
<td>0.000</td>
<td>1.089</td>
</tr>
<tr>
<td>HTN</td>
<td>1.068</td>
<td>0.794</td>
<td>1.538</td>
</tr>
<tr>
<td>CVA</td>
<td>1.000</td>
<td>0.273</td>
<td>0.999</td>
</tr>
<tr>
<td>CHF</td>
<td>1.001</td>
<td>0.001</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Note. Covariables in models were onset age, dementia duration, education, gender, APOE.
CHAPTER V
DISCUSSION

This project examined the association of health status and clinical milestones of dementia, specifically severe dementia, institutionalization, and death, in a population-based sample. An overall health rating of fair or poor health increased risk for progression to severe dementia and death by 59.2% and 43.3%, respectively. Having a history of stroke increased risk for death by 0.1% and a history of congestive heart failure increased risk of severe dementia by 0.1%. For each additional prescription medication, there was an increased risk for severe dementia by 10.4%, nursing home placement by 8.9% and death by 3.1%.

The results with overall health and risk for severe dementia and death are in line those reported by Leoutsakos et al. (2012) who also reported that among individuals with AD, that those with worse health, as measured by the GMHR, declined more rapidly in cognitive and functional domains. Worse health, as measured by the GMHR, has also been associated with both an increase in functional dependence and death (Lyketsos, 2005; Samus et al., 2009) in those with AD. It is possible that as suggested by Lyketsos and Leoutsakos et al., that since the GMHR takes multiple factors into account (presence of medical conditions, stability of medical conditions, physical appearance as an indicator of frailty, and number of medications for medical conditions) that it is a robust predictor of progression to severe dementia and mortality. Overall health assessed by the GMHR was not significantly associated with nursing home placement. It is believed that the GMHR is a useful tool because it accounts for medical instability that may be present in
some individuals and not accounted for by other constructs.

The only measure of overall health associated with nursing home placement was number of prescription medications. It is believed this is a broad measure of medical comorbidity. Number of prescriptions was significantly associated with all three clinical outcomes. Previous research looking at the number of medical conditions and number of all types of prescription medications associated with clinical outcomes in AD is sparse. Findings reported by Boksay et al. (2005) are consistent with the findings from this study in that they reported that individuals progress to severe dementia more rapidly when they endorse a greater number of medical conditions. This result is also in line with that of J. Li et al. (2010) who reported more medical conditions being associated with a faster rate of cognitive and functional impairment and Suh et al. (2005) who reported that more medical conditions were associated with a more rapid occurrence of death. Interestingly, Leoutsakos et al. (2012) found in the same population sample as the current study, that number of medical conditions and number of medications was not predictive of rate of decline to severe dementia or death. In her analysis, number of medical conditions was identified by a target list of conditions that included asthma, emphysema, bronchitis, pneumonia, TIA, CVA, MI, Parkinson’s disease, epilepsy, hypertension, hypercholesteremia, diabetes, coronary artery bypass grafting (CABG), angioplasty, headache, chronic pain, head injury, brain injury, arthritis, ulcers, constipation, thyroid conditions, cancer, and angina. Number of prescription medications were identified through a simple count and included any type of prescription.

The CCI was not significantly associated with any of the clinical outcomes. Many
of the studies that utilized the CCI and reported significant associations between CCI score and mortality sampled individuals that were hospitalized (Goldstetin et al., 2004; Lu et al., 2011; Rudolph et al., 2010; Slaughter & Hayduk, 2012). One study of persons with dementia found that the CCI was associated functional disability as measured by inability to walk and feed one’s self and suggested the CCI as being a more robust instrument when medical comorbidity was more severe (Slaughter & Hayduk, 2012). However, the sample for Slaughter and Hayduk, included individuals with AD, vascular dementia, mixed dementia, and unspecified dementia. Additionally, their whole sample consisted of individuals who were in nursing homes and only included those who were in the “middle” stages of their dementias as determined by score on the Global Deterioration Scale and those who were “at risk for losing ADLs” (Slaughter & Hayduk, 2012). Nuttall et al. (2006) reported the CCI predicted mortality; however, this was in a sample of individuals who did not have AD and had recently been hospitalized for cancer. The CCI is also significantly associated with mortality in a sample of individuals who did not have AD and followed post discharge from a hospitalization due to stroke (Goldstetin et al., 2004) and data from a database of veterans who were hospitalized for any reasons (Lu et al., 2011). It is possible that the CCI did not predict clinical outcomes in this study because of the relatively better health (nonhospitalized or institutionalized) sample. Another possible reason the CCI was not associated with any of the clinical outcomes in this study was because of the sample was restricted to AD type dementia only. Studies that have reported significant associations between the CCI and medical costs, hospitalization, and disability have included samples that included vascular
dementia, mixed dementia, unspecified dementia (Rudolph et al., 2010; Slaughter & Hayduk, 2012), senility, drug induced dementia, senile degeneration, and AD (Hill et al., 2002). Thus, use of individuals who were not currently or recently hospitalized as well as only those with possible or probable AD may explain the null findings with the CCI. Additionally, it is noteworthy that conditions on which the CCI is based were relatively uncommon in this AD sample. Low CCI scores in AD is consistent with another study of medical comorbidities in AD (Gill et al., 2011). In general, the CCI is likely too specific of a measure as it focuses on more severe medical conditions associated with death.

With respect to individual health conditions, hypertension was not significantly associated with any of the three clinical outcomes. Previous research reports contradictory findings in that hypertension, in AD, has been associated with faster rates of cognitive and functional decline (J. Li et al., 2010; Mielke et al., 2007) the absence of significant associations with cognitive and functional decline (Bhargava et al., 2006; Musicco et al., 2009) and a decreased rate of functional decline (Mielke et al., 2007; Rosenberg et al., 2008). Similarly, contradictory findings have been reported for the outcome of death as well (Helzner et al., 2008; Rountree et al., 2012). It is likely that the discrepancy in findings is related to two issues. One is how hypertension is defined. Mielke et al. reported their association was with individuals who had systolic hypertension greater than or equal to 160 while Bhargava et al. and Musicco et al. identified any type of hypertension. The other issue is that Mielke et al. and Rosenberg et al. found that use of antihypertensive medication, which is used to treat hypertension, to be protective against functional decline. Other studies did not account for this and this
may be another factor in discrepant result. Notably, in the current analyses, hypertension was defined based on health inventory and use of anti-hypertensive medication was not parsed out.

Models run to analyze associations between CVA and the three clinical outcomes and CHF and the three clinical outcomes had few participants who experienced either CVA or CHF (3.25% and 3.88% at baseline, respectively). It is possible that since these are serious medical conditions, individuals who may have been in this study passed away before they showed signs of, or developed, dementia. Neither of these medical conditions was a robust predictor of progression towards clinical outcomes. The only significant association with CVA was an increase in hazard of death and CHF was associated with an increase in hazard of severe dementia, though both effects were quite small. Past research has been controversial in that CVA has been reported to be associated with death among those in a study that looked at prevalent AD (Singer, 2005) and it has been reported to have no association with death when utilizing incident cases of AD (Helzner et al., 2008). The main limitation related to CHF is that it has often been included in vascular variables that are comprised of multiple conditions. However, these variables have been shown to be associated with rate of progression of cognitive decline (Helzner et al., 2008). Again, the current findings need to be interpreted with caution due to the low number of participants with CHF and CVA. Additionally, the contingency tables completed during exploratory work indicate that neither CHF nor CVA are significantly associated with any of the clinical outcomes. This may suggest that the significant findings involving CVA and CHF are a result of the small sample size.
With respect to other factors examined as predictors (covariates) in this project, gender, duration of dementia, onset age of dementia, and education were associated with various clinical outcomes. APOE was the only predictor that was not associated with any of the clinical outcomes.

Gender was significantly associated with the outcomes of institutionalization and death in Cox regression models for all of the predictors. The associations were consistent in that males always had a smaller hazard of being placed in a nursing home and a greater hazard of dying. This finding is consistent with previous studies that identified females as being more likely to be placed in a nursing home (Luppa et al., 2010). From the meta-analysis of 11 studies, Luppa et al. identified that admission rates of institutionalization were from 40% to 60% greater for women than men. They also noted that some of this variability was dependent upon how institutionalization was defined (Luppa et al., 2010). The authors went on to report that the rate of nursing home placement is greater for females because they have a longer life expectancy and tend to marry men who are slightly older in age, both of which contribute to females being more likely to be widowed and needing care (Luppa et al., 2010). They also suggested that widowed males remarry at a greater rate than widowed females, which results in males having a care taker more often (Luppa et al., 2010).

Duration of dementia was also significance in models where CCI, HTN, CVA, CHF, and number of medications were predictors and the outcome death. As the duration of dementia at baseline increased, the time to death decreased. However, there associations were not significant after the Bonferroni correction was applied. This finding
makes intuitive sense given the likelihood that such persons had more severe dementia symptoms at baseline and thus are more likely to reach the clinical endpoints after less time in the study compared to those who had shorter dementia duration prior to being in the study.

Onset age was a significant predictor of hazard to severe dementia in Cox regression models for GMHR and CHF. Specifically, younger onset age was associated with a greater hazard to severe dementia. Onset age was also a significant predictor of death in all Cox regression models such that older onset age was associated with greater hazard to death. These findings are consistent with current literature as reported by Park et al. (2015), who found that among a hospital based population of individuals with AD, that those who were younger than 65 had faster decline in cognitive ability, as measured by the MMSE. This association, where individuals who have a younger onset age of dementia have a faster cognitive decline, was also found among a sample of individuals who were diagnosed with probable AD and were being seen in a clinical setting (Rasmussen et al., 1996) and a longitudinal population study of individuals with AD (Tschanz et al., 2011). The association with death is also consistent with the literature reviewed previously where survival from dementia diagnosis, which is intuitively linearly associated with dementia onset, decreases as the age of dementia onset increases (Brookmeyer, 2002). Brookmeyer et al. suggested that death occur in fewer years in those who had an older onset age because there are other medical conditions (that increase with age) that also contribute to the likelihood of death. In addition, there are multiple studies that have identified that older chronological age of individuals with
dementia is associated with a more rapid time to death (Gambassi et al., 1999; Paradise et al., 2009; Xie et al., 2008; Zanetti et al., 2009). These studies have reached similar conclusions as Brookmeyer et al. and suggest that medical comorbidities likely play a significant role in survival time to death.

Education was associated with outcome of institutionalization, and consistently remained significant after Bonferroni corrections. These trends were such that as education increased, there was a decrease in rate of progression to nursing home placement. This is consistent with past research (Giley et al., 2004; Smith et al., 2000). The lack of an association with education and severe dementia is also consistent with one study (Nourhashemi et al., 2008).

The presence of one or more APOE E4 alleles was not significantly associated with any of the examined clinical outcomes. This is not completely unexpected because the literature regarding the influence of the APOE E4 allele is quite heterogeneous with regards to its findings (Alessandro, Kathryn, & Ames, 2013). Alessandro et al. completed a review of current literature and concluded that the covariate of APOE either has no influence on rate of progression to clinical endpoint, or, it has a very small effect.

The identification of associations of health status in clinical milestones is important because it suggests the role that medical conditions play in progression of AD. The information gained from the current project will hopefully influence individuals, especially those with an increased risk for AD, to address current medical conditions if not take preventative action against future conditions. This may be done through modification to certain lifestyle factors such as, but not limited to, change in diet, sleep,
exercise, substance use, and routine healthcare.

While this study adds to the limited body of empirical evidence concerned with the progression to severe dementia, institutionalization, and death after the onset of AD, further study is warranted. Specifically, a future direction to study in another sample would be the question of the role of CHF and CVA in AD as very few participants in the current sample suffered from either condition. Additionally, it may be insightful to account for the occurrence of a TIA or a CVA in one variable, instead of only accounting for CVA. While TIA supposedly is not associated with actual brain damage, it is an indicator of the health of the brain vascular system and reduced blood circulation may predict outcomes in AD. This study may also guide other healthcare professionals in the selection of measures to use with an AD population. Specifically, the GMHR and number of prescriptions may be more informative to healthcare professional than the CCI for the outcomes studied. Also, the CCI, as it was used in this study, may not be the best measure for research conducted with an AD population. In place of the CCI, researchers may consider investigating if any other well-established measures of medical comorbidity are associated with the time to severe dementia, institutionalization, or mortality. In predicting institutionalization, it is important to consider psychosocial variables of the person with dementia but also that of the caregivers. In this respect, information related to marital status, financial resources, and caregiver information may be stronger predictors of institutionalization and these conditions should also be considered for this outcome to improve predictive ability.

A strength of this study is that incident cases were used. This means that the
persons with dementia were relatively early in their course as they were diagnosed close to the onset of dementia. As the majority of cases (85.67%) had died over the study, information on much of the entire course of dementia was available on these individuals. Additionally, predementia health information was available and gathered from participants prior to the onset of dementia. This allowed for collection of accurate historical information that may have otherwise not been available from a caregiver. This sample was population based. Because it was not a clinical sample, which might be comprised of individuals seeking medical services for AD or some other condition, it is possible that fewer individuals were excluded and that the sample better represents the “average” individual with AD. The richness of the data collected allowed me to examine the relationship of comorbidities and clinical dementia outcomes using multiple methods and longitudinally across visits. This is more representative of an individual’s actual life as opposed to restricting analyses to inclusion of only baseline data. A related strength was the ability to examine separately, HTN, CVA, and CHF instead of grouped as one vascular or cardiovascular variable. Other studies have grouped vascular related variables together. While these conditions are similar with regards to being associated with the vascular system, there are individual characteristics that, since each condition is evaluated independently, can be studied. One other strength of this study was that severe dementia was captured through operational definitions that considered both cognitive and functional status, and that greater residential care needs were examined for both nursing home and assisted living placement.

This study was not without limitations. There were a small number of individuals
who experienced CVA or CHF. Because of this, results must be interpreted with caution. Another weakness of this study discussed previously was the use of baseline data for scoring the CCI. Additionally, about one third of participants were only seen for one visit. Another weakness is that sometimes caregivers would change during follow-up visits. The implication from this is report on participant health may be inconsistent across caregivers.

In summary, there is still much work that needs to be done to better understand the associations between the outcomes of severe dementia, institutionalization, and death and medical conditions. Also there is need for development of indices that incorporate medical comorbidities and related information in the prediction of the above outcomes. While there is room for more research, there is also a developing literature base that supports the idea that both prevention of medical conditions, and care for existing conditions, may help slow down the progression of AD. This is very important as it may not only provide extra time to those with AD, but more importantly this time may be one of less severe impairments and a higher quality of life. This will remain of invaluable importance until a cure or prevention for AD is discovered.
REFERENCES


endpoint for Alzheimer’s disease trials. Alzheimer’s and Dementia, 6, 602-610. doi: 10.1016/j.jalz.2011.01.005


Journal of the American Medical Association, 278, 1363-1371.


APPENDICES
Appendix A

CDR Staging
# CDR Staging

<table>
<thead>
<tr>
<th>Sub-item scores</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
</table>

Although rules for assigning CDR stages beyond CDR 3 have not been established, the following have been proposed to distinguish additional levels of Impairment in advanced dementia:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Dementia</td>
</tr>
<tr>
<td>0.5</td>
<td>Uncertain or deferred diagnosis</td>
</tr>
<tr>
<td>1</td>
<td>Mild Dementia</td>
</tr>
<tr>
<td>2</td>
<td>Moderate dementia</td>
</tr>
<tr>
<td>3</td>
<td>Severe Dementia</td>
</tr>
<tr>
<td>4</td>
<td>Profound dementia</td>
</tr>
<tr>
<td>5</td>
<td>Terminal dementia</td>
</tr>
<tr>
<td>91</td>
<td>Sensory-Motor Confound</td>
</tr>
</tbody>
</table>

- **Profound (4)**: Speech usually unintelligible or irrelevant, unable to follow simple instructions or comprehend commands. Occasionally recognizes spouse or caregiver. Uses fingers more than utensils, requires much assistance. Frequently incontinent despite assistance or training. Able to walk a few steps with help; usually chair-bound; rarely out of home or residence; purposeless movements often present.

- **Terminal (5)**: No response or comprehension. No recognition. Needs to be fed, may have NG tube and/or swallowing difficulties. Total incontinence. Bedridden, unable to sit or stand; contractures.

- **Sensory-Motor confound (91)**: Functional impairment could not be determined due to sensory/motor impairment.
Appendix B

GMHR Rating Subject
GMHR Rating Subject

RESIDENCE

1  HOME/OUTPATIENT

2  RESIDENTIAL/ASSISTED LIVING-UNLOCKED UNITS

2.1  ASSISTED LIVING-LOCKED UNITS

3  SKILLED NURSING FACILITY

Circle **one** of the numbers between 1 and 4 using the instructions next to each number. Please begin at the top and decide if the person meets each rating in sequence as written. If you are having trouble deciding between two adjacent ratings, rate the lower number.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>EXCELLENT</td>
</tr>
<tr>
<td>3</td>
<td>GOOD</td>
</tr>
<tr>
<td>2</td>
<td>FAIR</td>
</tr>
<tr>
<td>1</td>
<td>POOR</td>
</tr>
</tbody>
</table>

Other
Appendix C

Mini-Mental State Examination
MINI-MENTAL STATE EXAMINATION

Now I would like to ask you some questions to check your memory and concentration. Some of them may be easy and some may be hard.

1. What is the year?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

2. What is the season of the year?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

3. What is the date?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

4. What is the day of the week?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

5. What is the month?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

6. Can you tell me where we are right now? (For instance, what state are we in?)  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

7. What county are we in?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

8. What city/town are we in?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

9. What floor of the building are we on?  
   ERROR ...................................................... 0 IMP  
   CORRECT ........................................... 1 IMP  
   INCORRECT: PHYS IMP .......................... 6 IMP  
   NOT ASSESSED .................................. 9 IMP  

10. What is this address? (If institutionalized, what is the name of the institution?)  
    ERROR ...................................................... 0 IMP  
    CORRECT ........................................... 1 IMP  
    INCORRECT: PHYS IMP .......................... 6 IMP  
    NOT ASSESSED .................................. 9 IMP
11. I am going to name three objects. After I have said them, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

Please repeat the names for me:
SCORE FIRST TRY. REPEAT OBJECTS FOR UP TO THREE TRIALS ONLY.

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
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</tr>
<tr>
<td>PENNY</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

12. Now I am going to give you a word and ask you to spell it forwards and backwards. The word is WORLD. First, can you spell it forwards? Now spell it backwards. REPEAT IF NECESSARY. HELP SUBJECT SPELL WORD FORWARD, IF NECESSARY. SCORE NUMBER OF LETTERS GIVEN IN CORRECT ORDER.

```
W   O   R   L   D   D   L   R   O   W
```

<table>
<thead>
<tr>
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<tr>
<td>POSITION SCORE</td>
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<tr>
<td>INCORRECT/PHYS IMP</td>
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</tr>
<tr>
<td>NOT ASSESSED</td>
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<td></td>
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</table>

What were the three objects I asked you to remember?:

13. APPLE

<table>
<thead>
<tr>
<th></th>
<th>ERROR OR/OMISSION</th>
<th>IMP</th>
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14. TABLE

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<tr>
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15. PENNY

<table>
<thead>
<tr>
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<tbody>
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<tr>
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<tr>
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</table>

16. POINT TO A WATCH. What is this called?

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>CORRECT</td>
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<tr>
<td>INCORRECT/PHYS IMP</td>
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</tr>
<tr>
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</table>
17. SHOW A PENCIL. What is this called?

<table>
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<tr>
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<td>6</td>
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<tr>
<td>NOT ASSESSED</td>
<td>9</td>
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</tbody>
</table>

18. I would like you to repeat a phrase after me: (The phrase is) ‘No ifs ands or buts’. Allow only one trial. Phrase may be repeated if requested by subject before a first attempt.

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<thead>
<tr>
<th>Description</th>
<th>Score</th>
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<td>6</td>
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<td>NOT ASSESSED</td>
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</tbody>
</table>

19. Read the words on this page, then do what it says. The paper reads: "Close your eyes." Score correct if subject closes eyes.

<table>
<thead>
<tr>
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<th>Score</th>
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</thead>
<tbody>
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<tr>
<td>NOT ASSESSED</td>
<td>9</td>
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</tbody>
</table>

20. I am going to give you a piece of paper. When I do, take the paper in your right hand, fold the paper in half with both hands, and put the paper down on your lap. Read full statement, then hand paper to subject. Do not repeat instructions or coach.

- Right hand
<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
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<td>INCORRECT PHYS IMP</td>
<td>6</td>
</tr>
<tr>
<td>NOT ASSESSED</td>
<td>9</td>
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</table>

- Folds
<table>
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<th>Score</th>
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<tr>
<td>CORRECT</td>
<td>1</td>
</tr>
<tr>
<td>INCORRECT PHYS IMP</td>
<td>6</td>
</tr>
<tr>
<td>NOT ASSESSED</td>
<td>9</td>
</tr>
</tbody>
</table>

- In lap
<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERROR</td>
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<tr>
<td>CORRECT</td>
<td>1</td>
</tr>
<tr>
<td>INCORRECT PHYS IMP</td>
<td>6</td>
</tr>
<tr>
<td>NOT ASSESSED</td>
<td>9</td>
</tr>
</tbody>
</table>

21. Write any complete sentence on that piece of paper for me.

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>ERROR</td>
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</tr>
<tr>
<td>INCORRECT PHYS IMP</td>
<td>6</td>
</tr>
<tr>
<td>NOT ASSESSED</td>
<td>9</td>
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</tbody>
</table>

22. Here is a drawing. Please copy the drawing on the same paper. Score correct if the drawing includes two five-sided figures and if all angles in the five-sided figure are preserved.

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
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<tbody>
<tr>
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<tr>
<td>NOT ASSESSED</td>
<td>9</td>
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</table>

Total Score

Total Score

Fine Score
Appendix D

Distribution
Figure D1. GMHR distribution.

Figure D2. CCI distribution.
Figure D3. Prescription distribution.
Appendix E

Kaplan-Meier Plots (GMHR)
Figure E1. Survival to severe dementia by GMHR,

Figure E2. Survival to institutionalization by GMHR.
Figure E3. Survival to death by GMHR.
Appendix F

Log-Minus-Log Plots (GMHR)
Figure F1. Check of proportional hazards assumption for GMHR by severe dementia.

Figure F2. Check of proportional hazards assumption for GMHR by institutionalization.
Figure F3. Check of proportional hazards assumption for GMHR by death.
Appendix G

Kaplan-Meier Plots (CCI)
Figure G1. Survival to severe dementia by CCI.

Figure G2. Survival to institutionalization by CCI.
Figure G3. Survival to death by CCI.
Appendix H

Log-Minus-Log Plots (CCI)
Figure H1. Check of proportional hazards assumption for CCI by severe dementia.

Figure H2. Check of proportional hazards assumption for CCI by institutionalization.
Figure H3. Check of proportional hazards assumption for CCI by death.
Appendix I

Kaplan-Meier Plots (HTN)
Figure I1. Survival to severe dementia by HTN.

Figure I2. Survival to institutionalization by HTN.
Figure 13. Survival to death by HTN.
Appendix J

Line-Minus-Line Plots (HTN)
Figure J1. Check of proportional hazards assumption for HTN by severe dementia.

Figure J2. Check of proportional hazards assumption for HTN by institutionalization.
Figure J3. Check of proportional hazards assumption for HTN by death.
Appendix K

Kaplan-Meier Plots (CVA)
Figure K1. Survival to severe dementia by CVA.

Figure K2. Survival to institutionalization by CVA.
Figure K3. Survival to death by CVA.
Appendix L

Contingency Tables
### Table L1

*Contingency Table for CVA and Severe Dementia*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Never CVA</td>
<td>238</td>
<td>74</td>
<td>312</td>
<td></td>
</tr>
<tr>
<td>Prevalent CVA</td>
<td>12</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Incident CVA</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>255</td>
<td>80</td>
<td>335</td>
<td></td>
</tr>
</tbody>
</table>

*Note. p value from Chi-Square test is 0.060 (not significant).*

### Table L2

*Contingency Table for CVA and Institutionalization*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Institutionalization</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Never CVA</td>
<td>59</td>
<td>253</td>
<td>312</td>
<td></td>
</tr>
<tr>
<td>Prevalent CVA</td>
<td>2</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Incident CVA</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>66</td>
<td>269</td>
<td>335</td>
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</table>

*Note. p value from Chi-Square test is 0.088 (not significant).*

### Table L3

*Contingency Table for CVA and Death*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Death</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Never CVA</td>
<td>44</td>
<td>268</td>
<td>312</td>
<td></td>
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<tr>
<td>Prevalent CVA</td>
<td>1</td>
<td>12</td>
<td>13</td>
<td></td>
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<tr>
<td>Incident CVA</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td>48</td>
<td>287</td>
<td>335</td>
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*Note. p value from Chi-Square test is 0.289 (not significant).*
Table L4

*Contingency Table for CHF and Severe Dementia*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Severe dementia</th>
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<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
</tr>
<tr>
<td>Never CHF</td>
<td>245</td>
<td>77</td>
<td>322</td>
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<tr>
<td>Prevalent CHF</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Incident CHF</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>255</td>
<td>80</td>
<td>335</td>
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*Note.* $p$ value from Chi-Square test is 0.623 (not significant).

Table L5

*Contingency Table for CHF and Institutionalization*

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<th>Predictors</th>
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<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
</tr>
<tr>
<td>Never CHF</td>
<td>62</td>
<td>260</td>
<td>322</td>
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<tr>
<td>Prevalent CHF</td>
<td>2</td>
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<td>11</td>
</tr>
<tr>
<td>Incident CHF</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>66</td>
<td>269</td>
<td>335</td>
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</table>

*Note.* $p$ value from Chi-Square test is 0.078 (not significant).

Table L6

*Contingency Table for CHF and Death*

<table>
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<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
</tr>
<tr>
<td>Never CHF</td>
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<td>275</td>
<td>322</td>
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<tr>
<td>Prevalent CHF</td>
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<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Incident CHF</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>48</td>
<td>287</td>
<td>335</td>
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</table>

*Note.* $p$ value from Chi-Square test is 0.741 (not significant).
Appendix M

Log-Minus-Log Plots (CVA)
Figure M1. Check of proportional hazards assumption for CVA by severe dementia.

Figure M2. Check of proportional hazards assumption for CVA by institutionalization.
Figure M3. Check of proportional hazards assumption for CVA by death.
Appendix N

Kaplan-Meier Plots (CHF)
Figure N1. Survival to severe dementia by CHF.

Figure N2. Survival to institutionalization by CHF.
Figure N3. Survival to death by CHF.
Appendix O

Log-Minus-Log Plots (CHF)
Figure O1. Check of proportional hazards assumption for CHF by severe dementia.

Figure O2. Check of proportional hazards assumption for CHF by institutionalization.
Figure O3. Check of proportional hazards assumption for CHF by death.
Appendix P

Kaplan-Meier Plots (Medication)
Figure P1. Survival to severe dementia by prescription medication.

Figure P2. Survival to institutionalization by prescription medication.
Figure P3. Survival to death by prescription medication.
Appendix Q

Log-Minus-Log Plots (Medication)
Figure Q1. Check of proportional hazards assumption for prescription medication by severe dementia.

Figure Q2. Check of proportional hazards assumption for prescription medication by institutionalization.
Figure Q3. Check of proportional hazards assumption for prescription medication by death.
CURRICULUM VITAE

MAC J. GILBERT

435-764-2622
mgilbert@utah.gov

EDUCATION

Ph.D.  Utah State University, Logan, UT
8/15  Combined Clinical/ School/ Counseling Psychology (APA accredited)
Dissertation: The Association of Medical Comorbidities with Rate of Progression to Severe Dementia, Institutionalization, and Death in a Population of Individuals with Alzheimer’s Disease.
Advisor: JoAnn Tschanz, Ph. D.

M.S.  Loyola University, Baltimore, MD
9/10  Clinical Psychology
Thesis: The Association Between At-Risk Drinking and Medication Compliance in a Population of Acute Stroke Patients
Advisor: Martin F. Sherman, Ph.D.

B.A.  University of New Hampshire, Durham, NH
5/05  Psychology
Cum Laude

B.S.  University of New Hampshire, Durham, NH
5/05  Business Administration w/ concentration in Finance
Cum Laude
Honors Program

CLINICAL EXPERIENCE

7/14-8/15  Pre-doctoral Internship
Utah State Hospital – Provo, UT.
Responsibilities: Working with patients with severe mental illness. Provide therapy through individual and group modalities. Individual therapy includes CBT-P, DBT, and cognitive remediation. Group treatment focuses on DBT and ACT for psychosis. Management of behavioral support plans for improvement of patient behavior. Diagnostic and cognitive assessment. Participation as a member of an interdisciplinary team: patient clinicals, rounds, and staff training.
Direct Clinical Hours: 228 Total Hours: 1298
Supervisor: Amanda Rapacz, Psy.D. & Ted Barratt, Ph.D.
9/13-6/14  Graduate Assistant
Avalon Hills: Residential Eating Disorder Program – Petersboro, UT.
Responsibilities: Running process and didactic groups as well as individual therapy. Groups and individual treatment are consistent with Acceptance and Commitment Therapy. Didactic groups include mindfulness, Acceptance and Commitment Therapy, Dialectical Behavior Therapy, and recovery maintenance. Participation in morning rounds and weekly interdisciplinary treatment team meetings. Participation in Equine assisted therapy and family therapy sessions.
Direct Clinical Hours: 270  Total Hours: 488
Supervisor: Tera Lensegrav-Benson, Ph.D.

9/12-5/13  Practicum in Clinical Child/ School Psychology
Avalon Hills: Residential Eating Disorder Program – Petersboro, UT
Responsibilities: Engage with residents by running process group, individual therapy, and didactic groups focused on Acceptance Commitment Therapy, mindfulness, and recovery maintenance. Participation in morning rounds and weekly interdisciplinary treatment team meetings. Collaborating with existing body image therapist to incorporate A.C.T. into body image groups.
Direct Clinical Hours: 121; Total Hours: 326
Supervisor: Tera Lensegrav-Benson, Ph.D.

6/11-6/13  Graduate Assistant
Center for Persons with Disabilities – Utah State University, Logan, UT
Responsibilities: Conduct intake interviews, provide in depth assessment and evaluation which focused on autism spectrum disorders, learning disabilities, and behavior related problems. Report writing, feedback sessions, consultation with speech and language pathologists, occupational therapists, and physicians in a multidisciplinary team format, presentation of cases to a multidisciplinary team, supervise practicum students in their assessments and report writing.
Population: Children, adolescents, and adults from the community frequently diagnosed with an autism spectrum disorder, learning disabilities, oppositional defiant disorder, ADHD, and other disorders that impair an individual’s ability to function.
Direct Clinical Hours: 390; Total Hours: 1389
Supervisor: Martin Toohill, Ph.D.

9/11-7/12  Practicum in Clinical/Counseling Psychology
Brigham City Cardiac Rehabilitation – Brigham City Community Hospital, Brigham City, UT
Responsibilities: Monitor and assess patients for psychopathology while they are engaging in cardiovascular exercise on unit, develop treatment plan and provide ongoing therapy for individuals who have been identified as in need of services.
Population: Older adults from the community with acute cardiac events, who are participating in a cardiac rehabilitation program. Adjustment disorder, depression, and anxiety are most commonly seen.

Direct Clinical Hours: 76; Total Hours: 115
Supervisor: M. Scott DeBerard, Ph.D.

9/11-5/12
Practicum in Clinical/Counseling Psychology
Anxiety Disorders Specialty Clinic - Utah State University, Logan, UT
Responsibilities: Conduct intake evaluations, administer assessments, treatment plan development, and provide ongoing individual therapy utilizing Acceptance and Commitment Therapy and Exposure.
Population: Adults and adolescents from the community who suffer from anxiety and related disorders (OCD, perfectionism, religious scrupulosity).
Direct Clinical Hours: 48.5; Total Hours: 136.5
Supervisor: Michael Twohig, Ph.D.

9/10-5/12
Practicum in Clinical/Counseling Psychology
Student Health and Wellness Center - Utah State University, Logan, UT
Responsibilities: Conduct intake evaluations and one-time consults, provide ongoing individual therapy, develop treatment plans, administer psychological evaluations, write reports, and consult with doctors and nurses in a multidisciplinary format.
Population: Traditional and non-traditional College students.
Direct Clinical Hours: 232; Total Hours: 644
Supervisor: M. Scott DeBerard, Ph.D.

8/10-10/10
Student Therapist
Utah State University Community Clinic, Logan, UT
Responsibilities: Conduct intake evaluations, develop treatment plans, provide ongoing therapy, and consult with other professionals.
Population: individual and couples therapy with adults from the community.
Direct Clinical Hours: 10; Total Hours: 28
Supervisor: M. Scott DeBerard, Ph.D.

6/10-8/10
Practicum in Psychology
Utah State University Community Clinic, Logan, UT
Responsibilities: Conduct intake evaluations, develop treatment plans, provide therapy, administer psychological assessments, write reports, and consult with others
Direct Clinical Hours: 24; Total Hours: 106
Supervisors: M. Scott DeBerard, Ph.D. & Gretchen Gimpel Peacock

9/09-5/10
Integrative Practicum with Adults, Adolescents, and Children
Utah State University Community Clinic, Logan, UT
Responsibilities: Conduct intake evaluations, develop treatment plans, provide ongoing therapy, administer psychological assessments, write reports,
and consult with other professionals.
Population: Individual and couples therapy with college students, children, adolescents, adults, and elderly.

Direct Clinical Hours: 58; Total Hours: 309
Supervisors: Susan L. Crowley, Ph.D. & Kyle Hancock, Ph.D.

9/09-8/12

Neuropsychological Technician
Dementia Progression Study and Cache County Study on Memory and Aging, Logan, UT
Responsibilities: Administration and scoring of neuropsychological tests with elderly individuals, conduct semi-structured interviews with informants of research participants, and participate in case meetings to review case material for diagnosis of dementia and other cognitive disorders. Population: elderly individuals with dementia.

Direct Clinical Hours: 231; Total Hours: 463
Supervisor/Principal Investigator: JoAnn Tschanz, Ph.D.

PROFESSIONAL EXPERIENCE

1/07-8/08
Outreach Worker
Main Street Mobile Treatment Associates, Reisterstown, MD.
Responsibilities: Provide supportive counseling, medication management, facilitate communication between client and psychiatrist as well as other outside resources, monitor client safety, and develop treatment goals. Clients were seen in a clinic, in a drug and alcohol rehabilitation facility, and client homes. Clients were voluntary and state mandated as part of rehabilitation treatment. Worked with a multi-disciplinary team and participated in weekly individual supervision with a licensed psychologist.
Population: adolescents, adults, and elderly. Predominantly low SES.
Clinical hours: 320; Total Hours: 820
Supervisor: Nicole Ryan, Psy. D.

RESEARCH EXPERIENCE

10/11-3/12
Research Assistant/ Group Leader
Healthy Sexuality Group
Logan,UT
Responsibilities: Running groups of five to 10 individuals that focused on Sexual education, health, and stereotypes. This group was part of a dissertation study in the area of sexual education.
Supervisor: Renee Galliher, Ph.D.

9/09-8/10
Research Assistant
Dementia Progression Study and Cache County Study on Memory and Aging, Logan, UT
Responsibilities: Conducted literature reviews in the areas of dementia,
cognitive functioning, head and brain injury, nursing home placement, caregiving of elderly individuals, writing abstracts, creation of data sets, poster presentation, and data management. 

Supervisor: JoAnn Tschanz, Ph.D.

4/07-5/08

**Psychology Externship**

*Johns Hopkins School of Medicine Department of Physical Medicine and Rehabilitation, Baltimore, MD.*

Responsibilities: Recruitment and administration of psychological battery to 146 individuals with acute stroke, database development and management, entry of data, observation and administration of neuropsychological assessments for dementia diagnosis, observations of neuropsychological assessments given to stroke patients to assess cognitive and functional status, participation in interdisciplinary team meetings for case reviews of patients, work with psychologists, physicians, nurses, social workers, and occupational, vocational, physical, and speech therapists.

Supervisors: Douglas Johnson-Greene, Ph.D. & Patricia R. Roger, Ph.D.

4/07-7/08

**Volunteer Position**

*Johns Hopkins School of Medicine Department of Physical Medicine and Rehabilitation, Division of Rehabilitation Psychology and Neuropsychology, Baltimore, MD.*

Responsibilities: Literature reviews in area of positive psychological variables, spinal cord injury, cancer, arthritis, traumatic brain injury, physical and emotional outcome from physical injury, quality of life, and manuscript writing and editing.

Supervisor: Kathleen Kortte, Ph.D.

Peer Reviewed Articles


PRESENTATIONS

Progression Study. Poster session presented at the Alzheimer’s Association International Conference (AAIC), Vancouver, Canada.


AWARDS

11/14 Awarded paper of the year from the journal *International Psychogeriatrics* for role as first author of the article titled *The association of traumatic brain injury with rate of progression of cognitive and functional impairment in a population based cohort of Alzheimer’s disease: The Cache County dementia progression study.*

10/14 Awarded paper of the month from the journal *International Psychogeriatrics* for role as first author of the article titled *The association of traumatic brain injury with rate of progression of cognitive and functional impairment in a population based cohort of Alzheimer’s disease: The Cache County dementia progression study.*

TEACHING EXPERIENCE

**Trainer**

*Utah State University*, Logan, UT,

Trained undergraduate research assistants on how to administer and score the Mini Mental Status Examination (MMSE). A focus on how to give this assessment to older individuals was included in the training. This was part of a study involving participants with Alzheimer’s disease.
Guest Lecturer
*Utah State University,* Logan, UT.
12/10 Lectured to a graduate level ethics class on ethics and confidentiality with specific attention to forensic psychology and how technology impacts psychology and confidentiality issues.
12/10 Lectured to an undergraduate honors seminar on therapy and research specific to depression and empirically based practice of psychology.
11/10 Lectured to a graduate level class on the assessment of alcohol use in a college population using the Brief Alcohol Screening and Intervention of College Students (BASICS) manual.
1/09 Lectured to an undergraduate introduction to psychology class on the biological basis of psychology.

Teaching Assistant
*Utah State University,* Logan, UT.  
*Undergraduate Psychology 1010 (intro to psych)*
Responsibilities: Teaching assistant for four sections, taught 2 lab sessions each week, development of new labs, grading of exams and lab assignments, proctored exams, meet with students outside of class. 
*Supervisors:* Scott Bates, Ph.D. (2 sections); Tamara Ferguson, Ph.D. (1 section); Jared Cox (1 section).

Teaching Assistant
*Loyola University,* Baltimore, MD.  
*Undergraduate Research Methods and Statistics*
Taught classes and labs on t-tests, ANOVAs, linear regression, and Chi-Square, research methods, SPSS, and presentation formats. Assisted students with development of research projects, provided study sessions before exams and graded exams and assignments. 
*Supervisor:* Beth Kotchick

Outreach

Radio Interview
*Cool Science Radio, KPCW,* Park City, Utah
Discussed the article *The association of traumatic brain injury with rate of progression of cognitive and functional impairment in a population based cohort of Alzheimer’s disease: The Cache County dementia progression study and its implications for everyday life.*

Community Presentation  
*Science Unwrapped, Utah State University,* Logan, Utah
Presented information to the community on dementia, Alzheimer’s, the Cache County Study on memory and Aging. Using a brain specimen, highlighted anatomical structures and their corresponding roles.
Community presentation
Alzheimer's Walk, through the Alzheimer’s Association, Logan, Utah
Presented information to the community on dementia, Alzheimer’s, the Cache County Study on memory and Aging. Provided information on resources for those concerned about dementia and for caregivers of individuals with dementia.