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The Social Environment, APOE-e4, and Dementia: The Social Environment as a Moderating Factor Among Individuals Genetically Predisposed to Develop Dementia

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THE SOCIAL ENVIRONMENT, APOE-E4, AND DEMENTIA:

THE SOCIAL ENVIRONMENT AS A MODERATING FACTOR AMONG INDIVIDUALS GENETICALLY PREDISPOSED TO DEVELOP DEMENTIA

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ABSTRACT

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Many studies have shown a relationship between the APOE-e4 allele and dementia, as well as a relationship between the social environment and dementia. However, relatively little investigation into the potential moderating effect of the social environment on the relationship between the APOE-e4 allele and cognitive well-being has been reported. Further, studies that did examine these relationships typically have employed clinical populations, along with regional and non-U.S. samples. This study contributed to the research literature, in part, by using the first U.S. nationally representative sample of older adults that included clinical diagnosis of cognition and dementia (Aging, Demographics, and Memory Study from the Health and Retirement Study). A combination of descriptive analyses and multinomial logistic regression

models were used to investigate these relationships. Overall, the prevalence of unique APOE genotypic combinations was similar in the ADAMS sample as compared to samples taken from other developed nations. Descriptive results also showed that respondents with and without the APOE-e4 allele were only found to differ on race and ethnic status. Regression results indicated that the APOE-e4 allele was associated with a higher risk of cognitive difficulty, and that being more socially engaged and more socially connected to others was associated with a lower risk of cognitive difficulty and dementia. All aspects of the social environment, except social engagement, were found to moderate the relationship of the APOE-e4 allele to cognitive diagnosis. The relationship of the social environment to dementia, as well as its moderating influence, indicated a need for further investigation into the unique contributions of the social environment for cognitive well-being in later life.

DEDICATION

To Mom and Dad,
who always told me I could do anything.

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To my brother, your willingness to listen to me vent and ability to make me laugh, in spite of myself, kept me sane through it all. I couldn't ask for a better big brother.

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CHAPTER 1

INTRODUCTION

Dementia is defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as a disorder that involves cognitive difficulties that are severe enough to interfere with one's daily life, whether at work or home. Memory impairment is often a symptom of dementia. Dementia can also result in a loss of executive functioning and the ability to process information taken in through the senses. Individuals with dementia may experience a loss of vision, language, and mobility (American Psychiatric Association, 1994; McKhann, et al., 2011). There are many types of dementia, such as vascular dementia, Lewy bodies dementia, and frontotemporal lobar degeneration. The most common type of dementia is Alzheimer's disease.

Recent advancements in understanding the processes associated with the development of Alzheimer's disease led the National Institute on Aging (NIA) and the Alzheimer's Association to commission a group of investigators to develop new criteria to define Alzheimer's disease that incorporates knowledge about the disease that has been gleaned since 1984. These criteria were published in a series of articles in 2011 (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Sperling, et al., 2011). There are two primary differences between the previous definition of Alzheimer's disease and the

current definition. First, the stages of the disease have changed. Previously, the stages of Alzheimer's disease were considered to be mild, moderate, and severe. The new criteria identify these stages as pre-clinical, mild cognitive impairment (MCI) due to Alzheimer's disease, and dementia due to Alzheimer's disease. Second, the workgroup has suggested the inclusion of biomarkers to aid in the diagnosis of Alzheimer's disease. This resulted in the identification of Alzheimer's disease by either the pathophysiological processes underlying the disease (AD-P) or its clinical manifestations (AD-C). This distinction is based on the use of biomarkers. Individuals may demonstrate physiological changes related to Alzheimer's disease (AD-P) without exhibiting the symptoms often associated with the disease (AD-C). The distinction of AD-P from AD-C allows for the identification of pre-clinical stages of Alzheimer's disease as well as MCI due to Alzheimer's disease (Alzheimer's Association, 2012; Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Sperling, et al., 2011).

The risk of developing dementia in general, or Alzheimer's disease specifically, doubles every five years after 65 years of age (Read, Roberts, Linnenbringer, & Green, 2008; Snyder, 1999). It was projected that at least 15% of the population in 42 states will be over 65 years of age by 2020 (AARP, 2006), with age being identified as one of the risk factors for developing Alzheimer's disease (Alzheimer's Association, 2008, 2012). It has been found that individuals who are 65 years of age have a 10.5% risk of being diagnosed with Alzheimer's disease (Sperling, et al., 2011). There are an estimated 2.5 million adults over 60 years of age in the United States who have Alzheimer's disease and 3.7 million who have dementia (Brookmeyer, et al., 2011). The prevalence of Alzheimer's disease is projected to increase to more than 13.5 million cases in the United

States by 2050 (Sperling, et al., 2011). The prevalence and projected increase in the number of people with dementia and Alzheimer's disease warrants increased attention to understand better the potential risk factors and possible preventive measures associated with this disease.

Alzheimer's disease is more prevalent at older ages and age has been identified as a risk factor for the disease (Alzheimer's Association, 2012; American Psychiatric Association, 1994; Brookmeyer, et al., 2011). Late onset Alzheimer's disease, which occurs after 65 years of age, is more common than early onset Alzheimer's disease. As age increases, the prevalence of Alzheimer's disease and other types of dementia increases (American Psychiatric Association, 1994; Brookmeyer, et al., 2011; Fratiglioni, et al., 1997; Launer, et al., 1999). Women have historically been found to be at greater risk of developing dementia and Alzheimer's disease than men (American Psychiatric Association, 1994; Azad, Bugami, & Loy-English, 2007; Fratiglioni, et al., 1997). In 2010 it was estimated that 3.3 million women over 65 years of age had Alzheimer's disease compared to 1.8 million men (Evans as cited in Alzheimer's Association, 2012). A recent study of a representative sample of U.S. older adults found men to have a lower risk of developing Alzheimer's disease (Plassman, et al., 2011). Individuals with parents or siblings who have Alzheimer's disease are at greater risk of developing the disease (Bekris, Yu, Bird, & Tsuang, 2010; Green, et al. as cited in Alzheimer's Association, 2012; Fratiglioni, Ahlbom, Viitanen, & Winblad as cited in Alzheimer's Association, 2012; Mayeux, Sano, Chen, Tatemichi, & Stern as cited in Alzheimer's Association, 2012; American Psychiatric Association, 1994) and is likely due to a combination of genetic heritability in families (Jack, et al., 2011) and a shared environment (Alzheimer's

Association, 2012; Bekris, et al., 2010). Depression (Lehman, Black, Shore, Kasper, & Rabins as cited in Alzheimer's Association, 2012; Barnes, et al., 2012; Read, et al., 2008; Saczynski, et al., 2010; Wang, Karp, Winblad, & Fratiglioni, 2002; Zunzunegui, Alvarado, Del Ser, & Otero, 2003), age (Alzheimer's Association, 2012; Brookmeyer, et al., 2011; Holtzman, et al., 2004; Wang, et al., 2002), being in poorer health (Barnes, et al., 2007; Wang, et al., 2002; Wysocki, et al., 2012), and less education (Holtzman, et al., 2004; Kivipelto, et al., 2006; Seeman, et al., 2005; Sharp & Gatz, 2011) have all been identified as risk factors for developing dementia and Alzheimer's disease.

Two additional risk factors that have been found to be associated with Alzheimer's disease are the apolipoprotein E (APOE) gene and the social environment. The APOE-e4 allele is the most commonly researched and prevalent genetic risk factor for late onset Alzheimer's disease (Bekris, et al., 2010; Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Corder, et al., 1993; Plassman, et al., 2007). Individuals who have two e4 alleles have an even greater risk of developing Alzheimer's disease (Bekris, et al., 2010). Despite the increased risk associated with the APOE-e4 allele, not everyone with this allele develops Alzheimer's dementia (Alzheimer's Association, 2012; Bekris, et al., 2010; Myers, et al., 1996). This indicates environmental influences on Alzheimer's disease development associated with the APOE-e4 allele (Alzheimer's Association, 2012; Bekris, et al., 2010; Ryff & Singer, 2005).

Dimensions of the social environment such as the size of social networks, more frequent contact with social network members, and emotional support have been associated with a decreased risk of dementia and Alzheimer's disease. However, not all studies have found a significant relationship between the social environment and

dementia or Alzheimer's disease (Alzheimer's Association, 2012; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Seeman, Lusignolo, Albert, & Berkman, 2001; Seidler, Bernhardt, Nienhaus, & Frolich, 2003). These mixed findings indicate that additional factors may influence this relationship and thus more research is needed.

This study examines the gene-environment relationship as it relates to the expression of dementia among older individuals. Specifically, this study examines whether the social environment moderates the relationship of the APOE-e4 allele and late onset Alzheimer's disease. This includes dementia as a separate category inclusive of individuals who may have mixed dementia and several other forms of dementia, such as vascular dementia, frontotemporal dementia, and Lewy body dementia. These other types of dementia were combined in order to account for small sample size of these distinct dementia diagnoses. This study contributes to the literature by using the first U.S. nationally representative population-based data on dementia to examine these complex relationships. These data, the Aging, Demographics, and Memory Study (ADAMS) data, are contained in a special module of the Health and Retirement Study (HRS) and represent an ideal opportunity to further explore these questions.

CHAPTER 2

LITERATURE REVIEW

This chapter provides an overview of the literature for several key areas of importance to the conceptual framework of this study. First, a discussion about genetic risk factors of Alzheimer's disease is included. Next, several aspects of the social environment that are related to the development of Alzheimer's disease and dementia are presented. Last, a brief overview of additional factors that have been associated with Alzheimer's disease and dementia are discussed in order to provide some background for the selection of covariates included in this study.

Genetic Predisposition

There are three well documented rare familial genetic mutations that have been found to cause Alzheimer's disease. These mutations are found on the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) and account for approximately 1% to 5% of Alzheimer's disease cases (Bekris, et al., 2010; Tanzi, 2013). Mutations on APP, PSEN1, and PSEN2 tend to be early onset, which can occur from 30 years of age up to 60 years of age and run in families. APP has been linked to Alzheimer's disease among individuals with Down's Syndrome. Age at onset with APP mutations tends to be in the fourth and fifth decades of life. PSEN1 accounts for the

greatest prevalence of early onset cases of Alzheimer's disease. The average age at onset among individuals with a PSEN1 mutation is 58 years, although ages have been found to range from 25 years to 65 years of age. Individuals with a PSEN2 mutation tend to be older, ranging in age from 45 years to 88 years. Greater variability in the age at onset of the disease has been found among individuals with a PSEN2 mutation. It has been speculated that the PSEN2 mutation may be more sensitive to environmental or other genetic factors, which may account for the greater variability in the age at onset observed (Bekris, et al., 2010).

Progranulin (GRN) and microtubule associated protein tau (MAPT) mutations have been found to cause frontotemporal dementia (FTD) in families. However, mutations of these genes have also been found in individuals who were diagnosed with clinical Alzheimer's disease (Coppola, 2012; Cruchaga, et al., 2012). One study identified the rare variant p.A152T as the first MAPT genetic risk factor associated with Alzheimer's disease. This variant has been found to be associated with tau functioning (Coppola, 2012). Tau is one of the primary pathological indicators of Alzheimer's disease (Coppola, 2012; McKhann, et al., 2011). Nevertheless, the mechanisms through which GRN and MAPT may influence disease expression are not well understood. It has been suggested that the association of GRN and MAPT with Alzheimer's disease may be the result of misdiagnosis (Cruchaga, et al., 2012).

Since 2008, genome-wide association studies (GWAS) have found an association of late onset Alzheimer's disease with several genetic risk factors: CD33 (Bertram et al. as cited in Griciuc, et al., 2013; Hollingworth, et al. as cited in Griciuc, et al., 2013; Naj, et al. as cited in Griciuc, et al., 2013; Tanzi, 2013), CLU (clusterin; apolipoprotein J),

BIN1 (bridging integrator 1), PICALM (phosphatidylinositol binding clathrin assembly protein), CR1 (complement component (3b/4b) receptor 1), CD2AP, EPHA1, ABCA7, MS4A6A/MS4A4E (Harold, et al. as cited in Griciuc, et al., 2013; Hollingworth, et al. as cited in Griciuc, et al., 2013; Lambert, et al. as cited in Griciuc, et al., 2013; Naj, et al. as cited in Griciuc, et al., 2013; Seshadri et al. as cited in Griciuc, et al., 2013; Tanzi, 2013), and TREM2 (triggering receptor expressed on myeloid cells 2) (Guerreiro, et al. as cited in Griciuc, et al., 2013; Jonsson, et al. as cited in Griciuc, et al., 2013; Tanzi, 2013). Generally, these risk factors are associated with amyloid-beta metabolism, lipid metabolism, immune function, or cell signaling (Tanzi, 2013). Researchers believe that TREM2 and CD33 may work together to affect amyloid-beta levels, inflammation, and cell death, which could ultimately serve to reduce or delay deleterious physiological changes which result in clinical disease symptoms (Talan, 2013). TREM2 is associated with the removal of cell debris (such as amyloid-beta) and inflammatory response, both of which have been associated with Alzheimer's disease. Early findings suggest that the risk associated with TREM2 is comparable to that of the APOE-e4 genotype. However, the occurrence of the TREM2 variant that may be associated with Alzheimer's disease is very rare (Jonsson, et al., 2013; Talan, 2012). CD33 levels have been found to coincide with amyloid-beta levels in the brain. Higher levels of CD33 have been associated with more amyloid-beta in the brain. Lowering levels of CD33 have been found to clear space for microglia to remove amyloid-beta deposits from the brain (Talan, 2013; Tanzi, 2013).

The apolipoprotein E (APOE) e4 allele is a well-known risk factor for sporadic and late onset Alzheimer's disease (Bekris, et al., 2010; Carchaga, et al., 2012). "Apolipoprotein E (APOE) is a polymorphic protein associated with plasma lipoproteins"

(Poirier, et al., 1993; Soininen & Riekkinen, 1996, p. 697) and is involved in the transportation of cholesterol and lipids (Read, et al., 2008; Soininen & Riekkinen, 1996). It has been found to be particularly important in the nervous system due to its involvement in neuron regeneration and growth (Poirier, et al., 1993; Soininen & Riekkinen, 1996). During development or after injury, APOE transports cholesterol that is used in the growth, maintenance, and repair of myelin and neurons (Poirier, et al., 1993).

APOE not only transports these lipids, it also binds to amyloid-beta and tau protein, and is found in the plaques and tangles associated with Alzheimer's disease (Kobayashi, et al., 2011; Poirier, et al, 1993; Soininen & Riekkinen, 1996). Amyloid-beta is found outside neurons and tau is found inside neurons in the brain. The accumulation of amyloid-beta outside the neuron is believed to interfere with the synaptic communication between neurons. The build-up of tau within the cells creates tangles and interferes with the nutrition of the neuron. Excessive amounts of amyloid-beta and tau protein are considered to contribute to cell death (Alzheimer's Association, 2012). Amyloid-beta is normally cleared away by microglia. However, in the Alzheimer's brain, there is an overabundance and accumulation of amyloid-beta that disrupts normal function. Excessive levels of amyloid-beta are associated with greater deposition of tau proteins, which is associated with inflammation and neuronal death (Talan, 2013).

There are three different types of APOE alleles: e2, e3, and e4, resulting in six possible genotypic combinations: e2/e2, e2/e3, e2/e4, e3/e3, e3/e4, and e4/e4 (Poirier, et al., 1993). These alleles have been found to clear and transport lipoproteins and cholesterol at different rates, resulting in different levels of lipoproteins and cholesterol

depending upon the genotypic combination (Mahley, Weisgraber, & Huang as cited in Bekris, et al., 2010; Poirier, et al., 1993). The e2 allele has been found to protect against the development of Alzheimer's disease (Corder, et al. as cited in Tanzi, 2013). Presence of the APOE-e4 allele is associated with a greater risk of cognitive decline and developing Alzheimer's disease (Alzheimer's Association, 2012; Bretsky, et al., 2003; Corder, et al., 1993; Kobayashi, et al., 2011; Landau, et al., 2010; Tanzi, 2013). The e4 allele is a significant predictor of MCI in the ADAMS data, which is a nationally representative sample of U.S. older adults (Brainerd, Reyna, Petersen, Smith, & Taub, 2011). It is associated with higher cholesterol levels (Liu, Hong, Wang, et al. as cited in Borenstein, et al., 2010) and an increased risk of developing cerebrovascular disease and non-Alzheimer's dementia (Borenstein, et al., 2010; Myers, et al., 1996), such as Lewy body dementia (Kobayashi, et al., 2011). It is also associated with earlier age at onset for Alzheimer's disease (Caselli, et al., 2009; Corder, et al, 1993; Kobayashi, et al., 2011) as well as faster disease progression among individuals with Alzheimer's disease (Lam, Tang, Ma, et al. as cited in Borenstein, et al., 2010). While a higher prevalence of the APOE-e4 allele is found among individuals diagnosed with Alzheimer's disease, it is not always predictive of Alzheimer's disease development (Kobayashi, et al., 2011; Myers, et al, 1996). Myers and colleagues (1996) found that most individuals with the APOE-e4 allele do not develop any type of dementia. However, half of the individuals in their study with Alzheimer's disease had the e4 allele and the e4 allele is associated with an increased risk of vascular dementia. Having two e4 alleles is associated with a dramatically increased risk of Alzheimer's disease (Myers, et al, 1996).

The literature strongly suggests a relationship between the APOE-e4 allele and Alzheimer's disease, although the exact mechanisms through which APOE affects the expression of Alzheimer's disease are still under investigation (Alzheimer's Association, 2012; Soininen & Riekkinen, 1996). Additional genetic and environmental influences are also involved in the expression of disease symptoms (Bekris, et al., 2010). This fact lends itself to exploring environmental factors that may influence the development of Alzheimer's disease in individuals with the e4 allele, such as the social environment.

Social Environment

In a review article, Berkman & colleagues (2000) describe a meta-model of how the social environment and health are related. Their model suggests that social networks influence the resources available to individuals, which in turn influences behavior and health outcomes (Berkman, Glass, Brissette, & Seeman, 2000). They describe both "upstream" and "downstream" social environment factors. Upstream factors include social network characteristics like size, composition, and frequency of contact; as well as larger social system characteristics, such as government policies; or cultural factors, like racism. Downstream factors include psychosocial characteristics such as social support, social engagement, psychological characteristics, and health behaviors (Berkman, et al., 2000). These factors overlap somewhat with a model proposed by Cornwell and Waite, which is discussed below.

There has been debate about the measures used to examine the social environment, and thus what aspects of the social environment are actually being measured. For example, some social network measures look at the structure of the social network while

others examine social support. Network size is measured as the number of members in an individuals' network. Research has demonstrated that the absence of adequate social networks is associated with mortality risk. Most studies examining social support have focused on examining the expected positive aspects of social support. More recently, studies have begun examining some of the potentially deleterious effects of the social environment, such as stress, that may result from negative social relationships (Berkman, et al., 2000). Some social relationships have negative qualities that may be detrimental for a person's health. In sum, Berkman and colleagues argue that it is important to include a wide-range of social environment characteristics in models of health.

There are objective aspects of the social environment, such as network size (upstream factors) and social engagement (downstream factors) (Berkman, et al., 2000). Social exchange is also an objective component of the social environment and can be examined from the perspective of receiving support, giving support, or through an evaluation of whether the exchange of support is even or balanced (reciprocity) (Jung, 1990). In addition to these objective components of the social environment, there are subjective aspects of the social environment, such as perceptions of support and loneliness. "Social isolation" is a subjective component of the social environment and has been found to have deleterious effects on individuals (Cornwell & Waite, 2009). This study examines these social environment constructs using a combination of strategies proposed by Berkman and colleagues (2000), Cornwell and Waite (2009), and Jung (1990).

Although studies have found that negative aspects of the social environment can affect cognition, it should be noted that the positive or negative aspects (quality) of the

social relationships cannot be ascertained with the HRS data. Thus my goal is to organize the social environment into three main constructs: social connectedness, perceived isolation, and reciprocity. In the methods chapter, I discuss the measures of the social environment variables that are included in this study and place these within the three constructs.

Social Connectedness

Research demonstrates that social isolation has a negative influence on physical health (Berkman, et al., 2000) and accelerates cognitive decline (Fratiglioni, Paillard-Borg, & Winblad, 2004). Social isolation is measured by examining whether individuals live alone, by the size of their social networks, their level of engagement in social activities, and how lonely they feel (Cornwell & Waite, 2009). Cornwell and Waite (2009) examined social isolation and categorized this concept into two main components: social disconnectedness (the inverse of connectedness) and perception of social isolation. Social disconnectedness deals with objective aspects of the social environment and situational factors such as social engagement and network size. Social engagement is considered being actively involved in one's social environment. For example, getting together with friends, attending church, volunteering, and working are all considered demonstrations of social engagement (Berkman, et al., 2000; Cornwell & Waite, 2009). In this study, social connectedness rather than disconnectedness is explored. It was reasoned that people who are more socially connected would be at less risk of developing dementia or Alzheimer's disease. The social network, frequency of contact with and geographic proximity to friends and family, social engagement, as well as marital status

and living arrangement are explored as measures to define social connectedness in this study.

Social Network Characteristics

The social network is defined as "the web of social relationships that surround an individual and the characteristics of those ties" (Berkman, et al., 2000, p. 847). There are structural aspects to the social network, such as network size or frequency of contact with individuals in the social network. There is also a qualitative component, such as emotional support (Holtzman, et al., 2004; Zunzunegui, et al., 2003). Emotional support is associated with feeling cared for and loved (Berkman, et al., 2000).

The social network is one aspect of the social environment that is associated with cognitive functioning (Holtzman, et al., 2004; Middleton & Yaffe, 2010; Zunzunegui, et al., 2003). Holtzman and colleagues (2004) used the Epidemiologic Catchment Area (ECA) survey to examine social network relationships with cognitive function as measured by the Mini Mental State Examination (MMSE). The sample consisted of 354 participants in Baltimore, Maryland who were available for longitudinal analysis. Baseline data was taken from Wave 1 which was collected in 1981. Wave 3, collected from 1993-1996, was used for follow-up. Findings indicate that network size and frequency of contact significantly correlate with cognitive function. Having a larger social network, or more people with whom one is in contact, is associated with better cognitive function. Individuals who have larger social networks maintain higher cognitive performance and have less odds of demonstrating cognitive decline (Holtzman, et al., 2004; Middleton & Yaffe, 2010).

Bassuk, Glass, and Berkman (1999) used the New Haven cohort of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) data for their study. The study was restricted to individuals 65 years of age and older. They found individuals with no social network to be at an increased risk of cognitive decline (Bassuk, et al., 1999). A German study examined the psychosocial network and dementia. The researchers conducted personal interviews with 108 patients with possible Alzheimer's disease, 59 with possible vascular dementia, and 28 from other types of dementia and 229 control subjects. They found that having more confidants, friends, and relatives serves a protective role, with people who have more confidants being less likely to have Alzheimer's disease or vascular dementia. This was also the case in an analysis of a sample of older adults in Stockholm, Sweden that was conducted from 1987-1996, the Kungsholmen Project. It was a longitudinal study that initially assessed 1,810 participants in 1987 (Fratiglioni, et al., 2000; Seidler, et al., 2003). Analysis of the Kungsholmen Project data revealed that a poor social network (being childless, unmarried, and living alone with no close social ties) is associated with an increased risk of all-cause dementia (Fratiglioni, et al., 2000). The Study of Osteoporotic Fractures (SOF) also found that women over the age of 65 who maintain optimal cognitive functioning are less likely to have poor social networks. The study sample was selected from Maryland, Minnesota, Oregon, and Pennsylvania. Baseline assessments were conducted from 1986-1987. Follow-up assessments were completed at 6, 8, 10, and 15 year intervals. Investigators found that the social network is one of the strongest predictors of optimal cognitive function in the sample (Barnes, et al., 2007). Individuals with small social networks are also more likely to demonstrate greater cognitive decline than individuals with larger

social networks (Middleton & Yaffe, 2010; Arbuckle, Gold, & Andres as cited in Seeman, et al., 2001).

Frequency of Contact and Geographic Proximity

Previous research has shown that individuals who have more contact with their social networks demonstrate better cognitive functioning (Holtzman, et al., 2004; Zunzunegui, et al., 2003). Better cognitive functioning was even found among individuals whose frequent contact is more demanding or involves interpersonal conflict (Seeman, et al., 2001). A longitudinal study was conducted in Leganés, Spain with community-dwelling adults 65 years of age and older. Baseline interviews and examinations were conducted in 1993 with follow-up assessments in 1997. This resulted in a sample size of 964 participants included in the analysis. It was found that people who see their families more frequently have a lower probability of demonstrating cognitive decline (Zunzunegui, et al., 2003).

Cornwell and Waite (2009) suggest that situational factors are significantly related to frequency of contact. Port and colleagues (2001) interviewed 1,441 significant others of nursing home residents as part of the Maryland Long-Term Care Project (LTCP). The sample was taken from a representative sample of nursing homes in Maryland. The study examined factors that are related to the frequency of contact residents have with individuals from their social network after being admitted to a nursing home. Researchers found a positive correlation between geographic proximity and frequency of contact. Residents who have friends or relatives that live within an hour's drive of the nursing home have more frequent contact with members of their social

network than residents who do not have someone who lives within an hour's drive (Port, et al., 2001). Stoller, Foster, and Duniho (1992) conducted in person interviews with 753 community dwelling adults 65 years of age and older living in upstate New York. They found children of respondents who live in close geographic proximity to be more likely to be included in their parents' helping network and to provide instrumental support. Geographic proximity of family and friends is related to frequency of contact in the literature (Greenwell & Bengtson, 1997).

Social Engagement

Engagement in social activities is another aspect of the social environment that has been found to be related to cognitive functioning. Participation in sports, cultural activities, and club membership are some examples of social activities that have been examined in prior research (Seidler, et al., 2003). Social engagement expands upon formal social activity and is described as "getting together with friends, attending social functions, participating in occupational or social roles, group recreation, [and] church attendance" (Berkman, et al., 2000, p. 849). A pattern of social disengagement is associated with cognitive decline (Bassuk, et al., 1999; Middleton & Yaffe, 2010), while social engagement is associated with better cognitive health (Alzheimer's Association, 2012; Middleton & Yaffe, 2010).

The Kungsholmen Project, conducted from 1987-1996, is a longitudinal clinical assessment of participants from Stockholm, Sweden. Analyses based on these data used a sample of 732 respondents. Participation in social activities was found to be associated with a lower risk of all-cause dementia among older adults. It should be noted that the

researchers included the APOE variable in their analyses and did not find it to alter the results. Participation in social activities was associated with better cognitive function among respondents with and without the APOE-e4 allele (Wang, et al., 2002). Individuals who participate more frequently in social activities (Middleton & Yaffe, 2010; Wang, et al., 2002) or who participate in sports and cultural activities have a lower risk of developing dementia, including Alzheimer's disease and vascular dementia (Seidler, et al., 2003). An examination of 964 community-dwelling adults 65 years and older from an area outside of Madrid, Spain found participation in more social activities to serve a protective role against cognitive decline (Zunzungeui, et al., 2003). It may be that social activities help individuals sustain a positive self-concept through continuation or creation of a valued social role (Wang, et al., 2002).

Marital Status and Living Arrangement

Prior research shows a mixed relationship between marital status and living alone with dementia risk. A study of 2,881 French participants from southwest France found marital status to be a significant predictor of a later diagnosis of Alzheimer's disease or dementia. Findings revealed that respondents who have never been married are at significantly greater risk of developing either Alzheimer's disease or another type of dementia (Helmer, et al., 1999). One study examined the relationship of marital status and living arrangement among Taiwanese residents 65 years of age and older. In-person interviews were conducted with 4,989 respondents. They found that married respondents have a lower risk of all-cause dementia than respondents who are not married, although living alone does not have a significant relationship to cognition (Yeh & Liu, 2003). A

study using the Kungsholman Project data examined the relationship of marital status and living arrangement to risk of all-cause dementia. Researchers found that individuals who live alone and those who are unmarried are at greatest risk of developing dementia (Fratiglioni, et al., 2000).

The characteristics of the social network are found to vary by marital status as well. One study used the MacArthur Studies of Successful Aging data to examine the social network and cognition. Participants were recruited from samples in North Carolina, Massachusetts, and Connecticut. The sample was restricted to individuals 70-79 years of age. Baseline assessments were conducted from 1988-1989 and follow-up assessments were conducted in 1991 and 1996. Using these data, Seeman and colleagues found the size of the social network to differ for men and women based on marital status. Married men were found to have larger social networks, whereas married women have smaller social networks (Seeman, et al., 2001). Another study found women who have friends and men who spend time with their children are less likely to decline cognitively (Zunzunegui, et al., 2003). Married women report less emotional support, although married men report more instrumental and emotional support. This emotional support is found to predict better cognitive function (Seeman, et al., 2001).

Perceived Isolation

Perceived isolation considers the subjective nature of the social environment and examines how isolated individuals feel. This includes feeling lonely or perceptions of social support (Cacioppo, Hawkley, Norman, and Berntson, 2011; Cornwell & Waite, 2009). There are different types of social support. These include instrumental support,

emotional support, appraisal support, and informational support. Instrumental support includes assistance with tangible needs, such as transportation and grocery shopping. Emotional support refers to feeling loved and cared for, while appraisal support refers to receiving feedback and assistance with making decisions. Informational support is associated with getting advice. Research has demonstrated that individuals who know social support is available to them, even if they do not use it, have decreased levels of stress (Berkman, et al., 2000). Given the difference between objective aspects of social isolation and subjective experiences of it, Cornwell and Waite (2009) make a distinction based upon the premise that individuals could be considered socially connected yet feel socially isolated or appear socially disconnected yet not experience feelings of isolation.

This was found to be the case among 274 older adults in Tasmania. Although older respondents have smaller social networks than younger individuals, they report greater satisfaction with their social networks. Women also demonstrate increased attachment with age (Henderson, et al., 1986). Another study examined the difference between feelings of loneliness and objective measures of social isolation in relation to incidence of all-cause dementia. The study analyzed this relationship in 2,173 community-dwelling older adults in the Netherlands over a 3 year period. Findings indicate that feelings of loneliness are associated with an increased incidence of dementia. However, social isolation (living alone, not married, and not receiving social support) was not found to be a risk factor for dementia (Holwerda, et al., 2012).

It has been suggested that loneliness is related to cognitive processing (Cacioppo and Hawkley, 2009). Respondents who are lonely process events differently than individuals who are not lonely. Lonely individuals tend to have a stronger response to

negative social situations or negative stimuli and to derive less pleasure from positive social interactions. They remember more negative past events and are more likely to interpret a social situation with a negative bias. Respondents who report being lonely experience negative physiological effects such as high blood pressure, an increase in cortisol levels (high cortisol levels are associated with higher stress levels), and poorer executive functioning as well as decreases in the expression of genes that regulate glucocorticoid functioning (which is associated with decreasing stress levels and inflammation) (Cacioppo and Hawkley, 2009; Cacioppo, et al., 2011; Hawkley and Cacioppo, 2010). Loneliness is associated with poorer physical and mental health. Disrupted sleep patterns and poor health behaviors are often reported by individuals who are lonely. Loneliness is associated with depression and more significantly predicts depressive symptomatology than depression predicts loneliness. It is also associated with cognitive decline, dementia and Alzheimer's disease (Hawkley and Cacioppo, 2010) as well as an increased risk of morbidity (Cacioppo and Hawkley, 2009; Cacioppo, et al., 2011; Hawkley and Cacioppo, 2010).

While loneliness is defined as the discrepancy between one's desired level of social contact and one's actual level of contact (Hawkley and Cacioppo as cited in Hawthorne, 2008), perceived social isolation is described as the absence of social support and feeling a lack of social support (Hawthorne, 2008). A study of 3,015 Australian participants reported prevalence rates in this population. It was found that 16% of respondents felt socially isolated. The study was conducted across age groups and found that younger respondents (15-30 years) report higher rates of perceived social isolation than older adults (60 years and older). Perceived isolation varies by marital status, with

respondents who are married or in relationships reporting less isolation. Respondents with more health conditions also report being more socially isolated (Hawthorne, 2008). Face-to-face interviews were conducted with 34,653 individuals as part of the National Epidemiological Survey on Alcohol and Related Conditions. Respondents ranged in age from 21 years to 99 years and were asked to report about their perceptions of interpersonal social support. It was found that respondents who report lower perceived social support have higher rates of mental illness, such as major depression and anxiety, as well as more reported health issues (Moak and Agrawal, 2010).

Findings from previous research have yielded mixed results about the relationship of perceived isolation to cognitive function. Yeh and Liu (2003) reported the results of 4,989 in-person interviews with Taiwanese adults aged 65 years and older. Cognitive function was measured using the 10-item Short Portable Mental Status Questionnaire (SPMSQ). They found that respondents who perceive having social support available to them demonstrate significantly better cognitive function than respondents who do not perceive this support to be available. However, they found no significant relationship between feeling lonely and cognition (Yeh & Liu, 2003). The Rush Memory and Aging Project served as a pool to recruit 823 older adults from the Chicago area to examine the relationship of perceived isolation to incident Alzheimer's dementia. Participants underwent rigorous evaluations of cognitive status and completed a modified version of the de Jong-Gierveld Loneliness Scale to measure feelings of loneliness. Follow-up data were collected for 791 of the 823 participants over an almost six-year period. Researchers found that respondents who report feeling lonely have more than twice the risk of developing Alzheimer's disease than individuals who do not report feeling lonely. They

suggest additional physiological mechanisms associated with loneliness that may place individuals who report feeling lonely at greater risk of cognitive decline. These mechanisms may also account for the more rapid cognitive decline observed among respondents who are lonely (Wilson, et al., 2007).

Reciprocity

Under the premise of equity theory, Jung (1990) discusses the role of reciprocity in social relationships. Equity theory suggests that relationships are strengthened by an even exchange of resources rather than an inequitable giving or receiving of support. Studies have demonstrated that respondents prefer and experience greater benefit from reciprocal relationships (Rook as cited in Jung, 1990) and even avoid situations that would create inequitable exchanges of support (Nadler, Mayseless, Peri, & Chemerinski as cited in Jung, 1990). Reduced anxiety levels (Griffith as cited in Jung, 1990) and greater well-being (Maton as cited in Jung, 1990) have been found among individuals engaged in reciprocal relationships. Berkman and colleagues (2000) include reciprocity in their discussion of social network characteristics. They define reciprocity as "the extent to which exchanges or transactions are even or reciprocal" (Berkman, et al., 2000, p. 848).

The timeframes in which reciprocity is repaid can vary. Support may be provided by one party initially, with the understanding that need may determine when support is reciprocated (Phan, Blumer, & Demaiter, 2009; Schwarz, Trommsdorff, Zheng, & Shi, 2010). Children may provide instrumental or emotional support to aging parents years after having received support from parents (Schwarz, et al., 2010; Plickert, Cote, &

Wellman, 2007). Reciprocal relationships are not purely dyadic either. Individuals who receive greater amounts of support often feel more obligated, or inclined, to provide greater amounts of support in return. If this cannot be provided to the individual who directly provided the support, then respondents often indicate a desire to help someone else (Williams as cited in Hamilton & Sandelowski, 2003). A qualitative study of 28 African American cancer patients explored this triadic exchange of support. Researchers found that network members who receive support often provide support to other network members who may not have been the ones who provided the initial support to the patient. Thus, reciprocity and support can work as a type of social support bank among network members. Members make deposits and withdrawals of social support, but not necessarily to or from the individuals directly involved in the provision of support (Hamilton & Sandelowski, 2003).

Offer (2012) suggests that income status is related to one's ability or willingness to engage in reciprocal relationships. Low-income individuals have fewer resources which limits their ability to participate in reciprocal exchanges in social networks (Offer, 2012; Phan, et al., 2009). Since many individuals strive to maintain reciprocity in their relationships, he found that people are either excluded or withdraw from social networks in order to maintain reciprocity. Network members often exclude a member who is considered to be too great a strain on already scant resources. Individuals themselves choose not to engage in or draw support from social networks if they view themselves as unable to provide an equivalent amount of support in return. People also withdraw from, or do not draw on, social networks if they think network members will judge or criticize

them. In turn, network members exclude individuals who are not considered socially desirable and who they think will negatively affect their own reputations (Offer, 2012).

The nature of the exchange is associated with psychological well-being. Negative exchanges are found to have a more deleterious effect on psychological well-being than the benefits derived from positive exchanges. The individual's perception of the support also plays a role. For example, some people may consider receiving some type of instrumental support as a weakness and view it negatively (Newsom, Rook, Nishishiba, Sorkin, & Mahan, 2005). Researchers in the Netherlands conducted a study of 106 cancer patients and their significant others. They examined the correlation of equity in the relationship to feelings of depression. They found that partners who view the relationship as inequitable are more prone to depression. Cancer patients who feel that they receive more than they are able to give are more likely to be depressed. However, caregivers who feel they give more than they receive are also at greater risk of being depressed (Ybema, Kuijer, Buunk, DeJong, & Sanderman, 2001).

Other Factors

This study's primary focus is on the relationship of the social environment and genetic predisposition to dementia development. Previous research has examined other aspects of health and demographic characteristics in relation to dementia development. This section provides a brief overview of the variables that are included as covariates in this study. Health factors include cognitive score at baseline, depressive symptomatology, comorbidity, and physical activity. Demographic characteristics are gender, age,

education, and race/ethnicity. A brief discussion about early life factors that may be related to later dementia development is also included.

Health Factors

Previous research has found symptoms of cognitive decline to be present years before a diagnosis of dementia or Alzheimer's disease is obtained (Panza, et al., 2005). Cognitive score at baseline is often predictive of later cognitive function. Individuals that have lower cognitive scores at baseline are often later diagnosed with dementia or found to have lower cognitive functioning (Barnes, et al., 2007; Wang, et al., 2002). However, cognitive difficulty is not always predictive of later dementia development. Previous research has found individuals that experience cognitive difficulty, or even MCI, do not always progress to dementia or Alzheimer's disease in follow-up assessments (Landau, et al., 2010; Panza, et al., 2005).

Depressive symptomatology has been found to be predictive of being diagnosed with all-cause dementia (Wang, et al., 2002). Men who are depressed are more likely to exhibit cognitive decline than those who are not depressed (Zunzunegui, et al., 2003), while women who demonstrate optimal cognitive function are less likely to be depressed (Barnes, et al., 2007). Depression is identified as one of the common risk factors for dementia (Read, et al., 2008). It has been identified as both a risk factor for dementia and a prodromal symptom of Alzheimer's disease (Holwerda, et al., 2012). It may be that depressive symptomatology throughout the life span is a risk factor for dementia, while late life depression may be a prodromal symptom of Alzheimer's disease specifically (Barnes, et al., 2012). A seventeen year longitudinal study, using a sample of 949 older

adults from the Framingham Heart Study, found depression to be associated with an increased risk of dementia and Alzheimer's disease (Saczynski, et al., 2010). Depression is identified as the most common neuropsychiatric symptom among respondents from the ADAMS study who have CIND or mild dementia (Okura, et al., 2010). Although previous research has found more women to report depressive symptomatology, an examination of the ADAMS sample found a similar proportion of men and women to report depressive symptomatology (Steffens, Fisher, Langa, Potter, & Plassman, 2009). Depression may also serve an indirect role in dementia development. Individuals who are depressed may be less socially engaged than those who are not depressed (Saczynski, et al. as cited in Saczynski, et al., 2010). Higher levels of cortisol are also found in depressed individuals as well as those demonstrating cognitive decline (Fratiglioni, et al., 2004).

Being in poorer health is associated with having fewer social connections (Bassuk, et al., 1999), while having more comorbidity at baseline is found to correlate with later dementia development (Wang, et al., 2002). Women who have fewer medical conditions, such as diabetes and high blood pressure, are more likely to maintain optimal cognitive function (Barnes, et al., 2007). Vascular conditions and diabetes are associated with an increased risk of vascular dementia and Alzheimer's disease (de la Torre, 2004). Previous research has demonstrated that some of the risk factors for vascular dementia and Alzheimer's disease are similar, particularly those pertaining to vascular disease (de la Torre, 2004; Middleton & Yaffe, 2010). Autopsy reports have found that 24% to 28% of Alzheimer's disease cases have vascular pathology. Another study found correlations as high as 45% of Alzheimer's cases with vascular pathology (Langa, et al., 2004).

Decreased cerebral blood flow (hypoperfusion) has been identified as a risk factor for both Alzheimer's disease and vascular dementia. Individuals with atherosclerosis have three times the risk of developing Alzheimer's disease as well as vascular dementia. Stroke and other cerebrovascular pathologies have been associated with an increased risk of vascular dementia and the expression of disease symptoms in individuals with Alzheimer's disease (de la Torre, 2004). High blood pressure, cardiovascular disease, and stroke were found to be risk factors for progression from MCI to Alzheimer's disease and vascular dementia (Artero, et al., 2008).

Middleton and Yaffe (2010) reviewed the literature and found that high blood pressure is the most common vascular condition associated with an increased risk of vascular dementia as well as Alzheimer's disease. While it may be expected that vascular disease would be a risk factor for vascular dementia, it has been suggested that the increased risk of Alzheimer's disease and cardiovascular disease associated with the APOE-e4 allele may contribute to the correlation between vascular disease and Alzheimer's disease risk (Langa, et al., 2004; Myers, et al., 1996). It has been suggested that an insufficient blood supply may contribute to the formation of the plaques and tangles found in Alzheimer's disease (Langa, et al., 2004).

Diabetes has been associated with faster cognitive decline and to be a risk factor for dementia. A review of the literature found that the risk of vascular dementia associated with diabetes was stronger than with Alzheimer's disease. Although, diabetics with Alzheimer's disease were found to decline more slowly after diagnosis than individuals without diabetes. It was suggested that diabetes may have contributed to an earlier manifestation of Alzheimer's disease symptoms with less severe pathology, thus

resulting in an earlier diagnosis and slower disease progression after diagnosis (Middleton & Yaffe, 2010).

The literature shows that physical activity is associated with a lower risk of dementia (Larson, et al., 2006), especially vascular dementia and Alzheimer's disease (Rivaglia, et al. as cited in Middleton & Yaffe, 2010; Rockwood & Middleton as cited in Middleton & Yaffe, 2010). It is also associated with better cognitive function and has been found to lessen cognitive decline among older adults (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees as cited in Middleton & Yaffe, 2010; Colcombe & Kramer as cited in Middleton & Yaffe; Heyn as cited in Middleton & Yaffe, 2010). One study found women who are physically active to be more likely to maintain optimal cognitive function (Barnes, et al., 2007). Examination of transgenic mice found exercise to be associated with a reduction in memory difficulty, hippocampal damage, and an increase in neuroplasticity (Pietropaolo, Sun, Li, et al. as cited in Flicker, 2009). Physical activity serves a protective role in individuals who have been active from earlier in life as well as those who become active later in life (Middleton & Yaffe, 2010). However, it is unclear whether individuals with the APOE-e4 allele derive the benefits associated with physical activity on cognitive functioning. One study did not find exercise to be associated with a lower risk of incident all cause dementia among individuals with the e4 allele (Podewils, et al., 2005), although the benefits of exercise were consistent among individuals with Alzheimer's disease (Rivaglia, et al. as cited in Middleton & Yaffe, 2010; Rockwood & Middleton as cited in Middleton & Yaffe, 2010).

Demographic Characteristics

Gender differences in the social environment and cognitive decline have been identified in the literature. Married women have smaller social networks than men (Seeman, et al., 2001). Women who have friends are less likely to show cognitive decline (Zunzunegui, et al., 2003) and derive a greater benefit from having friends than their male counterparts (Beland, Zunzunegui, Alvarado, Otero, & del Ser, 2005). Women over 75 years of age have more comorbidities, such as high blood pressure and diabetes, than men (Azad, et al., 2007). These conditions have been shown to be related to Alzheimer's disease and vascular dementia (Middleton & Yaffe, 2010). The relationship of the APOE-e4 allele to risk of Alzheimer's disease has also been found to be sensitive to differences in gender. Women who have the e4 allele are at greater risk of developing Alzheimer's disease (Bekris, et al., 2010) and have greater hippocampal damage and memory related issues than their male counterparts (Azad, et al., 2007). Women's greater risk of developing dementia is consistent across the age spectrum (Azad, et al., 2007; Fratiglioni, et al., 1997). The risk factors for developing dementia (defined as Alzheimer's disease, vascular dementia, Lewy Body, and all other types of dementia) differ between men and women who have MCI. The APOE-e4 allele, stroke, and low education are the biggest risk factors identified for men while the primary risk factors for women are a loss of function in independent activities of daily living (IADLs), the APOE-e4 allele, and low education (Artero, et al., 2008). One study did find gender differences in the relationship of low education and smoking status to Alzheimer's disease risk. Women with low education had a greater risk of Alzheimer's disease than men, while men who smoked were at greater risk of developing Alzheimer's disease than women smokers (Launer, et

al., 1999). It has been suggested that the gender differences in risk of Alzheimer's disease may be due to greater survivorship of women into older ages, behavioral differences (Launer, et al., 1999), and biological factors (Goodman, Bruce, Cheng, & Mattson as cited in Launer, et al., 1999). It should be noted that not all studies have found significant gender differences in rates of dementia (Corrada et al. as cited in Katz, et al., 2012; Fitzpatrick, et al. as cited in Katz, et al., 2012; Jorm and Jolley as cited in Katz, et al., 2012; Katz, et al., 2012), although gender differences in the rate of Alzheimer's disease have been more consistent (Fitzpatrick, et al. as cited in Katz, et al., 2012; Jorm and Jolley as cited in Katz, et al., 2012; Kukull, et al. as cited in Katz, et al., 2012; Launer, et al. as cited in Katz, et al., 2012).

Older age is associated with dementia development and reduced cognitive function (Holtzman, et al., 2004; Wang, et al., 2002). Being on the younger side of the age range is associated with a greater likelihood of maintaining optimal cognitive function among women 65 years of age and older (Barnes, et al., 2007). The incidence of vascular dementia, mixed dementia and Alzheimer's disease steadily increases with age, even among those in the oldest age categories (Fratiglioni, et al., 1997; Launer, et al., 1999). Although the rate of increase in all cause dementia incidence is not as high after 75 years of age, there is still an increase in the rate of dementia observed among individuals in this age range (Launer, et al., 1999). Age was found to predict the transition from MCI to all types of dementia for both men and women (Artero, et al., 2008) and to be predictive of later all-cause dementia development in a 20 year longitudinal study (Kivipelto, et al., 2006).

Education is related to cognitive function. Individuals with more education have a lower risk of cognitive decline (Holtzman, et al., 2004; Seeman, et al., 2005) and are more likely to maintain optimal cognitive function (Barnes, et al., 2007). Less education is associated with fewer social connections (Bassuk, et al., 1999) and an increased risk of conversion from MCI to Alzheimer's disease and non-Alzheimer's dementias (Artero, et al., 2008). Low education is predictive of later all-cause dementia development in a 20 year longitudinal study (Kivipelto, et al., 2006). One study found an inverse relationship between Alzheimer's disease risk and years of education among women only. The reasons for the relationship between education and Alzheimer's disease have been mixed (Launer, et al., 1999). It may be that the increased risk of Alzheimer's disease associated with low education is reflective of socioeconomic factors or a bias towards more educated individuals because they would perform better on cognitive tests (Mortimer & Graves as cited in Launer, et al., 1999). It may also be that individuals' self-assessment of educational performance plays a role. A preliminary study of the ADAMS sample found individuals who report "below average" academic performance to be at greater risk of being diagnosed with Alzheimer's disease (Mehta, et al., 2009). Education may also be reflective of cognitive reserve, with more educated individuals having a higher level of cognitive reserve (Richards & Deary as cited in Mehta, et al., 2009; Stern as cited in Mehta, et al., 2009). Cognitive reserve suggests that some individuals have developed adaptive cognitive processing strategies to compensate for damage in the brain that may have occurred. This greater coping ability allows for the delay of disease symptomatology compared to someone with a less adaptive cognitive processing strategy (Stern, 2009).

Holtzman and colleagues (2004) found race to be significantly associated with maintenance of cognitive function. Being White versus being non-White is positively associated with maintaining cognitive function. Some studies have found a higher prevalence and incidence of dementia among Blacks compared to Whites (Demirovic, et al. as cited in Katz, et al., 2012; Gurland, et al. as cited in Katz, et al., 2012; Tang, et al. as cited in Katz, et al., 2012), although one study found no racial/ethnic differences in prevalence of non-Alzheimer's dementia or Alzheimer's disease (Katz, et al., 2012). Black respondents are at greater risk of nonamnestic MCI than their White counterparts. However, there is no difference in prevalence rates of amnestic MCI between Black and White respondents over the age of 80 years (Katz, et al., 2012). Barnes and colleagues (2004) found frequent social engagement to be more strongly associated with less decline in cognitive function among White respondents than Black respondents.

Ofstedal and Herzog (as cited in Ofstedal, Fisher, & Herzog, 2005) found significant racial differences in cognitive status scores. White respondents had higher scores on cognitive measures than their Black counterparts. Although these racial differences were found, it is difficult to clearly determine which differences may be attributable to race and which may be due to educational or other socioeconomic disparities. Previous research has found education, age, and other factors to minimize the difference in incidence of dementia and Alzheimer's disease between Black and White respondents (Fillenbaum, et al. as cited in Katz, et al., 2012; Fitzpatrick, et al. as cited in Katz, et al., 2012). Cognitive tests have also been found to have a cultural bias, thus often resulting in cognitively intact Black participants being identified as demented. It was suggested that "test-wiseness" may contribute to the disparity found in cognitive scores

rather than true differences in ability (Manly, Jacobs, Touradji, Small, & Stern, 2002). White respondents may be more adept at using the format of the test (Scruggs & Lifson as cited in Manly, et al., 2002) or gleaning from the context the correct answer than Black respondents (Borrello & Thompson as cited in Manly, et al., 2002), which would reflect an artificial discrepancy in test scores. Quality of education has been found to play a role in cognitive test scores as well. Older Black respondents were matched with White respondents on educational level and were administered cognitive tests. Results demonstrated lower scores for Black respondents. However, further analysis could attribute these findings to discrepancies in quality of education. For example, Black respondents who had gone through segregation in the South were not provided equivalent educational facilities and often had to work in order to help support their families. This resulted in significant disparities in quality of education despite an equivalent number of years of education (Manly, et al., 2002).

Prevalence rates of the APOE-e4 allele differ by race as well. Individuals of African ancestry have higher prevalence rates of the APOE-e4 allele than individuals of European decent (Evans, et al. as cited in Teruel, et al., 2011; Hendrie, et al. as cited in Teruel, et al., 2011; Hendrie, et al. as cited in Teruel, et al., 2011; Tang, et al. as cited in Teruel, et al., 2011), thus African ancestry may be associated with an increased risk of dementia (Teruel, et al., 2011). However, previous research has found that respondents of African ancestry living in Nigeria and the United States differ in the association of the APOE-e4 allele to the development of Alzheimer's disease. Prevalence rates of the APOE-e4 allele are similar between the groups, but the association of the e4 allele to Alzheimer's disease is much lower among those living in Nigeria. It has been suggested

that this may be related to the lower rate of vascular disease in the Nigerian sample (Hendrie, et al., 1995; Hendrie, et al., 2001). Environmental factors, such as diet, (Sepehrnia, et al. as cited in Hendrie, et al., 1995) may contribute to the lower prevalence of vascular disease observed in the Nigerian sample (Hendrie, et al., 1995), which has been identified as a risk factor for Alzheimer's disease (de la Torre, 2004; Middleton & Yaffe, 2010). It may also suggest a deleterious influence of Western culture and diet on individuals with the e4 allele. Since the APOE-e4 allele has been associated with cholesterol absorption, this increased absorption may prove beneficial in environments where low cholesterol absorption is a risk. Conversely, in environments where high cholesterol is a risk, the e4 allele may instead prove detrimental (Corbo & Scacchi, 1999).

Early Life Factors

It has been suggested that early life factors, such as childhood socioeconomic status (SES) or childhood health, may have a relationship to later cognitive function. One study of eastern Finnish men (n=496) found that respondents whose parents were the least educated and employed in low skill occupations have the lowest cognitive functioning. Father's occupation and mother's educational attainment maintained significance when examined independently on three out of five separate cognitive measures (Kaplan, Turrell, Everson, Helkala, & Salonen, 2001). In a representative sample of Seattle, Washington residents (n=377 controls; n=393 with Alzheimer's disease), father's occupation was significantly related to risk of Alzheimer's disease. Respondents whose fathers worked as unskilled laborers are at significantly greater risk of being diagnosed with Alzheimer's disease (Moceri, et al., 2001). Another study

examined childhood SES in relation to incidence of Alzheimer's disease among a sample of 859 clergymen. Measures of childhood SES that were used in the study were mean years of education for both parents, father's occupation, and number of children in the household. They found childhood SES to be associated with later cognitive function, but no relationship to incidence of Alzheimer's disease or rate of cognitive decline (Wilson, et al., 2005). A study using the ADAMS sample found that respondents whose mothers had less than an eighth grade education had greater odds of being diagnosed with CIND or dementia (Rogers, et al., 2009).

Some aspects of early life health have been examined as potential risk factors for the development of Alzheimer's disease. Borenstein, Copenhaver, and Mortimer (2006) examined the literature and found that low birth weight was found to have a strong relationship to cognitive functioning at age 8, however, no direct relationship could be drawn with later life cognition. Early life brain development was found to be associated with cognitive reserve. Chromosomal abnormalities, such as those associated with Down's syndrome, were identified as a risk factor for Alzheimer's disease. They also suggest other genetic factors, such as the APOE-e4 allele, as an early life risk factor for Alzheimer's disease (Borenstein, et al., 2006), which is one of the main variables of interest in this study.

In sum, demographic characteristics, health, and even early life events have been found to be potential risk factors for cognitive decline, dementia, and Alzheimer's disease. The literature demonstrates a strong relationship between the APOE-e4 allele and the risk of Alzheimer's disease and other types of dementia. However, not all individuals with the e4 allele demonstrate symptoms of Alzheimer's dementia. The social environment has

also been associated with an increased risk of dementia and Alzheimer's disease. Given these findings, it is a query of this study to investigate whether the risk of Alzheimer's disease associated with the APOE-e4 allele might be moderated by the social environment to either increase or decrease the likelihood of disease symptom manifestation.

CHAPTER 3

CONCEPTUAL FRAMEWORK

This chapter discusses the conceptual framework underlying the research questions that are explored in this study. It briefly reviews the relationship of the APOE-e4 allele and the social environment to dementia risk. The relationship between genetic predisposition and the environment to disease manifestation is then discussed. Next, the physiological mechanisms that connect the APOE-e4 allele and the social environment to the hippocampus and how these relate to cognitive functioning are presented. Last, the research questions that are examined in this study are listed.

APOE-e4 Allele

A well known risk factor for developing late-onset Alzheimer's disease is the APOE-e4 allele (Bekris, et al., 2010; Carchaga, et al., 2012). It plays a role in cholesterol transport in the brain, which is related to the growth, repair, and maintenance of neurons (Poirier, et al., 1993). The e4 allele is associated with the hallmark plaques and tangles of Alzheimer's disease (Kobayashi, et al., 2011; Poirier, et al, 1993; Soininen & Riekkinen, 1996) and has been identified as a risk factor not only for Alzheimer's disease (Alzheimer's Association, 2012; Kobayashi, et al., 2011; Landau, et al., 2010), but for non-Alzheimer's dementia and cerebrovascular disease as well (Borenstein, et al., 2010;

Myers, et al., 1996). Although most individuals with the APOE-e4 allele do not have Alzheimer's disease, most individuals with Alzheimer's disease do have the allele (Myers, et al, 1996). This suggests an environmental influence on the manifestation of disease symptoms (Bekris, et al., 2010).

Social Environment

A strong social environment is associated with better cognitive health. Having a larger social network (Holtzman, et al., 2004; Middleton & Yaffe, 2010) and being more socially engaged (Alzheimer's Association, 2012; Middleton & Yaffe, 2010) are associated with better cognitive functioning. However, a poor social network (Fratiglioni, et al., 2000) and being socially disengaged are associated with an increased risk of dementia (Bassuk, et al., 1999; Middleton & Yaffe, 2010). Loneliness is associated with deleterious physiological changes such as high blood pressure, an increase in cortical levels, and poor executive functioning (Cacioppo and Hawkley, 2009; Cacioppo, et al., 2011; Hawkley and Cacioppo, 2010). Loneliness has also been found to predict depression and is associated with an increased risk of dementia and Alzheimer's disease (Hawkley and Cacioppo, 2010; Wilson, et al., 2007). However, not all studies have found a significant relationship between the social environment and dementia or Alzheimer's disease (Fratiglioni, et al., 2000; Holwerda, et al., 2012; Seeman, et al., 2001). These mixed findings indicate that additional factors may influence this relationship.

Gene-Environment Interaction

Studies examining disease expression in monozygotic and dizygotic twin pairs have been instrumental in examining the gene-environment relationship. If genetic predisposition alone were enough to cause disease manifestation, it would be expected that in monozygotic twin pairs, both twins would develop the disease if they possessed the gene. Analysis of the Swedish Twin Registry found higher concordance among monozygotic than dizygotic twins, although not all monozygotic twins who are genetically predisposed manifest symptoms (Gatz, et al., 2006).

Studies have found genetic predisposition in combination with environmental factors to determine disease manifestation. Both monozygotic and dizygotic twins have been found to vary in their cognitive functioning with some monozygotic twins found to be discordant for Alzheimer's disease. This variation would indicate more than just genetic influences on cognitive functioning (Brandt, et al., 1993; Breitner, et al., 1995). The National Academy of Sciences twin registry data were used to examine genetic influences on cognition. Participants were adult male veterans in the United States originally born between 1917 and 1927. Brandt and colleagues (1993) found that 30% of the variation in cognitive scores can be attributed to genetics and the environment accounts for 16%-19% of the variation. Additionally, the length of time twin pairs are discordant for a disease suggests that the individual who manifests the disease has strong environmental influences that account for this difference (Breitner, et al., 1995).

While genes may increase susceptibility to a disease, the environment may influence whether the disease is manifested. For example, in a region of Finland called North Karelia, residents are known to be genetically susceptible to familial

hypercholesterolemia and to have high rates of heart disease. Environmental and behavioral changes were implemented to combat this issue, and in spite of genetic susceptibility to coronary disease, these changes were found to inhibit manifestation of the disease among residents (Ryff & Singer, 2005).

There are studies that have begun examining the relationship between APOE-e4 and environmental factors on cognitive functioning. Some have found a significant relationship, while others have not. Using the MacArthur Successful Aging Study data, one study found a significant relationship between education, APOE-e4, and cognition. Overall, individuals with more education are less likely to demonstrate cognitive impairment at baseline. When considering this pattern in the context of APOE-e4, individuals with the APOE-e4 allele demonstrate greater declines in cognition when compared to individuals without the allele. This indicates that the protective effect of education may be diminished in individuals with the APOE-e4 allele (Seeman, et al., 2005).

A study by Caselli and colleagues also found individuals with the APOE-e4 allele to experience more rapid cognitive decline when controlling for education. The study recruited 815 cognitively normal participants ranging in age from 21 years to 97 years. Participants 21 years of age and older were recruited from 1994 through 2007 in Maricopa County Arizona. Older participants, 65 years and older, were recruited from 2000 to 2007 in Maricopa and Pima Counties, also in Arizona. Individuals with the APOE-e4 allele tended to be younger, perhaps because older individuals with the allele may not have been eligible for the study due to cognitive impairment. Carriers of the

APOE-e4 allele experienced more rapid memory loss at younger ages and visuospatial decline (Caselli, et al., 2009).

In a study using Whitehall II data, investigators examined the influence of APOE-e4 and socioeconomic status (SES) on cognitive functioning. The data included British civil servants whose baseline interview was in 1985. Phase 3 (1991-1993) and phase 5 (1997-1999) waves were used in the analysis. No relationship was found between APOE-e4 and job status, which was used as an indicator of SES (Zhao, et al., 2005). Another study examined the relationship of participation in social, mental, and productive activities with dementia risk. They found participation in these activities to be associated with a lower risk of dementia, regardless of APOE-e4 status (Wang, et al., 2002). The mixed findings from studies that examine the gene-environment relationship in dementia development indicate a need for further study.

Physiological Mechanisms

The hippocampus is associated with spatial, declarative, and contextual memory in the brain. It is part of the hypothalamic–pituitary–adrenocortical (HPA) axis which is one of the systems in the body that maintains homeostasis (McEwen, 2002). One of the hormones secreted through the activity of the HPA axis is cortisol. Cortisol is the primary hormone that has been used to study this system due to its far reaching effects in the body (Miller, Chen, & Zhou, 2007). It has a significant role in metabolism, the immune system, learning, memory, and emotion (Sapolsky, Romero, & Munck as cited in Miller, et al., 2007).

The APOE gene has been found to alter both the structure and function of the hippocampus. Young respondents who are not experiencing cognitive difficulty but who have the e4 allele demonstrate greater activation of the hippocampal area of the brain during memory-related tasks than respondents without any e4 alleles (Filippini, et al., 2009). It is suggested that this increased activation may be an indication that the hippocampal area of the brain in individuals with the e4 allele must work harder in order to accomplish the same task as similar individuals without the e4 allele (Bondi, Houston, Eyler, & Brown as cited in Filippini, et al., 2009). Hippocampal atrophy has been observed in asymptomatic individuals who have the APOE-e4 allele when compared to individuals without the e4 allele (Wishart, et al. as cited in Filippini, et al., 2009).

The HPA axis and cortisol levels are found to be susceptible to stress, which affects the body's ability to maintain homeostasis. Chronically high stress levels are associated with dysregulation of the hormonal feedback system (Miller, et al., 2007) and is associated with permanent hippocampal damage (McEwen, 2002). Miller and colleagues (2007) conducted a meta-analysis of the literature and suggest that there is an initial surge of cortisol levels when a stressor is first presented, but over time, the levels drop to below normal. Low levels of cortisol are associated with pathology and negative outcomes. Susceptibility to pathology and negative outcomes are associated with an alteration in the HPA axis, induced by both high levels of cortisol and low levels of cortisol. The effects of the dysregulation of the HPA axis are shown to vary depending upon the type of stress, the psychological response of the individual, and when the stressor took place (Miller, et al., 2007). While the physiological changes that take place in response to stress are considered to be protective in the short term, over extended

periods of time, these elevated levels of stress hormones can cause permanent damage to the hippocampus (McEwen, 2002), a permanent loss of hippocampal neurons, and hippocampal atrophy (Berkman, et al., 2000).

It has been suggested that the social environment influences an organism's physiology. Frequency of contact with the social network is associated with physiological changes. Individuals who have more positive contact with their social network are found to have lower stress levels (Fratiglioni, et al., 2004). In contrast, those who are more isolated demonstrate higher cortisol, epinephrine, and norepinephrine levels which are all considered "stress hormones" (Berkman, et al., 2000). Individuals who report being lonely also have higher cortisol levels and blood pressure. This suggests that the HPA axis, which regulates the stress hormones, is adversely affected in people who are lonely. Chronically lonely individuals demonstrate a resistance to glucocorticoid functioning, which is associated with the ability to decrease stress levels (Cacioppo and Hawkley, 2009; Cacioppo, et al., 2011; Hawkley and Cacioppo, 2010).

It is hypothesized that chronically high levels of stress are associated with more rapid physiological aging (Berkman, et al., 2000) and high levels of stress are associated with an increased risk of Alzheimer's disease (Wilson, Evan, Bienias, et al. as cited in Fratiglioni, et al., 2004). The hippocampus is one of the areas in the brain damaged by Alzheimer's disease and hippocampal atrophy is found in people with dementia (Fratiglioni, et al., 2004). Hippocampal atrophy was also recently one of the biomarkers identified by the NIA-Alzheimer's Association workgroup that reflects neuronal injury in individuals with Alzheimer's disease (Albert, et al., 2011). The combined risk of hippocampal damage associated with stress resulting from a poor social environment and

the APOE-e4 allele may put individuals with the e4 allele who do not have an adequate social environment at greater risk of manifesting symptoms of dementia or Alzheimer's disease.

Summary

Previous research suggests a combination of genetic and environmental influences in the manifestation of Alzheimer's disease symptoms (Gatz, et al., 2006). The APOE e-4 allele is associated with an increased risk of developing dementia and Alzheimer's disease (Bretsky, et al., 2003; Corder, et al., 1993; Myers, et al., 1996; Soininen & Riekkinen, 1996). While the exact mechanisms through which the APOE-e4 allele increase risk are still being examined, it has been suggested that APOE-e4 is associated with the hippocampal damage observed in individuals with Alzheimer's disease (Soininen, & Riekkinen, 1996). Individuals that are more vulnerable to Alzheimer's disease due to the APOE-e4 allele associated with hippocampal damage may be more likely to manifest symptoms if they also suffer from hippocampal damage due to the social environment.

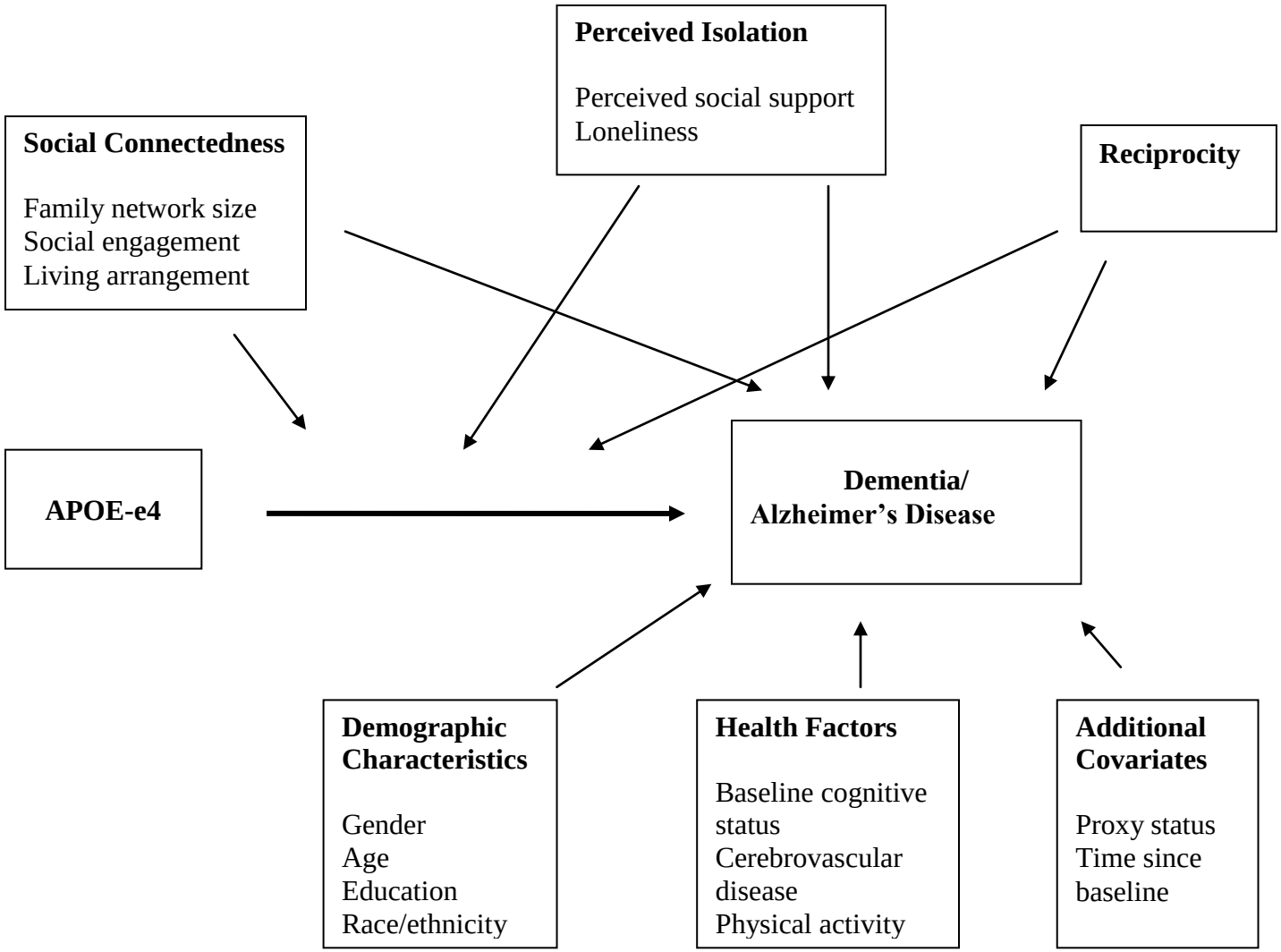
The relationship of the social environment to the APOE-e4 allele was chosen for examination in this study due to the physiological changes that are associated with the social environment. Studies suggest a relationship between the social environment and the limbic and cortical systems of the brain. These systems are also associated with memory (Bennett, Schneider, Tang, Arnold, & Wilson, 2006). Stress hypothesis suggests that a poor social environment can adversely affect an organism's physiology. Individuals that are more socially isolated were found to have higher levels of stress hormones

(Berkman, et al., 2000). High stress levels have been associated with an increased risk of Alzheimer's disease (Wilson, et al. as cited in Fratiglioni, et al., 2004) as well as an increase in cortisol and other stress hormone levels (Berkman, et al., 2000). The hippocampus can be damaged as a result of prolonged elevated stress levels. This area of the brain is one of the main areas damaged by Alzheimer's disease (Fratiglioni, et al., 2004).

Individuals with the APOE-e4 allele are also at greater risk for cardiovascular disease (Myers, et al., 1996). A decrease in cerebral blood flow has been found in people with Alzheimer's disease (de la Torre, 2004). It is suggested that a decrease in cerebral blood flow is a significant risk factor in the development of Alzheimer's disease (de la Torre, 2004; Scarmeas & Stern, 2004). However, when comparing socially engaged individuals with non-socially engaged individuals who have comparable levels of decreased cerebral blood flow, those who are socially engaged do not manifest symptoms as severely as individuals that are not as engaged. It is suggested that the cognitive reserve that can result from a socially engaged lifestyle may contribute to this difference in disease manifestation (Scarmeas & Stern, 2004). Cognitive reserve suggests that some people may have a more efficient system or compensatory method for storing and retrieving information which would serve to delay disease manifestation (Stern, 2006). The social environment may provide cognitive reserve in areas of the brain associated with memory, since both are located in the same regions of the brain (Bennett, et al., 2006). This reserve could serve to buffer against the manifestation of Alzheimer's disease symptoms in individuals that are predisposed to the disease (Scarmeas & Stern, 2004).

In sum, individuals with the APOE-e4 genotype may be predisposed to hippocampal damage. Individuals with a poor social environment have been found to experience higher stress levels, which is associated with hippocampal damage and a greater propensity to exhibit symptoms of Alzheimer's disease. A strong social environment has been found to abate the expression of Alzheimer's disease symptoms. Therefore, this study examines what influence the social environment may have on the relationship between genetic predisposition and cognitive diagnosis in a U.S. nationally representative sample of older adults. The conceptual framework for this study is illustrated in **Figure 1** and shows the inclusion of covariates in the model that may relate to cognitive diagnosis.

Figure 1. Conceptual Model



Research Questions

While the APOE-e4 allele has been shown to be a risk factor for developing Alzheimer's disease and dementia, not everyone with this allele develops Alzheimer's disease and dementia (Myers, et al., 1996). As stated earlier, some studies have begun to examine the relationship of the APOE-e4 allele with environmental features in the expression of dementia. A Swedish study examined social activity (such as traveling or going to the theater) in relation to dementia and the APOE-e4 allele, but did not find a significant effect. However, the sample was taken from the Swedish population in one particular area of Stockholm (Wang, et al., 2002). To this researcher's knowledge, no similar analysis has been reported with a nationally representative sample of individuals in the United States.

This study examines the gene-environment relationship on dementia development focusing on three social environment constructs: social connectedness, perceived isolation, and reciprocity. This study seeks to address the following questions:

1. What is the prevalence of the APOE allele combinations in a U.S. nationally representative sample of older adults and how do the rates generated from these data compare to rates from other study samples?
2. Do people with the APOE-e4 allele differ from individuals without it on measures of demographic characteristics, health factors, and the social environment at baseline and the time of the ADAMS data collection in a U.S. nationally representative sample of older adults?
3. Is there a relationship between the APOE-e4 allele and a diagnosis of dementia or Alzheimer's disease in a U.S. nationally representative population-based

sample? Is there a relationship between the social environment and a diagnosis of dementia or Alzheimer's disease in a U.S. nationally representative population-based sample?

4. Do characteristics of the social environment moderate the relationship of the APOE-e4 allele to cognitive diagnosis? From the perspective of examining the gene-environment relationship in dementia diagnosis, this study seeks to examine whether the genetic risks for developing Alzheimer's disease that have been associated with the APOE-e4 allele are moderated by aspects of the social environment.

CHAPTER 4

METHODOLOGY

This chapter provides an overview of the methodology that was implemented in this study. It includes a detailed description of the data that was used, the measures that were included, as well as the analytic strategies that were employed. The handling of missing data and sample weights that were included in the regression models is also discussed.

Data Description and Sample

This study examined data from the Aging, Demographics, and Memory Study (ADAMS) module of the Health and Retirement Study (HRS). The ADAMS module is a supplement to the HRS, which was sponsored by the National Institute of Aging (grant number NIA U01AG009740). The data collection was conducted jointly by Duke University and the University of Michigan (HRS, 2008). There were three waves of data collection for the ADAMS. The first wave of data was collected from 2001 to 2003 (n=856), the second wave was collected from 2006 to 2008 (n=315), and the third wave was collected from 2008 to 2009 (n=217). This study used the first wave of the ADAMS due to the substantial loss in sample size in the subsequent waves of data collection.

The data on dementia were based on detailed clinical and caregiver assessments. The assessments were collected to provide nationally representative information on the risk factors, prevalence, outcomes, and costs of dementia and cognitive impairment not demented (CIND). CIND is a broader term for the "intermediate state between normal cognitive functioning and dementia" (Plassman, et al., 2007, p. 129) and is not necessarily associated with memory loss. It refers to some type of cognitive difficulty, although not severe enough to warrant a diagnosis of dementia. Mild cognitive impairment (MCI) often refers to prodromal Alzheimer's disease and is associated with memory loss (Petersen, et al., 2009; van den Berg, Kessels, de Haan, Kappelle, & Biessels, 2005). The ADAMS study included 1,770 participants 70 years of age and older. Individuals were randomly selected for participation and assessment from either the 2000 or 2002 wave of the HRS. Both proxy respondents and self-respondents were included, with individuals who had limited cognitive functioning being over sampled. The sample included individuals with a range of cognitive abilities at baseline, from "low functioning" to "high normal." More detailed information regarding type of dementia was also collected. There were 856 initial assessments completed from this group. Researchers determined at the outset of conducting interviews that it would take two or more years to complete 856 assessments. This resulted in the initial assessments being conducted between August 2001 and December 2003 (Langa, et al., 2005).

While the majority of the diagnoses assigned at the initial assessment were considered conclusive, there were some cases where the diagnosis was uncertain. These uncertain cases included individuals who were considered borderline in their diagnosis, such as those with mild dementia, borderline normal cognition, or CIND. In a clinical

setting, these uncertain cases would not be assigned a diagnosis until later. However, since a diagnosis could not be assigned at a later time in this particular research setting, an initial diagnosis was assigned in uncertain cases. In these uncertain cases, a follow-up assessment was conducted to clarify the diagnosis. There were 252 follow-up assessments completed. The follow-up assessments were completed from November 2002 to March 2005 and a follow-up diagnosis was given (HRS, 2008).

Over half of the ADAMS sample was female (59%), with 58% of the sample over 80 years of age. The vast majority of the sample was non-Hispanic White (72%). Partly because the HRS oversampled non-Hispanic Black and Hispanic respondents, 29% of the ADAMS sample fell into one of these two groups. The ADAMS sample was comprised of three race/ethnic groups: non-Hispanic White, non-Hispanic Black, and Hispanic respondents (Heeringa, et al., 2009; Langa, et al., 2005). About half of the sample had less than a high school diploma (52%). Less than a quarter of the sample had a proxy respondent (23%). The vast majority of respondents lived in the community (Langa, et al., 2005). During participant recruitment and selection, individuals with normal cognition were divided into three groups of "high normal", "moderate normal", and "low normal" cognitive functioning. This categorization allowed for oversampling of individuals in the borderline normal cognitive group who were more likely to later be diagnosed with CIND or dementia (Heeringa, et al., 2009). This resulted in approximately one-third of the ADAMS sample falling into each of three cognitive diagnostic categories: normal cognition, CIND, and demented (Langa, et al., 2005). See **Table 4.1** for a more detailed description of the entire ADAMS sample that was assessed (n=856).

Table 4.1. ADAMS Sample Characteristics (n=856)

Characteristic	Category	Number of Cases	Percent of Cases
Age	70-79	359	42
	80-89	373	43
	90+	124	15
Sex	Male	355	41
	Female	501	59
Race/Ethnicity	Hispanic	84	10
	Non-Hispanic Black	159	19
	Non-Hispanic White	613	72
Education	<12 years	442	52
	12 years	196	23
	>12 years	218	25
Residence	Community	763	89
	Nursing home	93	11
Respondent Type	Self	657	77
	Proxy	199	23
Diagnosis	Normal	307	36
	CIND	241	28
	Mild-ambiguous	94	11.0
	Cognitive impairment secondary to vascular disease	20	2.3
	Mild cognitive impairment	4	0.5
	Depression	8	0.9
	Psychiatric disorder	2	0.2
	Mental retardation	8	0.9
	Alcohol abuse (past)	3	0.4
	Alcohol abuse (current)	3	0.4
	Stroke	34	4.0
	Other neurological conditions	10	1.2

Other medical conditions	55	6.4
Dementia	308	36
Probable Alzheimer's disease	122	14.3
Possible Alzheimer's disease	107	12.5
Probable vascular dementia	22	2.6
Possible vascular dementia	26	3.0
Parkinson's	2	0.2
Normal pressure hydrocephalus	1	0.1
Dementia of undetermined etiology	23	2.7
Frontal lobe dementia	1	0.1
Severe head trauma (with residual)	2	0.2
Alcoholic dementia	1	0.1
Probable Lewy body dementia	1	0.1

Study Sample

The ADAMS data were used in this analysis because they allow for assessment of a population-based sample of older adults from all regions of the U.S. and include information on both the APOE-e4 allele and social environment characteristics. This is an advantage of these data. Another advantage of the ADAMS data is the extensive cognitive assessment that was conducted to provide a diagnosis compared with other studies that may have used one cognitive measure or just assessed severe cognitive impairment. This detailed cognitive assessment in conjunction with information

pertaining to genetic predisposition, the social environment, and other risk characteristics contributed to the selection of these data for analysis.

Data from the ADAMS were linked back to the core HRS data to analyze and identify potential risk factors. A combination of the original data available from the HRS and cleaned versions of the HRS data provided by RAND were used in the analysis. The RAND HRS Data file is an easy to use longitudinal data set based on the HRS data. It was developed at RAND with funding from the National Institute on Aging and the Social Security Administration. The HRS data file provided by RAND has been cleaned and contains constructed variables from many of the original variables in the HRS, although the coverage is not complete. The RAND HRS data are available for all waves through 2010. The RAND Corporation also created the RAND Fat Files which are a cleaned version of the raw files for each wave of the HRS. They contain raw variables from both household level files and respondent level files that have been merged to the respondent level. The availability of some variables but not all in the RAND data is the reason that a combination of the RAND HRS Data, RAND Fat Files and original HRS data were used in this study. In addition to the ADAMS data, two waves of the HRS data were included in this analysis, the 1998 wave as baseline and the 2002 wave as follow-up, to assess changes in certain independent variables.

Baseline Sample

The 1998 wave of the HRS was used as the baseline observation due to availability of the social network variables in this wave and to allow for the largest sample size. The use of the 1998 wave as baseline allowed for a cross-sectional analysis

with lagged independent variables relative to 2002. It allowed for a greater separation in survey time of the independent variables from the dependent variable. It has been suggested that individuals may withdraw from their social environment as a result of cognitive decline, so it was considered preferable to use social environment variables that were measured prior to a cognitive diagnosis being administered. It was reasoned that the greater time difference between the 1998 wave and ADAMS wave (2000 or 2002) would help to clarify whether any observed relationship between the social environment and cognition was a result of the social environment's influence on cognition rather than the influence of cognition on the social environment, after controlling for initial cognitive status. However, it is recognized that with these data it was not possible to untangle the likely reciprocal causality that exists between cognition and social environment characteristics.

The 1998 wave was the first year that the AHEAD and HRS data were combined, and this ensured that the greatest number of individuals from the ADAMS data were present in the baseline sample. Changes in certain variables between the 1998 and the 2002 waves were also assessed. It should be noted as a limitation of the study that the sample may be biased since the healthiest individuals were the ones most likely to have survived from the 1998 sample.

Follow-Up Sample

The 2002 wave of the HRS was used as the follow-up sample in order to allow for a greater separation in survey time of the data given that the ADAMS sample was drawn from both the 2000 and 2002 waves of the HRS. A limitation of the data is attrition of the

sample from 1998 to 2002. While the data from the 1998 wave contained 779 cases, due to attrition and missing data, the 2002 sample was comprised of 700 cases. There were twenty cases that were lost between waves. Sixteen of these individuals were known to be deceased and three were presumed to have died by the 2002 wave. One respondent was still alive in the 2002 wave although no core interview was obtained. The remaining 59 cases were lost due to missing data.

Differences Between Baseline and Follow-Up

Statistically significant differences found between the 1998 and 2002 waves on demographic characteristics, health status, and the social environment are reported in this section. **Table 4.2** reports the statistically significant differences found on measures of the social environment while **Table 4.3** reports statistically significant differences on health indicators and proxy status. Variables that were not statistically significant showed little difference between waves.

There were significant differences in living arrangement from 1998 to 2002 (p=.008). Fewer respondents in the 2002 wave were married and living with someone than those who were in the 1998 wave (39.5% and 48.0% respectively). Correspondingly, there were more respondents who reported being single and living alone in 2002 than in 1998 (40.7% and 33.9% respectively). There was a sharp increase in the proportion of respondents who reported not being engaged in any activities (44.8% in 1998 vs. 61.2% in 2002; p=.000). This coincided with a decrease of approximately 7% or 8% of respondents who were engaged in one or two activities. The proportion of individuals who were engaged in three activities also decreased slightly (4.1% in 1998 vs. 3.2% in

2002). Perceived isolation significantly increased from 1998 to 2002 as well (p=.001). Approximately 9% more respondents in 2002 did not believe that they had social support available to them other than their spouse.

There were significant differences found between the samples based on proxy status (p=.000). A larger proportion of respondents in 2002 had a proxy respondent than in 1998 (23.6% and 14.9% respectively). As might be expected, there was a significant difference in respondents' age between waves (p=.000). Respondents showed a significant decline on measures of health status from baseline to follow-up at the 1% level, except for depressive symptomatology. The proportion of respondents who had low functioning, borderline, and low normal cognitive scores increased between waves (see **Table 4.3**). The number of respondents who had at least one cerebrovascular condition increased from 67.3% in 1998 to 76.7% in 2002. The proportion of respondents who were physically active declined during this period (32.6% in 1998 to 25.6% in 2002). It should be noted that it was not clear how much of the observed difference between the waves was due to an actual change in status or to selectivity due to sample survivorship.

Table 4.2. Bivariate Differences from 1998 to 2002 in the Social Environment

	1998 Wave		2002 Wave		
Variable	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Living Arrangement					
Married and living with someone	374	48.0	300	39.5	.008
Single and living alone	264	33.9	309	40.7	
Single and living with others	141	18.1	150	19.8	
Total	779	100.0	759	100.0	

Social Engagement					
No activities	349	44.8	464	61.2	
1 activity	256	32.9	186	24.5	
2 activities	142	18.2	84	11.1	.000
3 activities	32	4.1	24	3.2	
Total	779	100.0	758	100.0	
Perceived Social Support					
No one other than spouse willing to provide care	317	40.7	372	49.5	
Has someone other than spouse willing to provide care	462	59.3	379	50.5	.001
Total	779	100.0	751	100.0	

Table 4.3. Bivariate Differences from 1998 to 2002 on Proxy Status, Age, and Health Factors

	1998 Wave		2002 Wave		
Variable	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Proxy Status					
Self-respondent	663	85.1	580	76.4	.000
Proxy respondent	116	14.9	179	23.6	
Total	779	100.0	759	100.0	
Age (mean)	77.0	n/a	81.0	n/a	.000
Baseline Cognitive Status					
Low functioning	88	11.3	134	18.1	
Borderline	65	8.3	114	15.4	
Normal—low	159	20.4	177	23.9	.000
Normal—medium	195	25.0	139	18.8	
Normal—high	272	34.9	177	23.9	
Total	779	100.0	741	100.1	
Cerebrovascular Disease					
No conditions	255	32.7	177	23.3	
At least one condition	524	67.3	582	76.7	.000
Total	779	100.0	759	100.0	
Physical Activity					
Not physically active	525	67.4	565	74.4	.002

Physically active	254	32.6	194	25.6
Total	779	100.0	759	100.0

Sample Weights

The special weights that were produced for the ADAMS sample were included in the analysis. According to the HRS technical documentation, the ADAMS weights accounted for the weight given by the HRS demonstrating how representative the case was of the U.S. population and the sampling methods used to select the ADAMS sample, including non-response and post-stratification to U.S. Census population controls. The person weights provided for the ADAMS sample also account for the over-sampling of Blacks and Hispanics and for survey non-response (Heeringa, et al., 2009). The probability weight command in STATA ("pweight") was used for the sampling weights in regression analysis. This command estimates the number of observations in the population that each case represents. STATA's "robust" adjustment option was used to adjust for any potential inconsistencies, such as heteroscedasticity or non-normality, in the variation of the standard errors.

Measures

This section provides a description of the variables that were included in the analysis, their definitions, and results of preliminary analyses. Descriptive statistics and bivariate regression models were used to determine what categories to include for certain variables and to allow for comparison of proxy respondents and self-respondents on key variables. It should be noted that many of the variables that are included are self-report

measures, unless a proxy respondent was used. While this could create concern regarding the reliability of self-report among individuals with dementia, previous research has demonstrated the reliability of self-report among individuals with dementia (Hoe, Katona, Roch, & Livingston as cited in Beer, et al., 2010) and have found individuals with dementia to be able to provide reliable information about their needs and quality of life (Orrell, et al. as cited in Moyle, Murfield, Griffiths, & Venturato, 2012).

Dependent Variable

This study utilized the cognitive diagnosis given at the initial assessment that was available in the ADAMS data as the outcome variable. This variable was based on an extensive cognitive assessment performed by neuropsychology technicians trained by a Duke University neuropsychologist as well as specially trained nurses.

The ADAMS evaluation was derived from detailed clinical analyses to ascertain cognitive status. In-person interviews were conducted with participants by both a neuropsychology technician and a nurse. Informants with daily knowledge of participants were also interviewed. Neuropsychological tests were administered and a complete medical history taken. Data from the HRS self-respondent cognitive measures were included in the ADAMS assessment. A neuropsychologist accompanied all neuropsychology technicians on initial visits to ensure understanding of how to perform evaluations. In addition, the neuropsychologist reviewed all audio tapes from interviews and test data. The administering technician assigned a score to each participant which was then reviewed by a second technician before the neuropsychologist performed the final review (HRS, 2008).

Including Alzheimer's Disease (AD) as a Separate Outcome Category

Assessments resulted in three general diagnostic categories: normal cognition, cognitive impairment not demented (CIND), and demented, with thirty-one possible subcategories within these three categories (Langa, et al., 2005). All of the thirty-one diagnostic subcategories were not used. It was reasoned that there would not be an adequate number of cases in each subcategory to allow for meaningful analysis. Probable Alzheimer's disease and possible Alzheimer's disease were subcategories of the final cognitive diagnosis. These two subcategories were combined into one category, Alzheimer's disease. This combined category was included to see if the observed relationship of the social environment and APOE-e4 with cognitive diagnosis differed for individuals with Alzheimer's disease, other types of dementia, CIND, or normal cognitive function. Preliminary examination of these categories revealed that 203 respondents (or about 75%) were considered to have probable or possible Alzheimer's disease out of a total of 271 respondents diagnosed with any type of dementia.

Cross-tabulations were examined in order to determine whether a sufficient sample size was present in each cell to warrant separation of Alzheimer's disease from other types of dementia. **Table 4.4** shows that there were a total of 23 cases of respondents who had two e4 alleles. The Pearson chi-square test for independence and bivariate regression analysis were used to determine whether there was a statistically significant relationship between the variables of interest. While both the three category and dichotomous versions of the APOE variable were significantly related to cognitive diagnosis ($p=.001$ and $p=.000$ respectively), there were very few cases of non-

Alzheimer's dementia or CIND that had two e4 alleles. Most respondents with two e4 alleles had been diagnosed with Alzheimer's disease. This might be expected since the literature has demonstrated that the APOE-e4 allele is primarily a risk factor for Alzheimer's disease (Alzheimer's Association, 2012; Soininen & Riekkinen, 1996). Preliminary regression analysis compared the use of the three category and two category APOE variables. Bivariate regression results indicated that the APOE variable was significantly related to risk of Alzheimer's disease when using both versions of the variable. Regression results for models with additional covariates demonstrated similar findings when using the two category versus the three category APOE variable, showing slight variation among variables that were marginally significant (i.e., at the 10% level).

When using the four category dependent variable, cell sizes appeared adequate for most of the social variables (see **Tables 1** to **7** in **Appendix A**). Social engagement was included as a count variable and had a small cell size for respondents who reported participating in three activities and had a diagnosis of non-Alzheimer's dementia (n=1). The smallest cell size was 12 cases for the other social environment variables. Results should be interpreted with caution due to the small sample sizes.

Preliminary regression analysis compared use of the four category dependent variable with the three category dependent variable that combined non-Alzheimer's dementia with Alzheimer's disease into one category. Findings showed that when the two categories were combined, results more closely resembled the results for the Alzheimer's disease category than for non-Alzheimer's dementia. This may be due to the larger proportion of respondents who received a diagnosis of Alzheimer's disease than non-Alzheimer's dementia (n=203 and n=68 respectively). The primary exception was for the

reciprocity variable. Respondents who gave more than they received were at significantly less risk of being diagnosed with Alzheimer's disease when using the four category dependent variable. This variable was no longer significant in models that used the three category dependent variable. This may be due to the small cell size of respondents who gave more than they received when compared to those who received more than they gave or gave and received an equal amount of support (n=45, n=112, and n=114 respectively).

It was concluded that cell sizes, while small in some cases, were adequate for each of the main independent variables to warrant including Alzheimer's disease as a separate category of the dependent variable. For the purposes of this study, four diagnostic categories were included in the outcome variable: normal cognition, CIND, Alzheimer's disease, and non-Alzheimer's dementia.

Table 4.4. Bivariate Relationship of 4 Category Cognitive Diagnosis Variable with APOE Variable

	3 Category APOE Genotype							Dichotomized APOE				
Cognitive Diagnosis	No e4		One e4		Two e4		P-Value	No e4		Any e4		P-Value
	Num	Pct	Num	Pct	Num	Pct		Num	Pct	Num	Pct	
Non-Alzheimer's Dementia	48	8.5	18	9.4	2	8.7		48	8.5	20	9.3	
Alzheimer's Disease	124	22.0	67	34.9	12	52.2	.001	124	22.0	79	36.7	.000
CIND	171	30.3	45	23.4	5	21.7		171	30.3	50	23.3	
Normal Cognition	221	39.2	62	32.3	4	17.4		221	39.2	66	30.7	
Total	564	100.0	192	100.0	23	100.0		564	100.0	215	100.0	

Cognitive Diagnosis: Initial Assessment vs. Secondary Assessment

The ADAMS conducted cognitive evaluations and assigned cognitive diagnoses at two separate times for some respondents. Initial assessments were completed for 856 participants between August 2001 and December 2003. In cases where the initial diagnosis was considered less certain (CIND, mild dementia, or borderline normal cognitive status), it was determined that a longitudinal follow-up assessment would help to clarify the diagnosis. Of the 856 initial assessments that were completed in the ADAMS module, 252 diagnoses were considered uncertain and a second assessment was administered. These follow-up assessments were completed between November 2002 and March 2005 (HRS, 2008).

Preliminary analysis was conducted in order to determine whether the initial diagnosis or a combination of the initial (Time 1) and follow-up (Time 2) diagnosis should be used as the outcome variable. Out of the 779 cases included in this study, 230 cases were administered a second assessment. A combined cognitive diagnosis variable was created from the initial assessment and second assessment. This combined variable used the diagnosis given at Time 1. However, in cases where there was a change in diagnosis at Time 2, the Time 2 diagnosis was included instead. It was reasoned that since the ADAMS conducted a second evaluation in order to clarify an uncertain diagnosis from Time 1, the Time 2 diagnosis would be considered the final diagnosis. There were 78 cases that had a change in diagnosis from Time 1 to Time 2.

Bivariate results for the ADAMS cognitive diagnosis at Time 1 and Time 2 for proxy and self-respondents is reported in **Table 4.5**, as well as whether there was a

change in diagnosis. The biggest difference between the combined diagnosis and the initial diagnosis was found among those diagnosed with CIND and Alzheimer's disease. This might be expected since cases that were considered uncertain at Time 1 were those that were identified as mild dementia, CIND, or borderline normal. Since approximately 6% of the sample (or 63% of those whose diagnosis changed) received a worse diagnosis at the second assessment, it would appear that many of those who had received an initial diagnosis of CIND received a later diagnosis of Alzheimer's disease. Approximately 4% of all cases showed an improvement in cognitive functioning (37% of those whose diagnosis changed). There was not a significant relationship between a change in cognitive diagnosis and any of the social environment or APOE variables that were included as measured by the chi-square statistic.

Table 4.5. Bivariate Results Comparing Proxy and Self-Respondents on Measures of Cognitive Diagnosis

	Self-Respondents		Proxies		P-Value	Total Sample	
Variable	**Num**	**Pct**	**Num**	**Pct**		**Num**	**Pct**
Cognitive Diagnosis Time 1							
Non-Alzheimer's dementia	49	7.4	19	16.4		68	8.7
Alzheimer's disease	147	22.2	56	48.3		203	26.1
CIND	194	29.3	27	23.3	.000	221	28.4
Normal cognition	273	41.2	14	12.1		287	36.8
Total	663	100.1	116	100.1		779	100.0
Cognitive Diagnosis Time 2							
Non-Alzheimer's dementia	4	2.0	1	3.8		5	2.2
Alzheimer's disease	41	20.1	5	19.2		46	20.0
CIND	112	54.9	14	53.8		126	54.8
Normal cognition	47	23.0	6	23.1	.460	53	23.0
Total	204	100.0	26	99.9		230	100.0
Combined Cognitive Diagnosis Time 1 & Time 2							
Non-Alzheimer's dementia	48	7.2	20	17.2		68	8.7
Alzheimer's disease	172	25.9	60	51.7		232	29.8
CIND	161	24.3	22	19.0		183	23.5
Normal cognition	282	42.5	14	12.1	.000	296	38.0
Total	663	99.9	116	100.0		779	100.0
Change in Diagnosis from Time 1 to Time 2							
Diagnosis improved	25	3.8	4	3.4		29	3.7
Diagnosis worsened	41	6.2	8	6.9	.947	49	6.3
No change	597	90.0	104	89.7		701	90.0
Total	663	100.0	116	100.0		779	100.0

Bivariate logistic regression models were used to compare any differences in the direction and significance of the relationship of cognitive diagnosis at Time 1 and the combined diagnosis at Time 1 and Time 2 with each of the main effects variables. Bivariate rather than multivariate analysis was conducted in order to show the simple relationship between the variables. While results may be biased due to the exclusion of additional control variables, bivariate analysis still allows for a comparison of the use of the two diagnoses. Results demonstrate very little difference in the relationship between the two diagnoses and the main effects variables. Significance levels were different for the Time 1 and combined cognitive diagnosis variables in three instances (see **Table 4.6**). Respondents who had family networks consisting of 12 to 17 family members did not have less risk of being diagnosed with CIND at Time 1 compared to respondents who had 6 or less family members (p=.143). This relationship was significant when using the combined diagnosis variable, with respondents who had 12 to 17 family members at less risk of being diagnosed with CIND (Relative Risk Ratio (RRR)=0.39; p=.007). Being single and living with others was not a significant risk factor for being diagnosed with non-Alzheimer's dementia at Time 1 (p=.223). This relationship was significant when using the combined cognitive diagnosis variable at the 10% level, with respondents who were single and lived with others being at greater risk of being diagnosed with non-Alzheimer's dementia (RRR=2.81; p=.080). Self-respondents who reported feeling lonely were at significantly greater risk of being diagnosed with CIND at Time 1 than respondents who did not feel lonely at the 10% level (RRR=2.67; p=.056). Loneliness was no longer a risk factor when using the combined cognitive diagnosis variable (p=.116). Thus in these three instances the significance of the relationships changed, but

the direction of the relationships remained consistent. It should be noted that if using a more conservative 5% p-value, only the living arrangement variable was different between the two diagnostic variables.

Respondents who received more support than they gave were at significantly greater risk of being diagnosed with Alzheimer's disease than otherwise similar individuals who gave and received an equal amount of support at Time 1 (p=.017). This significance was retained using the combined variable only at the less conservative 10% significance level (p=.070). The other social environment and APOE-e4 variables retained the same statistical significance when using either the Time 1 or combined cognitive diagnosis variables. These findings seem to indicate consistency in the relationship of the main effects variables to cognitive diagnosis even when including cases where the diagnosis changed.

Table 4.6. Bivariate Regression Results of Social Environment at Time 1 and Combined Time 1/Time 2 Cognitive Diagnosis (n=779)

	Cognitive Impairment not Demented vs. Normal Cognition			Non-Alzheimer's Dementia vs. Normal Cognition			Alzheimer's Disease vs. Normal Cognition		
Variable	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**
Time 1 Cognitive Diagnosis									
Living Arrangement									
Married and living with someone (reference)									
Single and living alone	1.51	0.40	.125	5.36	2.05	.000	2.22	0.60	.003
Single and living with others	1.63	0.56	.159	1.74	0.79	**.223**	2.87	1.08	.005
Family Network Size									
0 to 6 family members (reference)									
7 to 11 family members	0.72	0.22	.285	0.66	0.35	.426	0.90	0.31	.761
12 to 17 family members	0.61	0.21	**.143**	0.55	0.25	.191	0.66	0.24	.240
18+ family members	0.95	0.32	.876	1.14	0.56	.798	0.91	0.34	.797
Reciprocity									

Gave and received an equal amount of support (reference)									
Received more support than gave	1.53	0.47	.170	2.70	1.13	.017	2.02	0.59	**.017**
Gave more support than received	1.05	0.29	.861	0.88	0.43	.798	0.32	0.10	.000
Feelings of Loneliness (self-respondents only; n=663)									
Felt lonely	2.73	0.79	.001	2.67	1.37	**.056**	2.07	0.71	.036
Combined Time 1 and Time 2 Cognitive Diagnosis									
Living Arrangement									
Married and living with someone (reference)									
Single and living alone	1.07	0.31	.823	6.02	2.30	.000	2.00	0.53	.010
Single and living with others	1.59	0.58	.205	2.81	1.66	**.080**	2.74	1.05	.009
Family Network Size									
0 to 6 family members (reference)									
7 to 11 family members	0.64	0.21	.169	0.82	0.43	.701	0.98	0.32	.954
12 to 17 family members	0.39	0.14	**.007**	0.49	0.23	.131	0.81	0.29	.569
18+ family members	0.70	0.25	.319	1.58	0.78	.357	1.04	0.41	.919
Reciprocity									

Gave and received an equal amount of support (reference)									
Received more support than gave	1.08	0.36	.817	3.45	1.43	.003	1.68	0.48	**.070**
Gave more support than received	0.78	0.22	.385	0.74	0.39	.567	0.41	0.15	.013
Feelings of Loneliness (self-respondents only; n=663)									
Felt lonely	2.24	0.67	.007	2.30	1.21	**.116**	2.43	0.81	.008

Note: Bold text indicates differences in significance between the Time 1 diagnosis and the combined diagnosis.

Further sensitivity analyses were conducted in order to determine whether there was a difference in the relationship between the independent variables and the original Time 1 diagnosis and the Time 1-to-Time 2 change in cognitive status diagnosis. Logistic regression was used to examine if there was a relationship between any change in cognitive diagnosis and the social environment and APOE variables. Multinomial logistic regression was used to examine the relationship between the direction of the change and the main variables (i.e., no change, cognitive diagnosis improved, cognitive diagnosis worsened). None of the regression analyses showed a statistically significant relationship between the change in cognitive diagnosis variable and the main independent variables, except in two instances. Being more socially engaged was associated with a lower risk of receiving a worse cognitive diagnosis at follow-up (RRR=0.54; p=.022). Respondents who gave more support than they received had a significantly greater chance of showing an improvement in their cognitive diagnosis when compared to similar individuals who gave and received an equal amount of support and did not have a change in cognitive diagnosis at the 10% level (RRR=3.31; p=.056).

Based on the above analyses and in order to preserve consistency in the timing of the diagnosis, the initial diagnosis was used in the remaining regression analyses. Results of the sensitivity analysis seem to indicate that there are minimal differences when using the Time 1 diagnosis versus the combined Time 1 and Time 2 diagnosis. Also a change in diagnosis was not found to be significantly related to the main effects variables in the bivariate analysis. This would seem to indicate consistency in the relationship of the variables to cognitive diagnosis regardless of which diagnosis was used. It was also reasoned that the additional time that had passed from Time 1 to Time 2 would put

respondents who had not received a second assessment at greater risk of unobserved cognitive decline. Since it would be impossible to control for this additional risk among respondents who had only received the initial diagnosis, in addition to researcher judgment and the results of sensitivity analyses, it was decided that the initial diagnosis would be used as the dependent variable.

Independent Variables

APOE-e4 Allele

Two categorical variables were created to measure the APOE-e4 allele. The three categories included in the first version of the APOE variable were no e4 alleles, one e4 allele, and two e4 alleles. The dichotomous variable measured whether a respondent had at least one APOE-e4 allele. Bivariate regression results showed that respondents with the APOE-e4 allele were at greater risk of being diagnosed with Alzheimer's disease only (p=.004; see **Table 4.7**). Respondents who had two of the e4 alleles were at greater risk of being diagnosed with Alzheimer's disease than those with one e4 allele (RRR=11.65 and p=.004; RRR=1.74 and p=.034 respectively). Post-estimation testing using the Wald test demonstrated that the three category variable of APOE was significant, thereby substantiating the differences found between categories (p=.036). When using either the two or three category variable, the APOE-e4 allele was found to be a significant risk factor for being diagnosed with Alzheimer's disease, but not CIND or another type of dementia. Given these results, the three category APOE variable was included in the regression models rather than the two category variable to allow for greater specificity and to avoid a loss of information.

Table 4.7. Bivariate Regression Results for APOE-e4 and Cognitive Diagnosis

	Cognitive Impairment not Demented vs. Normal Cognition			Non-Alzheimer's Dementia vs. Normal Cognition			Alzheimer's Disease vs. Normal Cognition		
Variable	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**
APOE-e4 (dichotomous)									
None (reference)									
One or two e4	1.25	0.35	.424	1.92	0.80	.118	2.19	0.59	.004
APOE-e4 (3 categories)									
None (reference)									
One e4	1.20	0.34	.533	1.87	0.82	.150	1.74	0.45	.034
Two e4	2.32	2.04	.339	2.91	3.03	.305	11.65	9.85	.004

Social Environment Variables

This section describes the social environment variables which, in addition to genetic predisposition which was defined as the presence of the APOE-e4 allele, were the main risk factors of interest in this study. The social environment was divided into three main constructs: social connectedness, perceived isolation, and reciprocity in the exchange of instrumental support. In order to determine which variables to include in the final regression models, preliminary bivariate regression models were estimated with each of the social environment variables and cognitive diagnosis. Based on these regression results and the objective of maximizing parsimony in the models, some of the social environment variables were modified for inclusion in the final regression models reported in Chapter 5.

A summary of these constructs, including the potential indicators for each construct, and the decision about whether the variable was included in the final regression analysis are outlined in **Table 4.8**. A detailed description of each of the variables follows the table and is organized by social construct.

Table 4.8. Social Environment Variables

Social Environment Constructs	**Variables**	**Measures Used**	**Final Status**
Social Connectedness	Family Network Size—count variable (not including spouse)	# of Children # of Grandchildren # of Siblings	Included
	Social Engagement—count variable	Volunteers Helps friends/neighbors/relatives	Included

		Works for pay	
	Living Arrangement—categorical (combination of living alone and marital status)	Married and living with others Single and living with others Single and living alone	Included
	Geographic proximity—dichotomous	Have friends close by Have relatives close by	Dropped
Perceived Isolation	Perceived Social Support—dichotomous	Social Support—has someone other than a spouse who is willing to provide care if needed	Included
	Loneliness—dichotomous	Feels lonely	Included for self-respondents only
Reciprocity	+1 for situations where respondent gave support	Gave children money Gave money to friends/relatives Cared for grandchildren	Included
	-1 for situations where respondent received support	Received money from children Received money from friends/relatives Received help with chores	

Social Connectedness

Measures of family network size, social engagement, living arrangement, and geographic proximity were used to examine social connectedness. A detailed description of the creation of these variables and the final decision about how each concept was measured, as well as whether the variable was included in the primary analysis, is

contained in this section. The results of bivariate regression models for the social connectedness variables are reported in **Table 4.9**.

The core HRS does not collect information that allows for examination of the full extent of a respondent's social network, such as quantity and quality of relationships with coworkers, neighbors, and friends. Given the limitations of the data, family network size was proposed to be included as a proxy for the size of this important part of a person's social network. Family network size was ascertained by counting the number of children, number of grandchildren, and number of siblings reported by respondents. A higher number indicated a larger social network. Family network size ranged from 0 to 82 members.

Categories were created to account for outliers in the family network size variable. Family network size was divided into four categories: 0 to 6 members, 7 to 11 members, 12 to 17 members, and 18+ members. Family network size was not found to have a significant relationship to cognitive diagnosis. A sensitivity analysis compared the use of the categorical version of the variable, a dichotomous version (comparing 0 to 6 family members versus 7+ family members), and the continuous variable. There was no statistically significant relationship found with cognitive diagnosis when estimating bivariate regression models with the continuous, dichotomous, or categorical family network size variables. To streamline the analyses, the four-category family network size variable was used in regression models to account for outliers.

Social engagement, or respondents' involvement in their social environment, was measured by participation in volunteer activities, providing unpaid help to friends/neighbors/non-resident relatives, and current work status. This was a count

variable with a value of one (1) given for each response that indicated that the respondent volunteered, provided unpaid help to friends/neighbors/non-resident relatives, or worked. The minimum value was zero (0) for individuals that did not volunteer, did not provide unpaid help, and did not work. The maximum value was three (3) for individuals that were engaged in all three activities. Results from a bivariate regression model showed that as a respondent's social engagement increased, he/she had a significantly lower risk of being diagnosed with Alzheimer's disease, non-Alzheimer's dementia, and CIND compared to normal cognition (RRR=0.31 and p=.000; RRR=0.25 and p=.000; RRR=0.57 and p=.000 respectively).

It initially had been proposed to include marital status and whether respondents lived alone in the model separately. Variance inflation factors (VIF) and tolerance levels were used to test for issues of multicollinearity bias associated with marital status and living arrangement status. Results demonstrated that there were no issues of multicollinearity between the variables. The highest VIF found was 4.16. A cross-tabulation between the two variables showed that all but one married respondent lived with someone. Based on this analysis, marital status and living alone were combined to create the living arrangement variable. These were combined into respondents who were married and lived with others, single and lived with others, as well as single and lived alone. It should be noted that cases that were classified as living with others included respondents who lived with a spouse only. Cases were coded as living alone when respondents did not have anyone else living in the household, even if they reported being married. Ten cases were identified in the HRS as married spouse absent living with others and these were coded as married and living with others. One case was identified as

married spouse absent, living in a one-person household. This case was classified as single, living alone. Bivariate regression results were used to evaluate whether there was a difference between coding respondents who were married with an absent spouse as married versus classifying these cases as single. Regression results demonstrated no difference in the relationship of living arrangement to cognitive diagnosis when respondents who were identified as married spouse absent were classified as married versus being classified as single.

Bivariate regression models showed that respondents who were single and living with others were at significantly greater risk of being diagnosed with Alzheimer's disease than respondents who were married and living with others (RRR=2.87; p=.005). Respondents who were single and lived alone had a significantly greater risk of being diagnosed with Alzheimer's disease or another type of dementia than respondents who were married (RRR=2.22 and p=.003; RRR=5.36 and p=.000 respectively). A Wald test demonstrated that the differences between categories were significant (0.000).

Geographic proximity was initially proposed for inclusion because Cornwell and Waite (2009) identified "situational factors" as being significant in determining social contact. Other studies found geographic proximity to be related to frequency of contact (Port, et al., 2001; Stoller, et al., 1992). Since frequency of contact and quality of the relationship could not be measured, it was reasoned that including geographic proximity in the model might serve as a proxy for these factors. Preliminary analysis revealed that this variable did not achieve significance in unadjusted or fully adjusted regression models. It was reasoned that geographic proximity was less important than frequency of contact. Since the variable did not have a statistically significant relationship with

cognitive diagnosis in preliminary analyses, it was not included in the final regression models. However, this variable was still used in the creation of the social connectedness index (see below).

A social connectedness index was created to improve the measurement qualities of this construct and in order to establish a more parsimonious model. A value of one (1) was assigned if the respondent lived with someone and was single or married, one (1) if the respondent had a friend or relative who lived in close proximity, and one (1) to three (3) to reflect the respondent's level of engagement. The index had a range of 0 to 5. Bivariate regression models were estimated using this index and its components. The index was found to be associated with a significantly lower risk of being diagnosed with Alzheimer's disease, non-Alzheimer's dementia, and CIND (RRR=0.40 and p=.000; RRR=0.27 and p=.000; RRR=0.60 and p=.000 respectively).

Table 4.9. Bivariate Regression Results for Social Connectedness

	Cognitive Impairment not Demented vs. Normal Cognition			Non-Alzheimer's Dementia vs. Normal Cognition			Alzheimer's Disease vs. Normal Cognition		
Variable	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**
Living Arrangement									
Married and living with someone (reference)									
Single and living alone	1.51	0.40	.125	5.36	2.05	.000	2.22	0.60	.003
Single and living with others	1.63	0.56	.159	1.74	0.79	.223	2.87	1.08	.005
Family Network Size (categorical)									
0 to 6 family members (reference)									
7 to 11 family members	0.72	0.22	.285	0.66	0.35	.426	0.90	0.31	.761
12 to 17 family members	0.61	0.21	.143	0.55	0.25	.191	0.66	0.24	.240
18+ family members	0.95	0.32	.876	1.14	0.56	.798	0.91	0.34	.797
Family Network Size (continuous)	1.00	0.01	.740	1.01	0.02	.513	1.01	0.02	.356
Geographic Proximity									
No friends or relatives live close (reference)									

At least one friend or relative lives close	0.77	0.22	.375	0.87	0.36	.738	0.77	0.25	.423
Social Engagement									
Count of social activities	0.57	0.08	.000	0.25	0.07	.000	0.31	0.06	.000
Social Connectedness Index									
Level of connectedness (0 to 5 scale)	0.60	0.08	.000	0.27	0.05	.000	0.40	0.06	.000

Perceived Isolation

Perceived availability of social support was assessed by whether respondents reported having anyone in their social network, not including a spouse, that would be willing to provide care in the future if they required it. Respondents currently receiving care from someone other than a spouse who was not an agency caregiver were identified as having social support. Answering "yes" to this question was considered a positive perception of availability of social support and assigned a value of one (1). A value of zero (0) was assigned to individuals who did not believe they had this support available to them. This variable did not achieve statistical significance in preliminary analysis, but was still included in the final regression models due to its theoretical significance (see **Table 4.10**). Perceived social support provides insight into the subjective aspects of the social environment and has been found in many studies to have a stronger relationship with health than actual receipt of support (Cacioppo, et al., 2011; Cornwell & Waite, 2009). It was found to be related to stress levels, mental illness, and cognitive function (Berkman, et al., 2000; Moak and Agrawal, 2010; Yeh and Liu, 2003).

A measure to examine reported feelings of loneliness was included to examine perceived isolation. One item in the Center for Epidemiologic Studies Depression Scale (CES-D) asks whether participants felt lonely in the previous week. Despite its limitations as a single indicator of this complex construct, this item was used to measure perceived isolation. A value of one (1) was assigned to individuals who reported feeling lonely and zero (0) to those who did not feel lonely. It should be noted that this question was not asked of proxy respondents and thus any analyses including this variable only included self-respondents. Preliminary analysis showed that self-respondents who

reported feeling lonely in 1998 were at significantly greater risk of being diagnosed with Alzheimer's disease and CIND (RRR=2.07 and p=.036; RRR=2.73 and p=.001 respectively). Self-respondents who reported being lonely were at greater risk of being diagnosed with non-Alzheimer's dementia at a p-level of 10% (RRR=2.67; p=.056).

Reciprocity

Reciprocity is considered to be an equal exchange of support in a relationship. An index was created to measure reciprocity using variables that measure various types of instrumental support that were available in the HRS. A value of +1 was given for each situation in which the respondent gave to network members; a value of -1 was given for each situation in which the respondent received from network members.

The giving of support by respondents was measured using questionnaire items that asked whether respondents gave their children money, gave money to friends or relatives, or provided care to grandchildren. If respondents answered affirmatively to any of these variables, a value of +1 was assigned; a value of zero (0) was assigned if they did not give to network members. Receiving support was measured using the variables that asked respondents if they received money from their children, received money from friends or relatives, or received assistance with chores. A value of -1 was assigned to respondents indicating a "yes" response to any of these variables. A value of zero (0) was assigned if they did not receive any support from network members. These values were then added together to create the reciprocity index. A positive value indicated that the respondent gave more than he/she received, while a negative value indicated that the respondent received more than he/she gave. A value of zero indicated an even exchange.

It should be noted that respondents who did not give or receive support were included in the category of an even exchange. The index ranged from a value of -3 to +3. Preliminary results revealed that respondents who received more support than they gave were at greater risk of being diagnosed with Alzheimer's disease and non-Alzheimer's dementia than respondents who gave and received an equal amount of support (RRR=2.02 and p=.017; RRR=2.70 and p=.017 respectively). Respondents who gave more support than they received had a lower risk of being diagnosed with Alzheimer's disease than respondents with an equal exchange of support (RRR=0.32; p=.000).

Table 4.10. Bivariate Regression Results for Perceived Isolation and Reciprocity

	Cognitive Impairment not Demented vs. Normal Cognition			Non-Alzheimer's Dementia vs. Normal Cognition			Alzheimer's Disease vs. Normal Cognition		
Variable	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**
Perceived Social Support (Perceived Isolation)									
No one other than spouse willing to provide care (reference)									
Has someone other than spouse willing to provide care	1.01	0.24	.972	0.69	0.25	.308	1.42	0.38	.194
Perceived Loneliness—not asked of proxies (Perceived Isolation)									
Did not feel lonely (reference)									
Felt lonely	2.73	0.79	.001	2.67	1.37	.056	2.07	0.71	.036
Reciprocity									
Gave and received an equal amount of support (reference)									
Gave more support than received	1.05	0.29	.861	0.88	0.43	.798	0.32	0.10	.000
Received more support than gave	1.53	0.47	.170	2.70	1.13	.017	2.02	0.59	.017

Demographic Variables

Gender was included in the model to ascertain if there was a significant difference between men and women with respect to cognition and dementia. A dichotomous variable was included where one (1) indicated female and zero (0) indicated male.

Age at baseline was included as a continuous variable and taken from the RAND data file. It should be noted that one respondent in the sample was reported to be 58 years of age at baseline and 62 years at follow-up. However, HRS staff confirmed that the respondent was born in 1929 and was 72 years of age at the time of the ADAMS study, which was based upon the birth year variable (HRS Help Desk, personal communication, October 15, 2012). Further examination of the HRS and ADAMS data substantiated the information provided by the HRS Help Desk. To retain congruence with the age reported for this respondent in the ADAMS data, 68 years at baseline and 72 years at follow-up were imputed for this case.

Educational attainment was based on a measure used by the ADAMS. Similar to previous work (Bassuk, et al., 1999), this study dichotomized the education variable into respondents who had less than 12 years of education and respondents who had 12 or more years of education. Sensitivity analysis demonstrated that more education in both the continuous and dichotomous forms of the education variable was related to a significantly lower risk of non-Alzheimer's dementia, Alzheimer's disease, and CIND at the 5% level.

Race/ethnicity was included to determine if it was a significant risk factor for being diagnosed with CIND, Alzheimer's disease, or non-Alzheimer's dementia. Individuals in the ADAMS data were divided into three race-ethnic categories: non-

Hispanic White, non-Hispanic Black, and Hispanic. No other race-ethnic groups were identified in the ADAMS sample. Non-Hispanic Black and Hispanic respondents were combined and the race/ethnicity variable was dichotomized into non-Hispanic White respondents versus other due to small sample sizes.

Health Variables

Cognitive status at baseline was included as a control variable. Baseline cognitive scores (non-clinical) included both self- and proxy respondents. Self-respondents were assessed using the Telephone Interview for Cognitive Status (TICS), immediate word recall, delayed word recall, and the serial 7s tests. This resulted in a maximum possible score of 35 (Ofstedal, et al., 2005), where a higher score was indicative of higher cognitive function (Heeringa, et al., 2009). Cognitive status was assessed by proxy respondents with the shortened Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The shortened IQCODE consisted of 16 questions with a maximum possible score of 5.00. As opposed to the self-respondent measures, a higher score was indicative of lower cognitive function on the proxy measure (Heeringa, et al., 2009). The HRS created cut-off scores for both the proxy cognitive measure and the self-respondent measures in order to allow for uniform and joint categorization of cognitive status. Scores were divided into five categories: low functioning, borderline, low normal, medium normal, and high normal. Self-respondents with scores of 0 to 8 and those with a proxy who scored from 3.90 to 5.00 were classified as low functioning. Borderline scores for self-respondents ranged from 9 to 11 and respondents with a proxy ranged from 3.35 to 3.89. A score of 12 to 16 for self-respondents and a score of 3.10 to 3.34 for respondents

with a proxy were categorized as low normal. Self-respondents with a score of 17 to 20 and respondents with a proxy with a score of 1.00 to 3.10 were classified as medium normal. High normal scores ranged from 20 to 35 for self-respondents. There was no corresponding score provided for high normal among individuals with a proxy respondent (Heeringa, et al., 2009). These categories were used by the HRS to identify which respondents would be included in the ADAMS sample.

Including specific components of the cognitive measures, such as delayed memory measures, rather than the combined cognitive scores was also explored. Herzog and Wallace (1997) compared the use of the individual measures of cognitive status that were used in the HRS with the combined cognitive scores. They found the individual measures and combined scores to yield similar results and recommended the use of the combined scores rather than the individual scores. This study applied the five categories used to identify respondents for inclusion in the ADAMS to categorize baseline cognitive status for both respondents with a proxy and self-respondents. These categories were then dichotomized into medium normal/high normal cognitive status and low functioning/borderline/low normal in regression models.

In the HRS, depression was based on the respondent's score on the CES-D 8. The CES-D 8 is an abbreviated version of the original 20-item depression measure. This shortened version was used in the 1998 wave of the HRS and was comprised of eight measures of depressive symptoms (Steffick, 2000). As in the Cornwell and Waite (2009) study, one of the social environment variables that assessed perceived isolation used an item from the shortened CES-D measure. It assessed feelings of loneliness in respondents. This item was removed from the total score for depressive symptomatology, leaving

seven of the eight indicators for the measure of depressive symptoms. CES-D questions were not posed to respondents with a proxy. As a result, regression models were estimated with and without the CES-D and perceived loneliness measures to show any potential differences in the other variables in the model for the full sample (proxy and self-respondents) and the self-respondents only sample.

Variables that measure whether an individual reported being diagnosed by a physician with high blood pressure, diabetes, a heart condition or had suffered a stroke were included. It should be noted that variability between self-reported and objective assessments of health has been found (Baker, Stabile, & Deri, 2001; Bound, 1989; Hebert, et al., 1999; Newell, Girgis, Sanson-Fisher, & Savolainen, 1999; Schneider, Pankow, Geiss, & Selvin, 2012). This study created a combined cerebrovascular disease (CVD) variable that measured whether respondents reported having been diagnosed with at least one of the previously mentioned conditions. This was modeled after a variable created by Holtzman and colleagues (2004) in their study examining social network characteristics in relation to cognition. The variable was dichotomous with a one (1) indicating that a respondent had at least one of the conditions and a zero (0) if he/she did not have any of the conditions.

Physical activity was included as a dichotomous variable, whereby those individuals who reported being physically active were coded as one (1) and those who were not physically active were coded as zero (0). Individuals that reported engaging in vigorous activity or exercise at least three times per week were considered physically active. The HRS only asked about being active three times per week or more, so lower levels of physical activity could not be ascertained.

Childhood Variables

Measures of childhood SES and health were based on self-reports by respondents. The HRS asked respondents to report their SES with the following question: "Now think about your family when you were growing up, from birth to age 16. Would you say your family during that time was pretty well off financially, about average, or poor?" Respondents indicated whether they considered themselves to have been pretty well off financially, about average, or poor during their childhood. Respondents were also asked, "Consider your health while you were growing up, from birth to age 16. Would you say that your health during that time was excellent, very good, good, fair, or poor?" They indicated whether they considered themselves to have been in excellent, very good, good, fair, or poor health during childhood.

Preliminary analysis using bivariate logistic regression models were estimated with the childhood variables to determine if these were related to cognitive diagnosis. Childhood SES was categorized into respondents who reported being well off, average, and poor. Those who indicated that their family's finances varied while they were growing up were combined with those who reported being unsure about their family's SES into a fourth category. A post-estimation Wald test demonstrated that the overall childhood SES variable was not significantly related to cognitive diagnosis ($p=.451$). Childhood health was divided into three categories: respondents who reported being in excellent/very good health, good health, and fair/poor health. Bivariate logistic regression analysis of the childhood health variable demonstrated no statistically significant relationship between childhood health and cognitive diagnosis. A post-estimation Wald

test did not demonstrate a significant relationship between childhood health and cognitive diagnosis (p=.508). Multivariate logistic regression analysis demonstrated similar findings to the bivariate models and there was no significant relationship found between childhood SES or childhood health to cognitive diagnosis in multivariate analyses. The APOE, social, and other control variables did not differ in significance between models with and without the childhood variables. A Wald test did not find the childhood SES or childhood health variables to improve model fit (Wald statistic=.127 and Wald statistic=.109 respectively).

Possible limitations of the HRS childhood measures may be the lack of specificity of the measures compared to those used in the extant literature and recall bias. For example, one study used self-reports of parents' educational attainment and parent's occupation (Kaplan, et al., 2001) and another based childhood SES on parents' educational attainment, father's occupation, and number of children in the family (Wilson, et al., 2005). Although data about maternal and paternal education are available in the HRS, prior research has reported that it is only available in approximately 80% of the ADAMS sample for either variable (Rogers, et al., 2009). Since a primary goal of this study was examination of the social environment and genetic predisposition in relation to cognitive diagnosis rather than early life factors, it was determined that the potential benefit derived from inclusion of the parental education variables would not outweigh the loss of cases due to missing data given the low events per variable (EPV) in the model.

Other research about early life health examined very specific aspects of health such as chromosomal abnormalities and head injuries (Borenstein, et al., 2006), whereas the HRS asked respondents to provide a general childhood health rating. The differences

in the measures used may have accounted for the lack of significance of the HRS variables. In light of findings demonstrating that the childhood variables did not have a significant relationship with cognitive diagnosis in bivariate and multivariate analyses, differences in the HRS measures used versus those used in the literature, and to promote parsimony of the models, it was determined that the childhood variables would not be included in the final regression models.

Proxy Status

A dummy variable for proxy status was included in models that contained both self-respondents and proxy respondents. The results of preliminary analyses demonstrating significant differences that were found between respondents with a proxy and self-respondents are reported in **Table 4.11**. A t-test for independent samples or a chi-square test was used to compare self-respondents and proxies on measures of genetic predisposition, social environment, demographic characteristics, health factors, and childhood factors.

Of the total sample size of 779 cases included in this study, 663 were self-respondents and 116 were proxy respondents. P-values demonstrated a statistically significant difference between individuals with a proxy respondent and self-respondents on measures of family network size, social engagement, perceived social support, and reciprocity. More self-respondents reported family networks that had 11 or fewer members compared to individuals with a proxy respondent (56.3% and 44.8% respectively; p=.018). Self-respondents reported being more socially engaged than individuals with a proxy (59.7% and 29.3% respectively; p=.000). More individuals with

a proxy respondent reported having social support available to them (73.3%; p=.001) compared to only 56.9% of self-respondents. As might be expected, individuals with a proxy respondent were more likely to report receiving more support than they gave compared to self-respondents (43.1% and 26.1% respectively; p=.001).

Overall, individuals who needed a proxy respondent were older than self-respondents and were less educated (p=.000 and p=.001 respectively). Approximately 34% of respondents with a proxy compared to about 50% of self-respondents had 12 or more years of education. More individuals who had a proxy respondent had borderline or low functioning cognitive status (50.0% vs. 14.3% of self-respondents; p=.000) and were less physically active than self-respondents (18.1% and 35.1% respectively; p=.000). When examining significance at the 10% level, results show that more women were self-respondents than had a proxy respondent (59.4% and 50.0% respectively; p=.058). It should be noted that individuals who require the use of a proxy respondent are normally in poorer health or have cognitive difficulty which is likely to have contributed to the previous findings.

Table 4.11. Bivariate Relationships Comparing Respondents with a Proxy and Self-Respondents

	Self-Respondents		Proxies		P-Value	Total Sample	
Variable	**Num**	**Pct**	**Num**	**Pct**		**Num**	**Pct**
Family Network Size							
0 to 6 family members	183	27.6	21	18.1	.018	204	26.2

7 to 11 family members	190	28.7	31	26.7		221	28.4
12 to 17 family members	149	22.5	25	21.6		174	22.3
18+ family members	141	21.3	39	33.6		180	23.1
Total	663	100.1	116	100.0		779	100.0
Social Engagement							
No Activities	267	40.3	82	70.7		349	44.8
1 Activity	234	35.3	22	19.0		256	32.9
2 Activities	134	20.2	8	6.9	.000	142	18.2
3 Activities	28	4.2	4	3.4		32	4.1
Total	663	100.0	116	100.0		779	100.0
Perceived Social Support							
No one other than spouse willing to provide care	286	43.1	31	26.7		317	40.7
Has someone other than spouse willing to provide care	377	56.9	85	73.3	.001	462	59.3
Total	663	100.0	116	100.0		779	100.0
Reciprocity							
Gave and received an equal amount of support	301	45.4	44	37.9		345	44.3
Gave more support than received	189	28.5	22	19.0	.001	211	27.1
Received more support than gave	173	26.1	50	43.1		223	28.6
Total	663	100.0	116	100.0		779	100.0
Age (continuous)							
Mean Age	76.5 years		80.0 years		.000	77.0 years	
Education							

Less than 12th grade	326	49.2	76	65.5		402	51.6
12th grade or more	337	50.8	40	34.5	.001	377	48.4
Total	663	100.0	116	100.0		779	100.0
Baseline Cognitive Status							
Low functioning	45	6.8	43	37.1		88	11.3
Borderline	50	7.5	15	12.9		65	8.3
Normal—low	145	21.9	14	12.1		159	20.4
Normal—medium	151	22.8	44	37.9	.000	195	25.0
Normal—high	272	41.0	0	0.0		272	34.9
Total	663	100.0	116	100.0		779	100.0
Physical Activity							
Not physically active	430	64.9	95	81.9		525	67.4
Physically active	233	35.1	21	18.1	.000	254	32.6
Total	663	100.0	116	100.0		779	100.0
Gender							
Female	394	59.4	58	50.0		452	58.0
Male	269	40.6	58	50.0	.058	327	42.0
Total	663	100.0	116	100.0		779	100.0

Time since Baseline

An indicator of time from baseline to the ADAMS assessment was also included. Time was included in the model in order to account for any potential effect of the passage of time between the time when data for the control variables was gathered and cognitive diagnosis was assigned. While there was no expectation of a positive or negative correlation with cognitive diagnosis, it might be expected that if time was positively correlated with cognitive diagnosis that changes associated with the passage of time, such as declining health or negative changes in the social environment, may have contributed

to the observed correlation. A negative correlation may reflect positive changes, such as increased physical activity, that occurred during that time. The time from the 1998 interview to the time of the ADAMS initial assessment was calculated based on the month and year of the baseline assessment and the month and year of the ADAMS assessment. Since it was determined that the initial ADAMS assessment would be used as the outcome variable, time since baseline was calculated using the initial assessment only. This was included as a continuous variable that reported the number of years from the baseline interview to the time of the ADAMS initial assessment.

Change Variables

Variables were created in order to determine whether a change in the social environment, health factors, or proxy status from 1998 to 2002 was related to cognitive diagnosis. These change variables were only created for variables that were found to be significant in preliminary bivariate regression models. A dichotomous change variable was created in order to determine whether a change occurred from 1998 to 2002. If there was a difference between the two years, the variable was assigned a value of one (1) to indicate that a change had taken place, if there was no change a value of zero (0) was assigned. In certain instances the direction of the change could be determined and would add to the information gleaned. A value of one (1) was assigned to cases where an improvement took place, a value of minus one (-1) was assigned if it was considered to have changed for the worse, and a value of zero (0) was assigned when there was no change. For example, if a respondent reported feeling lonely at Time 1 and reported not feeling lonely at Time 2, then a value of one was assigned. If the respondent did not feel

lonely at Time 1 but later reported feeling lonely at Time 2, then a value of minus one was assigned. If the respondent reported feeling lonely at both Time 1 and Time 2 or reported not feeling lonely at Time 1 and Time 2, then a value of zero was assigned. There were a total of nine statistically significant variables for which change variables were created: living arrangement, social engagement, feelings of loneliness, reciprocity, depressive symptomatology, proxy status, physical activity, CVD status, and cognitive score.

Moderating Effect Terms

Moderating effect terms for genetic predisposition (APOE) and the social environment were created in order to test whether aspects of the social environment moderate the relationship of the APOE-e4 allele to cognitive diagnosis. A dichotomous version of the APOE variable was used with each of the social environment variables. Moderating effect terms were created two different ways.

First, cross-tabulations were performed on the dichotomous APOE variable and the categorical variable of interest. A dummy variable was then created to represent each cell within the table. These dummy variables were included in the regression model while excluding the original variables that comprised the moderating effect variable. For example, when running the model with the living arrangement moderating effect term, both the APOE-e4 variable and the living arrangement variable were not included in the model.

Second, moderating effect terms for count variables were created by multiplying the continuous variable by the dichotomous version of the APOE variable (standard

interaction terms). For example, the social engagement variable was multiplied by the APOE variable. Tests for multicollinearity did not reveal any statistical problems.

Missing Data

The RAND variables were used when they were available since RAND imputed missing values. Other variables were taken directly from the HRS data. If it was not feasible to impute values for missing data, then a listwise deletion of cases was implemented. A total of 77 cases were excluded due to missing data, reducing the sample size from 856 cases to 779 cases.

Analytic Strategy

Descriptive Statistics

Previous studies focused on non-U.S. populations, regional samples (both in the U.S. and outside of the U.S.), condition-specific groups, or convenience samples. The ADAMS data contain the first nationally representative population-based sample of the U.S. population that conducted clinical evaluations of cognitive function. Prevalence rates were generated for six APOE genotypic combinations in the ADAMS sample. The rates for the U.S. population were compared to those found in other sample groups, such as individuals with coronary artery disease and Japanese older adults.

Differences between ADAMS respondents with the APOE-e4 allele and those without it are reported in Chapter 5 for demographic characteristics, childhood factors, health factors, and aspects of the social environment. This comparison is reported for variables from both baseline and follow-up to see if there were any differences between

the waves. Results from cross-tabulations and chi-square statistics are reported. Relationships between the independent variables and cognitive diagnosis were examined using bivariate analysis for the full sample only. Results from cross-tabulations and measures of central tendency are reported.

Regression Analysis

Multinomial logistic regression was selected as the form of analysis given the inability to rank the categories of cognitive diagnosis, such as Alzheimer's disease and non-Alzheimer's dementia. As noted earlier, it was determined that separating Alzheimer's disease from other types of dementia would be beneficial to the analysis since preliminary analyses demonstrated that when combining the categories, results tended to reflect the relationship of the independent variables to Alzheimer's disease rather than the other types of dementia. This may be due to the larger proportion of Alzheimer's disease cases than non-Alzheimer's disease cases (n=203 and n=68 respectively). Thus the categories were separated to avoid this loss of information. Creating a binary outcome variable of Alzheimer's disease versus not Alzheimer's disease is not optimal for exploring this issue because with a binary outcome variable individuals who were demented and normal would be grouped together. In addition, since Alzheimer's disease is a form of dementia, it would be difficult to interpret the findings if individuals with dementia were grouped with those who had normal cognition or CIND. One modeling option was to use ordered logistic regression, because the cognitive categories could be rank-ordered. However, a test of the proportional odds assumption showed that this assumption was violated (p=.000).

Variables from the 1998 wave of the HRS were used as the independent variables in order to determine which variables were associated with cognitive diagnosis. Changes in some of the independent variables from 1998 to 2002 were also assessed to ascertain whether a change in some of the respondent characteristics was related to cognitive diagnosis. Bivariate regression analysis was conducted using the change variables for living arrangement, number of children, social engagement, feelings of loneliness, reciprocity, depressive symptomatology, proxy status, physical activity, CVD status, and cognitive score.

First, regression models controlling for genetic predisposition and the social environment were estimated to test the relationship of these variables with cognitive diagnosis. Next, demographic characteristics, health factors, time since baseline, and proxy status were added to the regression models. A separate model with the social connectedness index and all of the covariates was analyzed. Finally, moderating effect terms were added to the model that included genetic predisposition and the social environment variables, as well as a fully adjusted model, to test whether aspects of the social environment moderated the relationship between the e4 allele and cognitive diagnosis. It should be noted that using multiple models increases the chance of a Type I error. However, using a method to correct for multiple comparisons, such as the Bonferroni correction, would increase the chance of a Type II error. In recognition of this conundrum, p-values are reported throughout this paper to allow the reader to evaluate the results in light of a more conservative p-value, such as $p<.025$, that would reduce the risk of a Type I error without increasing the risk of a Type II error. However, results are generally discussed using a p-value of .05 or .10 due to the small sample size.

As noted above, the CES-D questions were not asked of individuals with a proxy respondent. As a result, regression models were run with and without the CES-D and perceived loneliness measures. These models were estimated with a reduced sample that excluded proxy respondents but included the measures for depression and perceived loneliness. The full sample, including proxy respondents, was analyzed without these two measures. Results of the descriptive and regression analyses are reported in Chapter 5. The results of the regression analyses are reported as relative risk ratios (RRR) and robust standard errors.

CHAPTER 5

RESULTS

This chapter reports the results of descriptive and regression analyses for the sample of 779 ADAMS participants that were included in this study. Bivariate descriptive analyses examining the relationship of the independent variables with cognitive diagnosis are reported first. The rest of the chapter is divided into sections according to the four research questions listed in Chapter 3. Each section includes a description of the type of analysis that was conducted, the research question being investigated, and a description of the results. It should be noted that in some cases, the sample size changed based on limitations associated with the HRS questionnaire design. For example two variables, loneliness and depressive symptomatology, were not asked of proxy respondents. In these cases separate analyses were conducted on self-respondents only. Thus results are reported for both the full sample and self-respondents only.

Bivariate Analysis of Independent Variables

Percentages and measures of central tendency and appropriate tests of statistical significance were used in the examination of the bivariate relationships among each of the independent variables and cognitive diagnosis. Results demonstrated that all of the independent variables had a statistically significant relationship with cognitive diagnosis,

except for family network size, time since baseline interview, and the social connectedness index (p=.246, p=.412, and p=.370 respectively). Percentages or mean values and p-values are reported in **Tables 5.1** through **5.3**. It should be noted that results are reported for the full sample (n=779) and not for measures of self-respondents only (feelings of loneliness and depressive symptomatology).

Almost 40% of respondents who did not have any e4 alleles were diagnosed with normal cognition (39.2%; p=.001). This was in contrast to over half of respondents who had two e4 alleles being diagnosed with Alzheimer's disease (52.2%; p=.001). Approximately 45% of respondents who were married and living with someone had normal cognition, while less than one-third of respondents who were single and living with someone else or were single and living alone were diagnosed as having normal cognition (29.2% and 29.8% respectively; p=.000). About 80% of respondents who were not socially engaged were diagnosed with CIND, Alzheimer's disease, or another type of dementia (27.8%, 37.8% and 13.8% respectively; p=.000). Most respondents who were engaged in at least one activity had normal cognition (1 activity=40.6%, 2 activities=62.7%, and 3 activities=68.8%).

Approximately 30% of respondents who believed that they had social support available to them were diagnosed with Alzheimer's disease while 34.2% were considered to be cognitively normal (p=.015). About half of the respondents who gave more support than they received had normal cognition, while about 40% of respondents who received more support than they gave had been diagnosed with Alzheimer's disease (51.2% and 39.5% respectively; p=.000).

Baseline cognitive status was significantly related to later cognitive diagnosis (p=.000). Respondents who had a baseline cognitive status of low functioning or borderline were later diagnosed with Alzheimer's disease (80.7% and 49.2% respectively). Among respondents who had a baseline cognitive status of low normal, 37.1% were later diagnosed with CIND and 29.6% were diagnosed with Alzheimer's disease. This seems to indicate a decline in cognitive functioning over time.

Almost half of respondents who did not have a cerebrovascular (CVD) condition were considered to have normal cognitive functioning (46.7%; p=.000). However, the proportion of respondents with at least one CVD condition was 11.8% versus 2.4% without a CVD condition who had been diagnosed with non-Alzheimer's dementia. More than half of respondents who were physically active were considered to be cognitively normal (53.2%; p=.000). The proportion of physically active respondents was around 20% for respondents with CIND and Alzheimer's disease. Very few respondents with non-Alzheimer's dementia were physically active (5.9%).

Among non-Hispanic Black and Hispanic respondents, the largest proportion in both groups had been diagnosed with CIND (32.6% and 40.5% respectively; p=.010). The largest proportion of non-Hispanic White respondents were considered to be cognitively normal (40.1%; p=.010). On average, the oldest respondents were diagnosed with Alzheimer's disease and non-Alzheimer's dementia, while the youngest respondents were cognitively normal (81.7 years, 78.9 years, and 73.4 years respectively; p=.000). Almost half of respondents with 12 or more years of education were also considered to be cognitively normal (47.5%; p=.000). Twice the proportion of female respondents were diagnosed with Alzheimer's disease than male respondents (33.2% and 16.2%

respectively; p=.000). Approximately one-third of female respondents had been diagnosed as having normal cognitive functioning as compared to about half of male respondents (33.9% and 41.0% respectively). A diagnosis of normal cognition was more common among self-respondents, whereas almost half of the respondents with a proxy had been diagnosed with Alzheimer's disease (41.2% and 48.3% respectively; p=.000).

In sum, bivariate analyses indicate that having at least one e4 allele has a significant relationship to cognitive functioning, but is not a certainty for a diagnosis of dementia or Alzheimer's disease. Being married and living with someone, being socially engaged, believing that social support is available, and giving more than one receives are associated with better cognitive functioning. These findings are consistent with the literature and support the assumption in this study that there is a significant relationship of the APOE-e4 allele and the social environment to cognitive diagnosis in a nationally representative sample of U.S. older adults.

Table 5.1. Relationship of Genetic Predisposition and the Social Environment to Cognitive Diagnosis (n=779)

	Normal		CIND		Alzheimer's Disease		Non-Alzheimer's Dementia		Total		
Variable	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
APOE-e4											
No e4 alleles	221	39.2	171	30.3	124	22.0	48	8.5	564	100.0	
One e4 allele	62	32.3	45	23.4	67	34.9	18	9.4	192	100.0	.001
Two e4 alleles	4	17.4	5	21.7	12	52.2	2	8.7	23	100.0	
Living Arrangement											
Married and living with someone	168	44.9	106	28.3	76	20.3	24	6.4	374	99.9	
Single and living alone	77	29.2	71	26.9	84	31.8	32	12.1	264	100.0	.000
Single and living with others	42	29.8	44	31.2	43	30.5	12	8.5	141	100.0	
Family Network Size											
0 to 6 family members	69	33.8	62	30.4	54	26.5	19	9.3	204	100.0	
7 to 11 family members	87	39.4	56	25.3	62	28.1	16	7.2	221	100.0	.246
12 to 17 family members	75	43.1	40	23.0	42	24.1	17	9.8	174	100.0	
18+ family members	56	31.1	63	35.0	45	25.0	16	8.9	180	100.0	
Social Engagement											
No activities	72	20.6	97	27.8	132	37.8	48	13.8	349	100.0	.000

1 activity	104	40.6	86	33.6	52	20.3	14	5.5	256	100.0	
2 activities	89	62.7	34	23.9	14	9.9	5	3.5	142	100.0	
3 activities	22	68.8	4	12.5	5	15.6	1	3.1	32	100.0	
Social Connectedness Index	2.75	2.7	2.20	2.2	1.86	1.9	1.69	1.7	2.27	n/a	.370
Perceived Social Support											
No one other than spouse willing to provide care	129	40.7	92	29.0	64	20.2	32	10.1	317	100.0	
Has someone other than spouse willing to provide care	158	34.2	129	27.9	139	30.1	36	7.8	462	100.0	.015
Reciprocity											
Gave and received an equal amount of support	126	36.5	105	30.4	87	25.2	27	7.8	345	99.9	
Gave more support than received	108	51.2	58	27.5	28	13.3	17	8.1	211	100.1	.000
Received more support than gave	53	23.8	58	26.0	88	39.5	24	10.8	223	100.1	

Table 5.2. Relationship of Health Factors to Cognitive Diagnosis (n=779)

	Normal		CIND		Alzheimer's Disease		Non-Alzheimer's Dementia		Total		
Variable	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Baseline Cognitive Status											
Low functioning	0	0.0	6	6.8	71	80.7	11	12.5	88	100.0	
Borderline	3	4.6	19	29.2	32	49.2	11	16.9	65	99.9	
Normal—low	35	22.0	59	37.1	47	29.6	18	11.3	159	100.0	.000
Normal—medium	77	39.5	66	33.9	31	15.9	21	10.8	195	100.1	
Normal—high	172	63.2	71	26.1	22	8.1	7	2.6	272	100.0	
CVD											
No CVD conditions	119	46.7	56	22.0	74	29.0	6	2.4	255	100.1	.000
At least one CVD condition	168	32.1	165	31.5	129	24.6	62	11.8	524	100.0	
Physical Activity											
Not physically active	152	29.0	163	31.1	157	30.0	53	10.1	525	100.2	.000
Physically active	135	53.2	58	22.8	46	18.1	15	5.9	254	100.0	

Table 5.3. Relationship of Demographic Characteristics to Cognitive Diagnosis (n=779)

	Normal		CIND		Alzheimer's Disease		Non-Alzheimer's Dementia		Total		
Variable	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Race/Ethnicity											
Non-Hispanic White	224	40.1	143	25.6	146	26.1	46	8.2	559	100.0	
Non-Hispanic Black	37	26.2	46	32.6	41	29.1	17	12.1	141	100.0	.010
Hispanic	26	32.9	32	40.5	16	20.3	5	6.3	79	100.0	
Age (mean)		73.4		77.0		81.7		78.9		n/a	.000
Education											
Less than 12th grade	108	26.9	132	32.8	121	30.1	41	10.2	402	100.0	.000
12th grade or more	179	47.5	89	23.6	82	21.8	27	7.2	377	100.1	
Gender											
Female	153	33.9	113	25.0	150	33.2	36	8.0	452	100.1	.000
Male	134	41.0	108	33.0	53	16.2	32	9.8	327	100.0	
Proxy Status											
Self-respondent	273	41.2	194	29.3	147	22.2	49	7.4	663	100.1	.000
Proxy respondent	14	12.1	27	23.3	56	48.3	19	16.4	116	100.1	
Time from Baseline (mean years)	4.75	4.8	4.74	4.7	4.53	4.5	4.44	4.4	4.66	n/a	.412

Prevalence of APOE Genotypic Combinations

In this section, descriptive statistics were used in order to address the following research question:

> ***Research Question 1:*** *What is the prevalence of the APOE allele combinations in a U.S. nationally representative sample of older adults and how do the rates generated from these data compare to rates from other study samples?*

Prior studies that examined the prevalence of the various APOE genotypic combinations have often been limited to individuals from a selected geographic region, people with a specific condition, or non-U.S. samples. This study compared prevalence rates found in the ADAMS data with prevalence rates found in studies of other sample groups. Percentages were reported in order to allow for cross-study comparison.

Table 5.4 reports the rates of the APOE genotypic combinations found in the ADAMS data compared to studies of some non-U.S. and regional samples. Rates found among individuals with certain chronic conditions are also reported. Overall, the e3/e3 genotypic combination was the most common across the non-U.S., "chronic conditions," and ADAMS study samples (range from 37.4% to 81.8%). The e2/e2 was the least common among these sample groups (range from 0.0% to 2.8%).

Prevalence rates in the ADAMS sample were not strikingly different from those found in some non-representative, non-U.S. sample groups. The ADAMS sample had the second highest prevalence rate of the e2/e3 combination (12.1%), with the Dutch sample demonstrating the highest rate of 14.8% (Slooter, et al., 1998). However, there was a

wide range of prevalence rates for the e2/e3 combination across studies. The highest rate was almost 3 times the rate of the lowest (4.9% to 14.8%). Rates for the e4 genotypic combinations showed 2.8% of the ADAMS sample had the e2/e4 combination, 21.8% had the e3/e4 combination, and 3.0% had the e4/e4 combination. The range across sample groups was 0.0% to 4.6% for the e2/e4 combination, 9.1% to 45.1% for the e3/e4 combination, and 0.0% to 18.3% for the e4/e4 combination.

An African American sample from Indianapolis (Sahota, et al., 1997) had higher rates of the e2/e4 (4.6%), e3/e4 (30.6%), and e4/e4 (4.2%) combinations compared to the ADAMS sample (2.8%, 21.8% and 3.0% respectively). This was consistent with previous findings that African American participants had higher prevalence rates of the e4 allele than their White counterparts (Borenstein, et al., 2006; Fillenbaum, et al., 2001). This might be expected since the majority of the ADAMS sample was non-Hispanic White. Interestingly, Sahota and colleagues (1997) suggested that although the e4 allele was associated with a higher risk of Alzheimer's disease among African Americans, the risk was not as high as it was among Whites.

The highest prevalence rates of the e4 allele were found among individuals who had been diagnosed with a chronic condition. A study of Finnish patients who had been diagnosed with coronary artery disease (CAD) had the highest rates of the e3/e4 genotypic combination (45.1%) (Kuusi, et al., 1989). The next highest prevalence rates of the e3/e4 combination were found among Dutch dementia patients and African Americans who had been diagnosed with Alzheimer's disease (31.3% and 30.0% respectively). The highest prevalence of the e4/e4 combination was found among African Americans that had been diagnosed with Alzheimer's disease (18.3%) (Sahota, et al.,

1997). Dutch dementia patients had the highest rates of prevalence of the e2/e4 combination (3.0%).

In sum, the ADAMS study did not vary greatly from non-U.S. samples on the prevalence of the APOE allele combinations. As might be expected, prevalence rates of the e4 allele were higher in sample groups homogenous for chronic conditions such as CAD or Alzheimer's disease. Additional nationally representative studies need to be conducted to determine how representative the ADAMS data are of APOE prevalence.

Table 5.4. APOE Allele Distribution in ADAMS Sample Compared with Other Samples (reported as percentage of sample)

			APOE Allele Combination					
Sample	**Sample Size**	**Citation**	**e2/e2**	**e2/e3**	**e2/e4**	**e3/e3**	**e3/e4**	**e4/e4**
U.S. nationally representative sample	779	ADAMS supplement, 2007.	0.5	12.1	2.8	59.8	21.8	3.0
Japanese Centenarians	33	Asada, et al., 1996.	0.0	9.1	0.0	81.8	9.1	0.0
Japanese adults <90 years	224	Asada, et al., 1996.	0.0	4.9	0.9	54.5	36.2	3.6
Danish	466	Gerdes, Klausen, Sihm, & Faergeman, 1992.	1.7	11.6	1.9	55.8	25.1	3.9
Finnish	615	Ehnholm, Lukka, Kuusi, Nikkila, & Utermann, 1986.	0.3	6.7	0.8	54.0	31.9	6.3
Italian control	398	Margaglione, et al., 1998.	1.0	7.8	1.8	72.9	16.6	0.0
Dutch control	997	Slooter, et al., 1998.	1.0	14.8	1.9	56.5	24.2	1.6

African American control (Indianapolis)	216	Sahota, et al., 1997.	2.8	11.1	4.6	46.8	30.6	4.2
Finnish patients with coronary artery disease	91	Kuusi, et al., 1989.	0.0	6.6	2.2	37.4	45.1	8.8
Italians who suffered a stroke	208	Margaglione, et al., 1998.	1.0	12.5	0.0	65.9	17.3	3.4
Dutch dementia patients	134	Slooter, et al., 1998.	0.7	7.5	3.0	52.2	31.3	5.2
African Americans with Alzheimer's disease (Indianapolis)	60	Sahota, et al., 1997.	0.0	6.7	1.7	43.3	30.0	18.3
Patients with cerebrovascular disease	635	Couderc, Mahieux, Bailleul, Fenelon, Mary, & Fermanian, 1993.	1.4	10.6	1.0	67.2	18.7	1.3

Comparison of Respondents with and without the APOE-e4 Allele

Cross-tabulations, with Pearson chi-square and tests of statistical significance, were used to examine the second research question of this study. Analysis focused on comparing respondents who had the e4 allele with those who did not have the allele, as well as differences between respondents from baseline to follow-up. This analysis sought to answer the question:

> ***Research Question 2:*** *Do people with the APOE-e4 allele differ from individuals without it on measures of demographic characteristics, health factors, and the social environment at baseline and the time of the ADAMS data collection in a U.S. nationally representative sample of older adults?*

Four variables were found to be significantly related to the APOE-e4 allele at baseline when examining aspects of the social environment, demographic characteristics, and health status at the 5% or 10% levels of statistical significance (see **Table 5.5**). Race/ethnicity was found to be significantly related to the e4 allele (p=.001). While the majority of respondents across race/ethnic groups did not have an e4 allele, non-Hispanic Black respondents had the highest prevalence of the e4 allele (39.7%). About one-fourth of non-Hispanic White respondents had at least one e4 allele (25.9%). This was consistent with previous findings that African American participants had higher prevalence rates of the e4 allele than their White counterparts (Borenstein, et al., 2006; Fillenbaum, et al., 2001). Respondents without the e4 allele were older than respondents who had the allele (77.3 years and 76.5 years respectively; p=.084).

Only cognitive status and physical activity were found to be significantly related to the e4 allele on measures of health (p=.010 and p=.027 respectively). A larger proportion of individuals with cognitive scores that were considered borderline or low functioning had at least one e4 allele. Almost half of respondents who were considered to be low functioning had at least one e4 allele (42.1%). Among respondents who scored in the normal range of baseline cognitive status, 22% to 28% had at least one e4 allele. Approximately 25% of respondents who were not physically active had at least one e4 allele compared to 75% of those without the e4 allele and 33% of physically active respondents had the e4 allele compared to 67% of respondents without the e4 allele (p=.027). It should be noted that differences between the two groups on measures of social engagement were almost significant at the 10% level (p=.103). Respondents who had at least one e4 allele were less engaged than those who did not have any e4 alleles.

Analysis of the 2002 variables revealed that race/ethnicity and proxy status were found to have a significant relationship with the e4 allele (p=.001 and p=.040 respectively). Race/ethnicity was significant in both the 1998 and 2002 waves. Proxy status became significant at follow-up (2002). Age, baseline cognitive status, and physical activity were no longer significant when using the 2002 variables.

These findings indicate that individuals with and without the APOE-e4 allele differ by race/ethnicity, age, baseline cognitive status, and physical activity. A larger proportion of non-Hispanic Black respondents had at least one APOE-e4 allele when compared to non-Hispanic White respondents. Respondents without any e4 alleles were older than respondents who had at least one e4 allele. This may be a selection effect due to the increased risk of dementia and vascular disease associated with the e4 allele.

Among respondents with at least one e4 allele, a larger proportion had low normal, borderline, or low cognitive functioning. This would be expected given the increased risk of dementia associated with the APOE-e4 allele. Interestingly, a larger proportion of respondents with at least one e4 allele were also physically active.

Table 5.5. Bivariate Comparison of Respondents with and without the e4 Allele at Baseline

	No e4 Allele		One or Two e4 Alleles		Total		P-Value
Variable	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	
Race/Ethnicity							
Non-Hispanic White	414	74.1	145	25.9	559	100.0	
Non-Hispanic Black	85	60.3	56	39.7	141	100.0	.001
Hispanic	65	82.3	14	17.7	79	100.0	
Age (mean years)		77.3		76.5		n/a	.084
Baseline Cognitive Status							
Low functioning	51	58.0	37	42.1	88	100.1	
Borderline	45	69.2	20	30.8	65	100.0	
Normal—low	115	72.3	44	27.7	159	100.0	.010
Normal—medium	153	78.5	42	21.5	195	100.0	
Normal—high	200	73.5	72	26.5	272	100.0	
Physical Activity							
Not physically active	393	74.9	132	25.1	525	100.0	
Physically active	171	67.3	83	32.7	254	100.0	.027
Social Engagement							
No activities	245	70.2	104	29.8	349	100.0	
1 activity	189	73.8	67	26.2	256	100.0	.103
2 activities	111	78.2	31	21.8	142	100.0	
3 activities	19	59.4	13	40.6	32	100.0	

Relationship of Genetic Predisposition and the Social Environment to Cognitive Diagnosis

Multinomial logistic regression models were estimated to address the third research question. Models were adjusted using a hierarchical inclusion of sets of variables. Model 1 was a bivariate regression analysis of the cognitive diagnosis variable regressed on the APOE variable. This model demonstrated the direct relationship between genetic predisposition and cognitive diagnosis without any additional covariates. The relationship of only the social environment variables with cognitive diagnosis was analyzed in Model 2. Model 3 included the main variables of interest in this study: APOE and all of the social environment variables (social connectedness, perceived isolation, and reciprocity). Health factors and demographic characteristics were added to Model 4, which was a fully adjusted model that included the APOE variable, social environment variables, health factors, and demographic characteristics. In order to compare inclusion of the separate social connectedness variables and the social connectedness index, Model 5 was a fully adjusted model that excluded the individual social connectedness variables, except for family network size, and included the social connectedness index instead (comprised of living arrangement, social engagement, and geographic proximity). Model 6 was a fully adjusted model for self-respondents only (n=663). This model included all of the covariates in addition to the loneliness and CES-D variables. A change analysis was also estimated to determine whether the baseline variables or a change in these variables was related to cognitive diagnosis. This section seeks to answer the following research question:

Research Question 3: *Is there a relationship between the APOE-e4 allele and a diagnosis of dementia or Alzheimer's disease in a U.S. nationally representative population-based sample? Is there a relationship between the social environment and a diagnosis of dementia or Alzheimer's disease in a U.S. nationally representative population-based sample?*

Findings for each of the models are reported in **Table 5.6** in several panels. Each panel reports the results for all of the models for each cognitive diagnosis: CIND, non-Alzheimer's dementia, and Alzheimer's disease when compared to normal cognition. In other words, although the dependent variable contained four categories and the models were estimated with multinomial logistic regression techniques, the results are reported in separate panels for ease of presentation.

CIND

Bivariate regression analysis demonstrated no statistically significant relationship between the e4 allele and a diagnosis of CIND. However, when controlling for all covariates and among self-respondents only (Models 4 to 6), having two e4 alleles was found to be a risk factor for being diagnosed with CIND (Model 4 RRR=3.77 and p=.065; Model 5 RRR=3.69 and p=.064; Model 6 RRR=3.61 and p=.084). Respondents who were involved in more social activities and were considered more socially connected, as measured by the social connectedness index, were at less risk of being diagnosed with CIND than respondents who were less socially engaged or connected (Social Engagement: Model 2 RRR=0.58 and p=.000; Model 3 RRR=0.58 and p=.000; Model 4

RRR=0.68 and p=.018; Model 6 RRR=0.74 and p=.098; Social Connectedness Index: Model 5 RRR=0.69 and p=.010). Better baseline cognitive status and being female were associated with a lower risk of being diagnosed with CIND (Baseline Cognition: Model 4 RRR=0.45 and p=.018; Model 5 RRR=0.58 and p=.046; Model 6 RRR=0.60 and p=.089; Female: Model 4 RRR=0.55 and p=.042; Model 5 RRR=0.44 and p=.014; Model 6 RRR=0.46 and p=.024). Older age and having a proxy respondent were both associated with a higher risk of CIND (Age: Model 4 RRR=1.10 and p=.000; Model 5 RRR=1.10 and p=.000; Model 6 RRR=1.10 and p=.000; Proxy Status: Model 4 RRR=2.86 and p=.051; Model 5 RRR=2.96 and p=.039). Self-respondents who reported feeling lonely were at greater risk of being diagnosed with CIND compared to those who were not lonely (RRR=1.90; p=.057). It may be that respondents at this stage of cognitive decline were aware of the changes taking place and may have been at greater risk of feeling socially isolated.

Non-Alzheimer's Dementia

Bivariate regression analysis demonstrated no significant relationship between the APOE-e4 allele and a diagnosis of non-Alzheimer's dementia. However, when controlling for the social environment, respondents who had one e4 allele were at twice the risk of being diagnosed with non-Alzheimer's dementia than respondents without any e4 alleles (Model 3 RRR=2.40; p=.076). This increased risk remained consistent in the fully adjusted model, when using the social connectedness index, and among self-respondents only (Model 4 RRR=2.09 and p=.054; Model 5 RRR=2.30 and p=.036; Model 6 RRR=2.27 and p=.058). Individuals who were engaged in more social activities

and were more socially connected (as measured by the social connectedness index) were at less risk of being diagnosed with non-Alzheimer's dementia at the 5% significance level across all models when compared to respondents who were less socially engaged and less socially connected (Social Engagement: Model 2 RRR=0.23 and p=.000; Model 3 RRR=0.23 and p=.000; Model 4 RRR=0.26 and p=.000; Model 6 RRR=0.32 and p=.001; Social Connectedness Index: Model 5 RRR=0.32 and p=.000). Respondents who believed that they had social support available to them were at less risk of being diagnosed with non-Alzheimer's dementia when controlling for the APOE-e4 allele and the social environment as well as in the fully adjusted model compared to respondents who did not believe they had social support available (Model 3 RRR=0.53 and p=.100; Model 4 RRR=0.51 and p=.096). Respondents who were single and lived alone were at greater risk of being diagnosed with non-Alzheimer's dementia across all models than respondents who were married and living with others (Model 2 RRR=5.61 and p=.000; Model 3 RRR=6.39 and p=.000; Model 4 RRR=6.18 and p=.000; Model 6 RRR=5.97 and p=.002). Older age and having a proxy respondent were associated with a higher risk of non-Alzheimer's dementia at the 5% level (Age: Model 4 RRR=1.10 and p=.003; Model 5 RRR=1.12 and p=.000; Model 6 RRR=1.13 and p=.001; Proxy: Model 4 RRR=9.27 and p=.000; Model 5 RRR=8.50 and p=.000). Having at least one CVD was associated with a significantly greater risk of being diagnosed with non-Alzheimer's dementia across all models at the 5% level (Model 4 RRR=8.48 and p=.002; Model 5 RRR=8.42 and p=.002; Model 6 RRR=9.97 and p=.009). Respondents who had medium or high normal baseline cognitive functioning were at less risk of being diagnosed with non-Alzheimer's dementia at the 5% significance level across models (Model 4

RRR=0.12 and p=.000; Model 5 RRR=0.11 and p=.000; Model 6 RRR=0.09 and p=.000). Being female was also associated with a lower risk of being diagnosed with non-Alzheimer's dementia (Model 4 RRR=0.38 and p=.037; Model 5 RRR=0.49 and p=.079; Model 6 RRR=0.36 and p=.045).

Alzheimer's Disease

Genetic predisposition via the APOE-e4 allele was found to be a significant risk factor for being diagnosed with Alzheimer's disease across models. Respondents who had one e4 allele had almost 2 to 3 times the risk of being diagnosed with Alzheimer's disease compared to respondents without an e4 allele (Model 1 RRR=1.74 and p=.034; Model 3 RRR=2.01 and p=.017; Model 4 RRR=2.84 and p=.002; Model 5 RRR=2.94 and p=.002; Model 6 RRR=2.49 and p=.012). The risk was even greater among respondents who had two e4 alleles (Model 1 RRR=11.65 and p=.004; Model 3 RRR=9.60 and p=.003; Model 4 RRR=19.96 and p=.000; Model 5 RRR=21.67 and p=.000; Model 6 RRR=15.90 and p=.000). The very large effect observed among respondents with two e4 alleles may be due to the small number of cases that fell into this category (n=23). Being engaged in more social activities or being more socially connected was associated with a lower risk of Alzheimer's disease compared to respondents who were less engaged and less connected (Social Engagement: Model 2 RRR=0.33 and p=.000; Model 3 RRR=0.33 and p=.000; Model 4 RRR=0.57 and p=.007; Model 6 RRR=0.65 and p=.046; Social Connectedness Index: Model 5 RRR=0.67 and p=.016). Respondents who gave more support than they received were also at less risk of being diagnosed with Alzheimer's disease compared to respondents who gave and

received an equal amount of support across all models (Model 2 RRR=0.38 and p=.006; Model 3 RRR=0.42 and p=.013; Model 4 RRR=0.41 and p=.043; Model 5 RRR=0.41 and p=.045; Model 6 RRR=0.46 and p=.085). Being single and living alone was a risk factor for being diagnosed with Alzheimer's disease when controlling for the social environment only or both the social environment and APOE (Model 2 RRR=1.74 and p=.061; Model 3 RRR=1.99 and p=.025). It was no longer a risk for being diagnosed with Alzheimer's disease when controlling for additional covariates, such as health or demographic characteristics. As might be expected, respondents who had better cognitive functioning at baseline were also at lower risk of being diagnosed with Alzheimer's disease (Model 4 RRR=0.06 and p=.000; Model 5 RRR=0.06 and p=.000; Model 6 RRR=0.06 and p=.000). Older age and having a proxy respondent were associated with a higher risk of Alzheimer's disease (Age: Model 4 RRR=1.22 and p=.000; Model 5 RRR=1.22 and p=.000; Model 6 RRR=1.22 and p=.000; Proxy: Model 4 RRR=7.63 and p=.000; Model 5 RRR=8.89 and p=.000).

Taken together, these findings seemed to indicate that there was a strong relationship between the APOE-e4 allele and Alzheimer's disease. Having the e4 allele was consistently associated with a greater risk of being diagnosed with Alzheimer's disease. The relationship of the e4 allele with CIND or non-Alzheimer's dementia was inconsistent. The results also seemed to indicate that being more socially engaged was associated with a lower risk of demonstrating cognitive difficulty. Older age was associated with a greater risk of cognitive difficulty while higher baseline cognitive function was associated with a lower risk of later cognitive difficulty.

Table 5.6. Results of Hierarchical Regression Models

Panel A. CIND vs. Normal Cognition

Variable	Model 1 RRR (se) *p-value*	Model 2 RRR (se) *p-value*	Model 3 RRR (se) *p-value*	Model 4 RRR (se) *p-value*	Model 5 RRR (se) *p-value*	Model 6 (n=663) RRR (se) *p-value*
Genetic Predisposition						
No e4 alleles (reference)						
One e4 allele	1.20 (0.34) *.533*		1.27 (0.37) *.412*	1.58 (0.47) *.129*	1.59 (0.47) *.126*	1.31 (0.42) *.409*
Two e4 alleles	2.32 (2.04) *.339*		2.31 (1.81) *.285*	3.77 (2.71) *.065*	3.69 (2.60) *.064*	3.61 (2.68) *.084*
Social Connectedness						
Married and living with others (reference)						
Single and living alone		1.42 (0.40) *.204*	1.48 (0.41) *.162*	1.43 (0.47) *.278*		1.05 (0.36) *.884*
Single and living with others		1.28 (0.47) *.498*	1.32 (0.48) *.450*	1.42 (0.59) *.395*		1.45 (0.59) *.361*
0 to 6 family members (reference)						

7 to 11 family members	0.70 (0.23) *.272*	0.70 (0.23) *.275*	0.81 (0.29) *.544*	0.85 (0.29) *.626*	0.76 (0.28) *.445*
12 to 17 family members	0.75 (0.26) *.413*	0.76 (0.27) *.438*	0.87 (0.32) *.714*	0.88 (0.32) *.719*	0.74 (0.28) *.419*
18+ family members	0.94 (0.33) *.855*	0.93 (0.33) *.840*	0.83 (0.31) *.612*	0.85 (0.31) *.650*	0.65 (0.26) *.290*
Count of social activities	0.58 (0.09) *.000*	0.58 (0.09) *.000*	0.68 (0.11) *.018*		0.74 (0.14) *.098*
Social Connectedness Index				0.69 (0.10) *.010*	
Perceived Isolation					
No one other than spouse willing to provide care (reference)					
Has someone other than spouse willing to provide care	0.98 (0.25) *.922*	0.97 (0.25) *.889*	0.94 (0.26) *.833*	0.97 (0.27) *.914*	0.90 (0.26) *.721*
Reciprocity					
Gave and received an equal amount of support (reference)					
Gave more support than received	1.19 (0.33) *.535*	1.21 (0.34) *.502*	1.25 (0.38) *.464*	1.25 (0.37) *.465*	1.13 (0.37) *.703*

Received more support than gave	1.32 (0.44) *.401*	1.33 (0.44) *.394*	1.23 (0.44) *.573*	1.27 (0.45) *.498*	1.11 (0.40) *.781*
Health Factors					
Low functioning/ borderline/low normal cognitive status (reference)					
Medium/high normal cognitive status			0.45 (0.15) *.018*	0.44 (0.15) *.014*	0.46 (0.16) *.024*
No CVD conditions (reference)					
At least one CVD condition			1.46 (0.40) *.173*	1.50 (0.42) *.148*	1.50 (0.44) *.172*
Not physically active (reference)					
Physically active			0.73 (0.22) *.288*	0.73 (0.22) *.289*	0.75 (0.24) *.372*
Demographic Characteristics					
Other race (reference)					
Non-Hispanic White			0.90 (0.32) *.769*	0.87 (0.31) *.696*	0.88 (0.32) *.728*

Age (mean)	1.10 (0.03) *.000*	1.10 (0.03) *.000*	1.10 (0.03) *.000*
Less than 12th grade (reference)			
12th grade or more	0.96 (0.28) *.883*	0.93 (0.28) *.806*	0.89 (0.27) *.702*
Male (reference)			
Female	0.55 (0.16) *.042*	0.58 (0.16) *.046*	0.60 (0.18) *.089*
No proxy respondent (reference)			
Proxy respondent	2.86 (1.54) *.051*	2.96 (1.56) *.039*	N/A
Time from Baseline (mean years)	1.23 (0.26) *.326*	1.25 (0.26) *.293*	1.30 (0.29) *.234*
Self-Respondents Only			
Did not feel lonely (reference)			
Felt lonely			1.90 (0.64) *.057*
Count of CES-D Score			1.03 (0.10) *.745*

Panel B. Non-Alzheimer's Dementia vs. Normal Cognition

Variable	Model 1 RRR (se) *p-value*	Model 2 RRR (se) *p-value*	Model 3 RRR (se) *p-value*	Model 4 RRR (se) *p-value*	Model 5 RRR (se) *p-value*	Model 6 (n=663) RRR (se) *p-value*
Genetic Predisposition						
No e4 alleles (reference)						
One e4 allele	1.87 (0.82) *.150*		2.40 (1.18) *.076*	2.09 (0.80) *.054*	2.30 (0.91) *.036*	2.27 (0.98) *.058*
Two e4 alleles	2.91 (3.03) *.305*		2.60 (3.01) *.408*	2.78 (3.16) *.369*	3.12 (3.26) *.274*	2.60 (3.36) *.460*
Social Connectedness						
Married and living with others (reference)						
Single and living alone		5.61 (2.70) *.000*	6.39 (3.33) *.000*	6.18 (3.055) *.000*		5.97 (3.41) *.002*
Single and living with others		1.17 (0.61) *.768*	1.35 (0.76) *.595*	1.53 (0.98) *.504*		2.35 (1.55) *.196*
0 to 6 family members (reference)						

7 to 11 family members	0.91 (0.53) *.864*	0.90 (0.50) *.850*	0.99 (0.49) *.989*	1.00 (0.49) *.991*	0.86 (0.47) *.785*
12 to 17 family members	1.13 (0.61) *.819*	1.17 (0.62) *.762*	1.42 (0.72) *.491*	1.35 (0.68) *.556*	1.33 (0.73) *.601*
18+ family members	1.51 (0.86) *.463*	1.41 (0.79) *.541*	0.65 (0.40) *.485*	0.81 (0.46) *.715*	0.37 (0.28) *.187*
Count of social activities	0.23 (0.07) *.000*	0.23 (0.06) *.000*	0.26 (0.09) *.000*		0.32 (0.11) *.001*
Social Connectedness Index				0.32 (0.07) *.000*	
Perceived Isolation					
No one other than spouse willing to provide care (reference)					
Has someone other than spouse willing to provide care	0.55 (0.21) *.123*	.533 (.204) *.100*	.505 (.207) *.096*	.548 (.220) *.134*	.533 (.232) *.148*
Reciprocity					
Gave and received an equal amount of support (reference)					
Gave more support than received	1.19 (0.65) *.751*	1.25 (0.70) *.692*	1.58 (0.77) *.344*	1.50 (0.73) *.405*	1.29 (0.66) *.617*

Received more support than gave	1.77 (0.82) *.220*	1.93 (0.91) *.165*	1.93 (0.94) *.174*	2.05 (0.96) *.125*	1.83 (0.93) *.233*
Health Factors					
Low functioning/ borderline/low normal cognitive status (reference)					
Medium/high normal cognitive status			0.12 (0.06) *.000*	0.11 (0.05) *.000*	0.09 (0.05) *.000*
No CVD conditions (reference)					
At least one CVD condition			8.48 (5.80) *.002*	8.42 (5.73) *.002*	9.97 (8.80) *.009*
Not physically active (reference)					
Physically active			1.43 (0.68) *.453*	1.52 (0.76) *.404*	1.46 (0.70) *.430*
Demographic Characteristics					
Other race (reference)					
Non-Hispanic White			1.03 (0.47) *.958*	1.21 (0.60) *.705*	1.28 (0.71) *.653*

Age (mean)	1.10 (0.04) *.003*	1.12 (0.04) *.000*	1.13 (0.04) *.001*
Less than 12th grade (reference)			
12th grade or more	0.70 (0.33) *.448*	0.69 (0.32) *.423*	0.55 (0.28) *.247*
Male (reference)			
Female	0.38 (0.18) *.037*	0.49 (0.20) *.079*	0.36 (0.18) *.045*
No proxy respondent (reference)			
Proxy respondent	9.27 (5.87) *.000*	8.50 (5.20) *.000*	N/A
Time from Baseline (mean years)	1.45 (0.40) *.180*	1.38 (0.38) *.235*	1.28 (0.39) *.423*
Self-Respondents Only			
Did not feel lonely (reference)			
Felt lonely			0.76 (0.42) *.623*
Count of CES-D Score			0.97 (0.13) *.838*

Panel C. Alzheimer's Disease vs. Normal Cognition

Variable	Model 1 RRR (se) *p-value*	Model 2 RRR (se) *p-value*	Model 3 RRR (se) *p-value*	Model 4 RRR (se) *p-value*	Model 5 RRR (se) *p-value*	Model 6 (n=663) RRR (se) *p-value*
Genetic Predisposition						
No e4 alleles (reference)						
One e4 allele	1.74 (0.45) *.034*		2.01 (0.59) *.017*	2.84 (0.98) *.002*	2.94 (1.02) *.002*	2.49 (0.91) *.012*
Two e4 alleles	11.65 (9.85) *.004*		9.60 (7.21) *.003*	19.96 (13.41) *.000*	21.67 (14.56) *.000*	15.90 (11.39) *.000*
Social Connectedness						
Married and living with others (reference)						
Single and living alone		1.74 (0.51) *.061*	1.99 (0.61) *.025*	0.86 (0.34) *.704*		0.86 (0.36) *.718*
Single and living with others		1.54 (0.66) *.318*	1.61 (0.63) *.223*	0.99 (0.48) *.977*		1.09 (0.53) *.861*
0 to 6 family members (reference)						

7 to 11 family members	0.91 (0.32) *.775*	0.96 (0.33) *.895*	1.48 (0.60) *.334*	1.61 (0.63) *.225*	1.35 (0.57) *.478*
12 to 17 family members	0.94 (0.34) *.870*	1.04 (0.37) *.920*	1.24 (0.54) *.624*	1.32 (0.58) *.536*	1.03 (0.48) *.948*
18+ family members	0.83 (0.33) *.645*	0.87 (0.33) *.713*	0.79 (0.36) *.608*	0.84 (0.38) *.695*	0.93 (0.43) *.878*
Count of social activities	0.33 (0.06) *.000*	0.33 (0.06) *.000*	0.57 (0.12) *.007*		0.65 (0.14) *.046*
Social Connectedness Index				0.67 (0.11) *.016*	
Perceived Isolation					
No one other than spouse willing to provide care (reference)					
Has someone other than spouse willing to provide care	1.15 (0.33) *.629*	1.20 (0.33) *.522*	1.13 (0.37) *.709*	1.16 (0.38) *.660*	1.04 (.369) *.909*
Reciprocity					
Gave and received an equal amount of support (reference)					
Gave more support than received	0.38 (0.14) *.006*	0.42 (0.15) *.013*	0.41 (0.18) *.043*	0.41 (0.18) *.045*	0.46 (0.21) *.085*

Received more support than gave	1.47 (0.46) *.219*	1.50 (0.47) *.200*	0.89 (0.35) *.764*	0.91 (0.35) *.804*	0.81 (0.32) *.594*
Health Factors					
Low functioning/ borderline/low normal cognitive status (reference)					
Medium/high normal cognitive status			0.06 (0.02) *.000*	0.06 (0.02) *.000*	0.06 (0.02) *.000*
No CVD conditions (reference)					
At least one CVD condition			0.72 (0.23) *.307*	0.73 (0.24) *.320*	0.67 (0.23) *.242*
Not physically active (reference)					
Physically active			1.06 (0.35) *.868*	0.96 (0.32) *.899*	1.01 (0.35) *.967*
Demographic Characteristics					
Other race (reference)					
Non-Hispanic White			1.63 (0.67) *.231*	1.56 (0.62) *.262*	1.50 (0.64) *.340*

Age (mean)	1.22 (0.03) *.000*	1.22 (0.03) *.000*	1.22 (0.04) *.000*
Less than 12th grade (reference)			
12th grade or more	1.24 (0.45) *.548*	1.24 (0.45) *.555*	1.44 (0.58) *.365*
Male (reference)			
Female	1.44 (0.55) *.340*	1.30 (0.47) *.475*	1.38 (0.55) *.426*
No proxy respondent (reference)			
Proxy respondent	7.63 (4.36) *.000*	8.89 (4.99) *.000*	N/A
Time from Baseline (mean years)	1.37 (0.31) *.161*	1.36 (0.31) *.165*	1.16 (0.26) *.490*
Self-Respondents Only			
Did not feel lonely (reference)			
Felt lonely			1.03 (0.43) *.937*
Count of CES-D Score			1.06 (0.11) *.552*

Change Analysis

Change variables were created in order to determine whether a change from 1998 to 2002 in the social environment or health was associated with cognitive diagnosis. The variables selected for the change analysis were those that were found to be significant in unadjusted regression models that examined the relationship between the baseline variables and cognitive diagnosis (see above). It should be noted that age, gender, education, and proxy status were found to be significant in preliminary bivariate regression analysis but were not included in the change analysis. Gender and education were not expected to change in the sample between waves, whereas age would increase between waves. Proxy status was not included in the change variable analysis since it is expected that respondents who required a proxy would be in poorer cognitive or physical health. Therefore, proxy status would be more a reflection of a respondent's health status than provide additional information about its relationship to cognitive status. There were a total of eight statistically significant variables that were analyzed: living arrangement, social engagement, feelings of loneliness, reciprocity, depressive symptomatology, physical activity, CVD status, and cognitive status score. It should be noted that it cannot be ascertained with these data when the observed changes took place in relation to a change in cognitive status. Thus it is unclear whether the observed change in social environment or health may be a result of a change in cognitive diagnosis. Percentages and bivariate regression results for the change variables are reported in **Tables 5.7** through **5.9**.

Approximately 17% of respondents experienced a change in living arrangement from 1998 to 2002 (see **Table 5.7**). About 33% of the sample became less socially

engaged and almost 14% of self-respondents reported feeling lonely at follow-up who had previously not reported feelings of loneliness. Almost half of the sample had a lower cognitive score at follow-up than they did at baseline.

Bivariate regression results demonstrated that a change in social engagement and feelings of loneliness correlated with risk of cognitive difficulty (see **Table 5.8**). Respondents who became more engaged in social activities had a significantly lower risk of being diagnosed with non-Alzheimer's dementia and Alzheimer's disease than individuals who experienced no change in their level of engagement between waves (RRR=0.14 and p=.011; RRR=0.48 and p=.052). Surprisingly, respondents who became less engaged were also at less risk of being diagnosed with Alzheimer's disease (RRR=0.59; p=.062). This result is reported at the 10% level of significance and may be reflective of a Type I error. Additionally, the variable for social engagement was based on whether respondents were working, volunteering, or reported helping friends. It may be that individuals became less involved in these activities due to increased involvement in other activities not captured in this study. When examining self-respondents only on feelings of loneliness, those who reported feeling lonely at follow-up who had not been lonely at baseline had a significantly greater risk of being diagnosed with Alzheimer's disease or another type of dementia (RRR=2.24 and p=.054; RRR=2.87 and p=.061). Respondents who no longer felt lonely at follow-up, but who had been lonely at baseline, were at greater risk of being diagnosed with non-Alzheimer's dementia (RRR=4.86 and p=.079). This may also be the result of a Type I error or it may be due to a limitation of the variable. The HRS asked respondents whether they had felt lonely in the week prior to the interview. Respondents may have responded based on immediate circumstances

(such as a visit from a child or not having seen a child recently) rather than overall feelings of loneliness.

A change in cognitive score, physical activity, and depressive symptomatology was also related to cognitive diagnosis (see **Table 5.9**). Respondents who had lower cognitive scores at follow-up than they did at baseline were at significantly greater risk of being diagnosed with non-Alzheimer's dementia, Alzheimer's disease, and CIND (RRR=7.10 and p=.000; RRR=6.70 and p=.000; RRR=4.38 and p=.000). Interestingly, individuals whose scores improved were also at greater risk of being diagnosed with Alzheimer's disease (RRR=2.76 and p=.021). This finding is unexpected and may be a reflection of a Type I error or related to the use of proxy respondents. The use of proxy respondents increases with age and since the ADAMS sample was older, more ADAMS respondents had a proxy. The majority of ADAMS participants with a proxy respondent (60%) had cognitive difficulty (Langa, et al., 2005). It has been noted that scores on the IQCODE (used in the HRS to determine cognitive score among individuals with a proxy respondent) can be affected by informant characteristics such as mental health, age, education, and relationship to the individual. Proxy respondents may tailor responses in order to achieve a desired outcome. For example, some respondents may report more severe cognitive decline in order to get support services. Thus the validity of the data obtained using the IQCODE can vary based on the proxy respondent and may be a reflection of informant characteristics or the informant's relationship to the respondent (Jorm, 2004) rather than an actual improvement in cognitive score.

Respondents who became physically active at follow-up had a lower risk of being diagnosed with Alzheimer's disease and another type of dementia (RRR=0.35 and

p=.020; RRR=0.13 and p=.053). Self-respondents who reported being depressed at follow-up who had not been depressed at baseline were at greater risk of being diagnosed with CIND (RRR=2.11 and p=.017).

Overall, a change in social engagement and an increase in physical activity were associated with a lower risk of cognitive difficulty. Experiencing a change in feelings of loneliness and cognitive status as well as becoming depressed were associated with a greater risk of cognitive difficulty.

Table 5.7. Change Variables from 1998 to 2002 Wave

Variable	Num	Pct
Living Arrangement		
Change	118	16.9
No change	582	83.1
Total	700	100.0
Social Engagement		
More engaged	81	11.6
Less engaged	234	33.4
No change	385	55.0
Total	700	100.0
Loneliness (self-respondents only)		
Became lonely	74	13.5
No longer lonely	51	9.3
No change	422	77.1
Total	547	99.9
Reciprocity		
Change	389	55.6
No change	311	44.4
Total	700	100.0
Cognitive Score		
Score improved	94	13.4
Score worsened	325	46.4
No change	281	40.1
Total	700	99.9
CVD		
Developed CVD	72	10.3
No change	628	89.7
Total	700	100.0
CESD Score (self-respondents only)		
Became depressed	180	32.9
No longer depressed	186	34.0
No change	181	33.1
Total	547	100.0
Physical Activity		
Became active	70	10.0
No longer active	125	17.9
No change	505	72.1
Total	700	100.0

Table 5.8. Bivariate Regression Results for Change in Social Environment

	Cognitive Impairment not Demented vs. Normal Cognition			Non-Alzheimer's Dementia vs. Normal Cognition			Alzheimer's Disease vs. Normal Cognition		
Variable	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**
Living Arrangement									
No change (reference)									
Change	1.47	0.50	.252	1.49	0.75	.427	1.51	0.48	.196
Social Engagement									
No change (reference)									
More engaged	0.52	0.22	.128	0.14	0.11	.011	0.48	0.18	.052
Less engaged	0.83	0.22	.486	0.73	0.38	.544	0.59	0.17	.062
Loneliness*									
No change (reference)									
No longer lonely	2.06	0.91	.102	4.86	4.36	.079	2.14	1.17	.163
Became lonely	1.22	0.47	.616	2.87	1.62	.061	2.24	0.93	.054
Reciprocity									
No change (reference)									
Change	0.82	0.20	.426	0.73	0.30	.442	0.68	0.18	.136

*Only asked of self-respondents (n=547).

Table 5.9. Bivariate Regression Results for Change in Health Factors and Proxy Status

	Cognitive Impairment not Demented vs. Normal Cognition			Non-Alzheimer's Dementia vs. Normal Cognition			Alzheimer's Disease vs. Normal Cognition		
Variable	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**	**Relative Risk Ratio**	**Robust Standard Error**	**P-Value**
Cognitive Score									
No change (reference)									
Score improved	1.25	0.47	.556	2.78	2.13	.182	2.76	1.22	.021
Score worsened	4.38	1.22	.000	7.10	2.93	.000	6.70	1.91	.000
CVD									
No change (reference)									
Developed CVD	0.82	0.17	.323	0.62	0.23	.207	0.93	0.19	.704
CESD Score*									
No change (reference)									
Became depressed	2.11	0.66	.017	1.09	0.68	.885	1.53	0.63	.302
No longer depressed	1.40	0.45	.297	0.69	0.45	.573	0.98	0.39	.955
Physical Activity									
No change (reference)									
Became active	0.56	0.24	.183	0.13	0.14	.053	0.35	0.16	.020
No longer active	0.90	0.30	.740	0.47	0.22	.109	0.86	0.28	.641

*Only asked of self-respondents (n=547).

Moderating Effects

This study sought to examine whether aspects of the social environment might serve as moderators of the relationship between genetic predisposition and cognitive diagnosis. Variables were created that combined the dichotomous version of the APOE-e4 allele and each of the social environment variables (living arrangement, family network size, social engagement, social support, reciprocity, and loneliness) to test this relationship. These moderating effect terms were included in a regression model that was adjusted for genetic predisposition and the social environment (Model 1) as well as a fully adjusted model that included all of the covariates (Model 3). The moderating effect terms were added to the models individually. Only statistically significant relationships for the terms that address the research question are discussed in this section. The results for the covariates included in the fully adjusted model are not presented or discussed.

A Wald test was used to determine whether inclusion of the moderating effect terms in the models improved model fit. In STATA this was achieved by first running a multinomial logistic regression, then using the "test" command followed by the moderating effect term being tested. The Wald test was employed on all the models analyzed in order to test for goodness of fit. The results of these analyses assist us in answering the following question:

> ***Research Question 4:*** *Do characteristics of the social environment moderate the relationship of the APOE-e4 allele to cognitive diagnosis? From the perspective of examining the gene-environment relationship in dementia diagnosis, this study seeks to examine whether the genetic risks for developing Alzheimer's disease*

that have been associated with the APOE-e4 allele are moderated by aspects of the social environment.

Living Arrangement Moderating Term

To examine the moderating effect of living arrangement, a set of dichotomous variables that capture the unique combinations of the living arrangement variable and the dichotomous APOE-e4 allele were added in Model 2 (see **Table 5.10**). Compared to married respondents who did not have the APOE-e4 allele (reference group), single persons who lived alone and had at least one APOE-e4 allele had an increased risk of non-Alzheimer's dementia relative to normal cognition (RRR=12.95; p=.000). It should be noted that the large effect observed is likely due to small sample size (n=10). The risk of Alzheimer's disease relative to normal cognition was highest among respondents who had at least one e4 allele and were single, either living with others or living alone, compared to respondents who were married without the e4 allele (RRR=5.88 and p=.021; RRR=3.78 and p=.004 respectively). The risk of being diagnosed with Alzheimer's disease relative to normal cognition was greater for married persons with the e4 allele compared to married persons without the e4 allele (RRR=2.16 and p=.055). Results from a Wald test demonstrated that the moderating term for living arrangement improved model fit (Wald Statistic=0.0049).

When examining the moderating effect of living arrangement in a fully adjusted model (Model 4), the results demonstrated that among married respondents, those with at least one e4 allele were at greater risk of being diagnosed with CIND than those who did not have the e4 allele (RRR=2.10 and p=.058). The risk of non-Alzheimer's dementia

was greatest among respondents with at least one e4 allele who were single and lived alone when compared to respondents who were married without the e4 allele (RRR=10.79 and p=.000; n=10). Respondents who were single and lived alone without the e4 allele were also at greater risk of being diagnosed with non-Alzheimer's dementia than married respondents with no e4 alleles (RRR=4.68 and p=.006). Married respondents who had at least one e4 allele were at greater risk of being diagnosed with Alzheimer's disease than married respondents without any e4 alleles (RRR=4.92 and p=.001). The risk of Alzheimer's disease was greater among respondents who had at least one e4 allele and were single and lived with others compared to married respondents without any e4 alleles (RRR=2.93 and p=.093). Addition of the moderating effect terms for living arrangement improved the model fit (Wald Statistic=0.0002).

Overall, being single and living alone was associated with a greater risk of non-Alzheimer's dementia among respondents with and without the e4 allele. Being single and having at least one e4 allele, regardless of living arrangement, was associated with a greater risk of Alzheimer's disease.

Table 5.10. Results of Hierarchical Regression Models with Living Arrangement Moderating Effect Terms

Panel A. CIND vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	1.31 (0.37)	.330			1.65 (0.48)	.084		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.46 (0.41)	.170			1.43 (0.47)	.282		
Single and living with others	1.32 (0.48)	.451			1.40 (0.58)	.415		
0 to 6 family members (reference)								

7 to 11 family members	0.70 (0.23)	.272	0.70 (0.22)	.260	0.81 (0.29)	.546	0.81 (0.29)	.547
12 to 17 family members	0.75 (0.27)	.421	0.75 (0.26)	.415	0.86 (0.32)	.687	0.86 (0.32)	.671
18+ family members	0.92 (0.33)	.819	0.91 (0.32)	.798	0.82 (0.31)	.591	0.79 (0.30)	.538
Count of social activities	0.58 (0.09)	.000	0.58 (0.09)	.000	0.68 (0.11)	.018	0.69 (0.11)	.023
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.97 (0.25)	.905	0.97 (0.25)	.896	0.95 (0.26)	.846	0.94 (0.26)	.830
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.20 (0.34)	.520	1.19 (0.33)	.543	1.24 (0.37)	.472	1.23 (0.37)	.493
Received more support than gave	1.34 (0.44)	.376	1.32 (0.44)	.398	1.26 (0.45)	.517	1.24 (0.44)	.545

Interaction Term				
Married, living with others with no e4 allele (reference)				
Married, living with others with at least one e4 allele	1.59 (0.60)	.213	2.10 (0.83)	.058
Single, living alone with no e4 allele	1.66 (0.53)	.117	1.66 (0.64)	.192
Single, living alone with at least one e4 allele	1.66 (0.82)	.307	1.92 (0.93)	.177
Single, living with others with no e4 allele	1.48 (0.62)	.344	1.67 (0.79)	.284
Single, living with others with at least one e4 allele	1.55 (1.02)	.503	1.78 (1.04)	.326

Panel B. Non-Alzheimer's Dementia vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.36 (1.12)	.071			2.05 (0.76)	.053		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	6.29 (3.26)	.000			6.26 (3.14)	.000		
Single and living with others	1.32 (0.72)	.615			1.45 (0.94)	.565		
0 to 6 family members (reference)								
7 to 11 family members	0.88 (0.49)	.812	0.85 (0.47)	.773	0.97 (0.49)	.957	0.94 (0.48)	.908

12 to 17 family members	1.16 (0.61)	.783	1.25 (0.66)	.669	1.38 (0.71)	.529	1.39 (0.71)	.519
18+ family members	1.41 (0.79)	.538	1.43 (0.79)	.519	0.64 (0.39)	.472	0.66 (0.41)	.505
Count of social activities	0.24 (0.07)	.000	0.23 (0.07)	.000	0.27 (0.09)	.000	0.27 (0.09)	.000
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.55 (0.21)	.116	0.54 (0.21)	.113	0.52 (0.21)	.112	0.52 (0.21)	.112
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.25 (0.70)	.693	1.40 (0.78)	.547	1.63 (0.79)	.317	1.66 (0.80)	.294
Received more support than gave	1.89 (0.89)	.176	1.90 (0.91)	.181	2.02 (0.97)	.144	1.95 (0.94)	.164

Interaction Term				
Married, living with others with no e4 allele (reference)				
Married, living with others with at least one e4 allele	0.51 (0.34)	.303	1.05 (0.70)	.938
Single, living alone with no e4 allele	3.21 (1.54)	.015	4.68 (2.64)	.006
Single, living alone with at least one e4 allele	12.95 (8.92)	.000	10.79 (7.14)	.000
Single, living with others with no e4 allele	0.89 (0.52)	.840	1.27 (0.94)	.749
Single, living with others with at least one e4 allele	1.81 (1.59)	.498	2.07 (1.89)	.427

Panel C. Alzheimer's Disease vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.47 (0.73)	.002			3.48 (1.14)	.000		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.95 (0.58)	.025			0.84 (0.32)	.645		
Single and living with others	1.70 (0.73)	.216			0.97 (0.46)	.942		
0 to 6 family members (reference)								
7 to 11 family members	0.91 (0.33)	.799	0.92 (0.33)	.808	1.50 (0.60)	.310	1.50 (0.60)	.306

12 to 17 family members	0.98 (0.36)	.956	0.97 (0.35)	.924	1.21 (0.53)	.664	1.19 (0.52)	.684
18+ family members	0.83 (0.33)	.627	0.83 (0.32)	.633	0.77 (0.36)	.583	0.75 (0.36)	.546
Count of social activities	0.33 (0.06)	.000	0.33 (0.06)	.000	0.56 (0.12)	.007	0.57 (0.12)	.008
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	1.14 (0.33)	.651	1.17 (0.33)	.578	1.09 (0.36)	.799	1.08 (0.35)	.820
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	0.40 (0.14)	.009	0.41 (0.14)	.010	0.40 (0.18)	.037	0.38 (0.18)	.036
Received more support than gave	1.57 (0.49)	.147	1.60 (0.50)	.129	0.99 (0.38)	.982	0.97 (0.37)	.934
Interaction Term								
Married, living with others with no								

e4 allele (reference)				
Married, living with others with at least one e4 allele	2.16 (0.87)	.055	4.92 (2.47)	.001
Single, living alone with no e4 allele	1.96 (0.70)	.060	1.07 (0.52)	.886
Single, living alone with at least one e4 allele	3.78 (1.73)	.004	2.52 (1.45)	.108
Single, living with others with no e4 allele	1.22 (0.56)	.668	1.25 (0.78)	.721
Single, living with others with at least one e4 allele	5.88 (4.528)	.021	2.93 (1.88)	.093

Note: Regression Models 3 and 4 were run with additional covariates for baseline cognitive status, CVD, physical activity, race/ethnicity, age, education, gender, proxy status, and time since baseline.

Family Network Size Moderating Term

Regression models were run to test the moderating effect of family network size on the relationship between the APOE-e4 allele and cognitive diagnosis. Dichotomous variables for each of the unique combinations of family network size and the dichotomous version of the APOE variable were included in the models and results are reported in **Table 5.11**. When the family network size moderating terms were added in Model 2, family network size was found to modestly moderate the relationship of APOE-e4 with cognitive diagnosis in two instances. The risk of CIND relative to normal cognition was lower among respondents who had 7 to 11 family members and did not have the e4 allele compared to respondents with 6 or fewer family members who did not have the e4 allele (RRR=0.52 and p=.076). The risk of non-Alzheimer's dementia relative to normal cognition was greater among respondents who had 18 or more family members and at least one e4 allele compared to respondents with 6 or fewer family members without the e4 allele (RRR=3.66 and p=.092). A Wald test did not demonstrate an improvement in model fit when adding the moderating effect terms for family network size to the unadjusted model (Wald Statistic= 0.2355).

The moderating effect terms for family network size were added in Model 4, which was a fully adjusted model. Regression results demonstrated that the risk of Alzheimer's disease was greater among respondents who had 7 to 11 family members or 12 to 17 family members and at least one e4 allele when compared to respondents who had 6 or fewer family members without any e4 alleles (RRR=5.82 and p=.004; RRR=3.37 and p=.080 respectively). A Wald test demonstrated a modest improvement in model fit with the addition of the family network size moderating effect terms (Wald

Statistic=0.0886). Overall, respondents who had more than 6 family members and at least one e4 allele were at greater risk of being diagnosed with Alzheimer's disease.

Table 5.11. Results of Hierarchical Regression Models with Family Network Size Moderating Effect Terms

Panel A. CIND vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	1.31 (0.37)	.330			1.65 (0.48)	.084		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.46 (0.41)	.170	1.48 (0.42)	.160	1.43 (0.47)	.282	1.48 (0.49)	.232
Single and living with others	1.32 (0.48)	.451	1.34 (0.48)	.416	1.40 (0.58)	.415	1.42 (0.58)	.384
0 to 6 family members (reference)								

7 to 11 family members	0.70 (0.23)	.272			0.81 (0.29)	.546		
12 to 17 family members	0.75 (0.27)	.421			0.86 (0.32)	.687		
18+ family members	0.92 (0.33)	.819			0.82 (0.31)	.591		
Count of social activities	0.58 (0.09)	.000	0.57 (0.09)	.000	0.68 (0.11)	.018	0.67 (0.11)	.015
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.97 (0.25)	.905	0.97 (0.25)	.914	0.95 (0.26)	.846	0.94 (0.27)	.826
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.20 (0.34)	.520	1.12 (0.32)	.678	1.24 (0.37)	.472	1.18 (0.36)	.579
Received more support than gave	1.34 (0.44)	.376	1.31 (0.44)	.423	1.26 (0.45)	.517	1.27 (0.46)	.508

Interaction Term				
6 or fewer family members with no e4 allele (reference)				
6 or fewer family members with at least one e4 allele	0.46 (0.27)	.184	0.59 (0.34)	.356
7 to 11 family members with no e4 allele	0.52 (0.19)	.076	0.60 (0.24)	.202
7 to 11 family members with at least one e4 allele	0.95 (0.49)	.923	1.48 (0.84)	.488
12 to 17 family members with no e4 allele	0.57 (0.23)	.157	0.70 (0.29)	.390
12 to 17 family members with at least one e4 allele	0.95 (0.60)	.934	1.24 (0.82)	.750
18+ family members with no e4 alleles	0.61 (0.25)	.233	0.55 (0.25)	.193
18+ family members with at least one e4 allele	1.42 (0.78)	.522	1.51 (0.85)	.458

Panel B. Non-Alzheimer's Dementia vs. Normal Cognition

Variable	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.36 (1.12)	.071			2.05 (0.76)	.053		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	6.29 (3.26)	.000	5.96 (2.95)	.000	6.26 (3.14)	.000	6.25 (3.13)	.000
Single and living with others	1.32 (0.72)	.615	1.29 (0.72)	.648	1.45 (0.94)	.565	1.58 (1.07)	.497
0 to 6 family members (reference)								
7 to 11 family members	0.88 (0.49)	.812			0.97 (0.49)	.957		

12 to 17 family members	1.16 (0.61)	.783			1.38 (0.71)	.529		
18+ family members	1.41 (0.79)	.538			0.64 (0.39)	.472		
Count of social activities	0.24 (0.07)	.000	0.24 (0.07)	.000	0.27 (0.09)	.000	0.27 (0.09)	.000
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.55 (0.21)	.116	0.55 (0.21)	.112	0.52 (0.21)	.112	0.57 (0.23)	.161
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.25 (0.70)	.693	1.26 (0.68)	.670	1.63 (0.79)	.317	1.61 (0.79)	.333
Received more support than gave	1.89 (0.89)	.176	1.87 (0.93)	.205	2.02 (0.97)	.144	1.97 (0.97)	.170
Interaction Term								
6 or fewer family members with no e4 allele (reference)								

6 or fewer family members with at least one e4 allele	2.57 (1.81)	.181	1.91 (1.36)	.363
7 to 11 family members with no e4 allele	0.77 (0.44)	.641	0.84 (0.50)	.769
7 to 11 family members with at least one e4 allele	3.00 (2.88)	.253	3.06 (2.18)	.117
12 to 17 family members with no e4 allele	1.74 (1.10)	.379	1.96 (1.18)	.261
12 to 17 family members with at least one e4 allele	0.45 (0.41)	.382	0.49 (0.47)	.453
18+ family members with no e4 alleles	1.54 (1.06)	.531	0.66 (0.50)	.579
18+ family members with at least one e4 allele	3.66 (2.82)	.092	1.64 (1.31)	.536

Panel C. Alzheimer's Disease vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.47 (0.73)	.002			3.48 (1.14)	.000		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.95 (0.58)	.025	1.98 (0.59)	.023	0.84 (0.32)	.645	0.88 (0.34)	.746
Single and living with others	1.70 (0.73)	.216	1.72 (0.74)	.210	0.97 (0.46)	.942	0.98 (0.47)	.965
0 to 6 family members (reference)								
7 to 11 family members	0.91 (0.33)	.799			1.50 (0.60)	.310		

12 to 17 family members	0.98 (0.36)	.956			1.21 (0.53)	.664		
18+ family members	0.83 (0.33)	.627			0.77 (0.36)	.583		
Count of social activities	0.33 (0.06)	.000	0.33 (0.06)	.000	0.56 (0.12)	.007	0.56 (0.12)	.007
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	1.14 (0.33)	.651	1.13 (0.33)	.668	1.09 (0.36)	.799	1.08 (0.36)	.812
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	0.40 (0.14)	.009	0.39 (0.14)	.009	0.40 (0.18)	.037	0.39 (0.17)	.035
Received more support than gave	1.57 (0.49)	.147	1.55 (0.49)	.165	0.99 (0.38)	.982	1.01 (0.38)	.981

Interaction Term				
6 or fewer family members with no e4 allele (reference)				
6 or fewer family members with at least one e4 allele	1.93 (1.07)	.240	1.96 (1.10)	.230
7 to 11 family members with no e4 allele	0.83 (0.35)	.652	1.19 (0.60)	.732
7 to 11 family members with at least one e4 allele	2.46 (1.40)	.113	5.82 (3.55)	.004
12 to 17 family members with no e4 allele	0.97 (0.43)	.938	1.11 (0.60)	.854
12 to 17 family members with at least one e4 allele	2.22 (1.35)	.191	3.37 (2.34)	.080
18+ family members with no e4 alleles	0.78 (0.39)	.620	0.64 (0.39)	.461
18+ family members with at least one e4 allele	2.08 (1.14)	.180	2.62 (1.84)	.170

Note: Regression Models 3 and 4 were run with additional covariates for baseline cognitive status, CVD, physical activity, race/ethnicity, age, education, gender, proxy status, and time since baseline.

Social Engagement Interaction Term

Results of regression models that included the interaction of social engagement with the APOE-e4 variable are reported in **Table 5.12**. Results for both Model 2 and Model 4 that included the social engagement interaction term did not demonstrate statistical significance. A Wald test to determine goodness of fit did not demonstrate an improvement in model fit for either Model 2 or Model 4 when the social engagement interaction term was added to the model (Model 2 Wald Statistic=0.6880; Model 4 Wald Statistic=0.6050).

Table 5.12. Results of Hierarchical Regression Models with Social Engagement Interaction Term

Panel A. CIND vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	1.31 (0.37)	.330	1.75 (0.78)	.208	1.65 (0.48)	.084	2.40 (1.15)	.066
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.46 (0.41)	.170	1.48 (0.41)	.155	1.43 (0.47)	.282	1.45 (0.48)	.258
Single and living with others	1.32 (0.48)	.451	1.33 (0.49)	.432	1.40 (0.58)	.415	1.46 (0.60)	.358
0 to 6 family members (reference)								
7 to 11 family members	0.70 (0.23)	.272	0.70 (0.23)	.270	0.81 (0.29)	.546	0.81 (0.28)	.539

12 to 17 family members	0.75 (0.27)	.421	0.75 (0.27)	.422	0.86 (0.32)	.687	0.88 (0.33)	.721
18+ family members	0.92 (0.33)	.819	0.93 (0.33)	.827	0.82 (0.31)	.591	0.82 (0.31)	.600
Count of social activities	0.58 (0.09)	.000	0.63 (0.10)	.003	0.68 (0.11)	.018	0.76 (0.13)	.110
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.97 (0.25)	.905	0.97 (0.25)	.910	0.95 (0.26)	.846	0.94 (0.26)	.829
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.20 (0.34)	.520	1.20 (0.34)	.509	1.24 (0.37)	.472	1.25 (0.38)	.464
Received more support than gave	1.34 (0.44)	.376	1.35 (0.44)	.359	1.26 (0.45)	.517	1.30 (0.46)	.468
Interaction Term								
Social engagement x APOE-e4			0.72 (0.30)	.438			0.67 (0.29)	.351

Panel B. Non-Alzheimer's Dementia vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.36 (1.12)	.071	2.22 (1.18)	.132	2.05 (0.76)	.053	2.04 (1.06)	.169
Social Connectedness								
Married and living with others (reference)								
Single and living alone	6.29 (3.26)	.000	6.26 (3.15)	.000	6.26 (3.14)	.000	6.36 (3.19)	.000
Single and living with others	1.32 (0.72)	.615	1.31 (0.71)	.623	1.45 (0.94)	.565	1.44 (0.94)	.575
0 to 6 family members (reference)								
7 to 11 family members	0.88 (0.49)	.812	0.89 (0.50)	.836	0.97 (0.49)	.957	0.97 (0.49)	.953

12 to 17 family members	1.16 (0.61)	.783	1.15 (0.61)	.793	1.38 (0.71)	.529	1.36 (0.70)	.547
18+ family members	1.41 (0.79)	.538	1.45 (0.82)	.515	0.64 (0.39)	.472	0.67 (0.41)	.507
Count of social activities	0.24 (0.07)	.000	0.21 (0.08)	.000	0.27 (0.09)	.000	0.25 (0.11)	.001
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.55 (0.21)	.116	.55 (0.21)	.118	0.52 (0.21)	.112	0.52 (0.21)	.108
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.25 (0.70)	.693	1.24 (0.68)	.696	1.63 (0.79)	.317	1.57 (0.76)	.351
Received more support than gave	1.89 (0.89)	.176	1.91 (0.90)	.173	2.02 (0.97)	.144	2.03 (0.98)	.140
Interaction Term								
Social engagement x APOE-e4			1.29 (0.71)	.642			1.24 (0.70)	.707

Panel C. Alzheimer's Disease vs. Normal Cognition

Variable	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.47 (0.73)	.002	2.38 (1.01)	.041	3.48 (1.14)	.000	3.39 (1.57)	.009
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.95 (0.58)	.025	1.97 (0.59)	.023	0.84 (0.32)	.645	0.86 (0.33)	.691
Single and living with others	1.70 (0.73)	.216	1.71 (0.74)	.215	0.97 (0.46)	.942	0.97 (0.47)	.951
0 to 6 family members (reference)								
7 to 11 family members	0.91 (0.33)	.799	0.92 (0.33)	.816	1.50 (0.60)	.310	1.47 (0.59)	.337

12 to 17 family members	0.98 (0.36)	.956	0.98 (0.36)	.954	1.21 (0.53)	.664	1.21 (0.52)	.663
18+ family members	0.83 (0.33)	.627	0.83 (0.33)	.635	0.77 (0.36)	.583	0.78 (0.37)	.597
Count of social activities	0.33 (0.06)	.000	0.30 (0.08)	.000	0.56 (0.12)	.007	0.51 (0.15)	.026
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	1.14 (0.33)	.651	1.13 (0.33)	.668	1.09 (0.36)	.799	1.05 (0.35)	.875
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	0.40 (0.14)	.009	0.40 (0.14)	.009	0.40 (0.18)	.037	0.39 (0.18)	.037
Received more support than gave	1.57 (0.49)	.147	1.56 (0.49)	.154	0.99 (0.38)	.982	1.01 (0.38)	.988
Interaction Term								
Social engagement x APOE-e4			1.17 (0.48)	.698			1.19 (0.56)	.713

Note: Regression Models 3 and 4 were run with additional covariates for baseline cognitive status, CVD, physical activity, race/ethnicity, age, education, gender, proxy status, and time since baseline.

Perceived Social Support Moderating Term

In order to test the moderating effect of the perception of social support on the relationship between the APOE-e4 allele and cognitive diagnosis, dichotomous variables for each of the unique combinations of perceived social support and the dichotomous version of the APOE-e4 allele were created and included in the model. Regression results obtained from running Model 2 that included the moderating effect terms for perceived social support are reported in **Table 5.13**. The risk of being diagnosed with Alzheimer's disease compared to normal cognition was greater among respondents who did not perceive they had social support available to them and who had at least one e4 allele compared to respondents who did not perceive they had social support available to them but who did not have any e4 alleles (RRR=2.72 and p=.035). The risk of Alzheimer's disease was found to be greater among respondents who perceived they had social support available to them and who had at least one e4 allele compared to respondents who did not perceive they had social support available and did not have any e4 alleles (RRR=2.83 and p=.011). However, the addition of the social support moderating effect terms were not found to improve model fit (Wald Statistic=0.1133).

The previous findings were consistent when including the perceived social support moderating effect terms in Model 4, which includes covariates that control for health factors and demographic characteristics. Among respondents who did not perceive they had social support available to them, those who had at least one e4 allele were at greater risk of being diagnosed with Alzheimer's disease and non-Alzheimer's dementia compared to respondents who did not have any e4 alleles (RRR=4.52 and p=.002; RRR=2.77 and p=.035). Respondents who perceived they had social support available to

them and had at least one e4 allele were at greater risk of being diagnosed with Alzheimer's disease than respondents who did not perceive they had social support available to them and did not have any e4 alleles (RRR=3.65 and p=.010). A Wald test did demonstrate that the addition of the social support moderating effect terms improved model fit in the fully adjusted model (Wald Statistic=0.0174). Overall, respondents who did not believe they had social support available to them and had at least one e4 allele were at greater risk of being diagnosed with non-Alzheimer's dementia and Alzheimer's disease.

Table 5.13. Results of Hierarchical Regression Models with Perceived Social Support Moderating Effect Terms

Panel A. CIND vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	1.31 (0.37)	.330			1.65 (0.48)	.084		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.46 (0.41)	.170	1.47 (0.41)	.168	1.43 (0.47)	.282	1.42 (0.47)	.285
Single and living with others	1.32 (0.48)	.451	1.32 (0.48)	.441	1.40 (0.58)	.415	1.40 (0.58)	.414
0 to 6 family members (reference)								

7 to 11 family members	0.70 (0.23)	.272	0.71 (0.23)	.279	0.81 (0.29)	.546	0.81 (0.29)	.556
12 to 17 family members	0.75 (0.27)	.421	0.76 (0.27)	.435	0.86 (0.32)	.687	0.86 (0.32)	.692
18+ family members	0.92 (0.33)	.819	0.92 (0.32)	.815	0.82 (0.31)	.591	0.82 (0.31)	.586
Count of social activities	0.58 (0.09)	.000	0.58 (0.09)	.000	0.68 (0.11)	.018	0.68 (0.11)	.018
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.97 (0.25)	.905			0.95 (0.26)	.846		
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.20 (0.34)	.520	1.20 (0.34)	.526	1.24 (0.37)	.472	1.25 (0.37)	.466
Received more support than gave	1.34 (0.44)	.376	1.33 (0.44)	.383	1.26 (0.45)	.517	1.27 (0.46)	.514

Interaction Term					
Does not have someone other than spouse willing to provide care with no e4 allele (reference)					
Does not have someone other than spouse willing to provide care with at least one e4 allele	1.18 (0.48)	.688		1.55 (0.65)	.295
Has someone other than spouse willing to provide care with no e4 allele	0.92 (0.27)	.765		0.92 (0.30)	.791
Has someone other than spouse willing to provide care with at least one e4 allele	1.33 (0.53)	.481		1.59 (0.70)	.287

Panel B. Non-Alzheimer's Dementia vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.36 (1.12)	.071			2.05 (0.76)	.053		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	6.29 (3.26)	.000	6.31 (3.29)	.000	6.26 (3.14)	.000	6.33 (3.14)	.000
Single and living with others	1.32 (0.72)	.615	1.32 (0.73)	.618	1.45 (0.94)	.565	1.47 (0.97)	.562
0 to 6 family members (reference)								
7 to 11 family members	0.88 (0.49)	.812	0.86 (0.46)	.778	0.97 (0.49)	.957	0.94 (0.46)	.892
12 to 17 family members	1.16 (0.61)	.783	1.15 (0.61)	.787	1.38 (0.71)	.529	1.41 (0.72)	.505

18+ family members	1.41 (0.79)	.538	1.40 (0.79)	.547	0.64 (0.39)	.472	0.64 (0.40)	.475
Count of social activities	0.24 (0.07)	.000	0.24 (0.07)	.000	0.27 (0.09)	.000	0.27 (0.09)	.000
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.55 (0.21)	.116			0.52 (0.21)	.112		
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.25 (0.70)	.693	1.25 (0.71)	.691	1.63 (0.79)	.317	1.58 (0.77)	.346
Received more support than gave	1.89 (0.89)	.176	1.90 (0.90)	.174	2.02 (0.97)	.144	2.03 (0.97)	.140
Interaction Term								
Does not have someone other than spouse willing to provide care with no e4 allele (reference)								

Does not have someone other than spouse willing to provide care with at least one e4 allele	2.65 (1.73)	.137	2.77 (1.34)	.035
Has someone other than spouse willing to provide care with no e4 allele	0.61 (0.27)	.267	0.65 (0.30)	.346
Has someone other than spouse willing to provide care with at least one e4 allele	1.22 (0.75)	.749	0.89 (0.57)	.854

Panel C. Alzheimer's Disease vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.47 (0.73)	.002			3.48 (1.14)	.000		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.95 (0.58)	.025	1.94 (0.58)	.027	0.84 (0.32)	.645	.84 (0.32)	.647
Single and living with others	1.70 (0.73)	.216	1.68 (0.71)	.220	0.97 (0.46)	.942	0.96 (0.47)	.938
0 to 6 family members (reference)								
7 to 11 family members	0.91 (0.33)	.799	0.91 (0.33)	.796	1.50 (0.60)	.310	1.50 (0.60)	.313

12 to 17 family members	0.98 (0.36)	.956	0.98 (0.36)	.950	1.21 (0.53)	.664	1.20 (0.51)	.674
18+ family members	0.83 (0.33)	.627	0.82 (0.32)	.621	0.77 (0.36)	.583	0.78 (0.37)	.594
Count of social activities	0.33 (0.06)	.000	0.33 (0.06)	.000	0.56 (0.12)	.007	0.58 (0.12)	.009
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	1.14 (0.33)	.651			1.09 (0.36)	.799		
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	0.40 (0.14)	.009	.40 (0.14)	.010	0.40 (0.18)	.037	0.40 (0.18)	.037
Received more support than gave	1.57 (0.49)	.147	1.58 (0.49)	.143	0.99 (0.38)	.982	0.98 (0.37)	.950

Interaction Term				
Does not have someone other than spouse willing to provide care with no e4 allele (reference)				
Does not have someone other than spouse willing to provide care with at least one e4 allele	2.72 (1.29)	.035	4.52 (2.20)	.002
Has someone other than spouse willing to provide care with no e4 allele	1.22 (0.42)	.558	1.29 (0.55)	.551
Has someone other than spouse willing to provide care with at least one e4 allele	2.83 (1.15)	.011	3.65 (1.84)	.010

Note: Regression Models 3 and 4 were run with additional covariates for baseline cognitive status, CVD, physical activity, race/ethnicity, age, education, gender, proxy status, and time since baseline.

Reciprocity Moderating Term

Regression models that included the main effects variables (Model 2) and all the covariates (Model 4) were estimated with moderating effect terms for reciprocity (see **Table 5.14**). These terms were created by generating a dichotomous variable for each unique combination of the reciprocity and APOE-e4 variables in order to test the moderating effect of reciprocity on the relationship between the APOE-e4 allele and cognitive diagnosis. Results from Model 2 demonstrated that respondents who received more support than they gave and who had at least one e4 allele were at greater risk of being diagnosed with both non-Alzheimer's dementia and Alzheimer's disease than respondents who gave and received an equal amount of support and did not have the e4 allele (RRR=4.64 and p=.026; RRR=4.02 and p=.001 respectively). The risk of Alzheimer's disease was greater among respondents who gave and received an equal amount of support and had at least one e4 allele compared to respondents who gave and received an equal amount of support and did not have any e4 alleles (RRR=2.10 and p=.092). There was a lower risk of being diagnosed with Alzheimer's disease among respondents who gave more support than they received and who did not have any e4 alleles when compared to respondents who gave and received an equal amount of support and did not have any e4 alleles (RRR=0.41 and p=.039). A goodness of fit test demonstrated an improvement in model fit with the addition of the reciprocity moderating effect terms in the unadjusted model (Wald Statistic=.0092).

When the reciprocity moderating effect terms were added to the fully adjusted model (see Model 4), results demonstrated that respondents who gave more support than they received and had at least one APOE-e4 allele were at greater risk of being diagnosed

with CIND and non-Alzheimer's dementia when compared to respondents who gave and received an equal amount of support and did not have any e4 alleles (RRR=2.59 and p=.055; RRR=4.22 and p=.051 respectively). Respondents who gave and received an equal amount of support and who had at least one e4 allele were at greater risk of being diagnosed with Alzheimer's disease rather than normal cognition when compared to respondents who gave and received an equal amount of support and did not have any e4 alleles (RRR=4.50 and p=.001). The risk of Alzheimer's disease was greater among respondents who received more support than they gave and who had at least one e4 allele when compared to respondents who gave and received an equal amount of support and did not have any e4 alleles (RRR=2.49 and p=.089). A Wald test demonstrated that the addition of moderating terms for reciprocity improved the fit of Model 4 (Wald Statistic=0.0362).

Overall, among respondents with at least one e4 allele, giving more support than one received was associated with a greater risk of being diagnosed with CIND and non-Alzheimer's dementia. Respondents who had at least one e4 allele and received more support than they gave were at greater risk of being diagnosed with non-Alzheimer's dementia and Alzheimer's disease. These findings may demonstrate the importance of maintaining equity in social exchanges. It may be more beneficial to maintain an equitable social exchange rather than to give more support than one receives or to get more support than one gives. Previous research has found that individuals go to great lengths in order to avoid inequitable relationships. Many will even withdraw from social exchanges in order to maintain this equity (Offer, 2012; Phan, Blumer, & Demaiter, 2009). It should also be noted that two out of the three items used to measure the giving

of support included the giving of financial support. It may be that respondents who were more cognitively impaired and required assistance paid family members in exchange for instrumental support not captured by this measure.

Table 5.14. Results of Hierarchical Regression Models with Reciprocity Moderating Effect Terms

Panel A. CIND vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	1.31 (0.37)	.330			1.65 (0.48)	.084		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.46 (0.41)	.170	1.46 (0.41)	.179	1.43 (0.47)	.282	1.45 (0.48)	.267
Single and living with others	1.32 (0.48)	.451	1.33 (0.48)	.440	1.40 (0.58)	.415	1.42 (0.60)	.401
0 to 6 family members (reference)								

7 to 11 family members	0.70 (0.23)	.272	0.69 (0.22)	.246	0.81 (0.29)	.546	0.80 (0.29)	.539
12 to 17 family members	0.75 (0.27)	.421	0.74 (0.26)	.388	0.86 (0.32)	.687	0.85 (0.32)	.665
18+ family members	0.92 (0.33)	.819	0.88 (0.32)	.712	0.82 (0.31)	.591	0.78 (0.30)	.504
Count of social activities	0.58 (0.09)	.000	0.58 (0.09)	.000	0.68 (0.11)	.018	0.68 (0.11)	.020
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.97 (0.25)	.905	.97 (0.25)	.918	0.95 (0.26)	.846	0.94 (0.26)	.825
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.20 (0.34)	.520			1.24 (0.37)	.472		
Received more support than gave	1.34 (0.44)	.376			1.26 (0.45)	.517		

Interaction Term				
Gave and received an equal amount of support with no e4 allele (reference)				
Gave and received an equal amount of support with at least one e4 allele	1.10 (0.46)	.823	1.58 (0.69)	.300
Gave more support than received with no e4 allele	0.99 (0.32)	.978	1.11 (0.39)	.772
Gave more support than received with at least one e4 allele	2.08 (0.98)	.118	2.59 (1.28)	.055
Received more support than gave with no e4 allele	1.42 (0.54)	.356	1.43 (0.59)	.387
Received more support than gave with at least one e4 allele	1.08 (0.61)	.898	1.13 (0.61)	.824

Panel B. Non-Alzheimer's Dementia vs. Normal Cognition

Variable	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.36 (1.12)	.071			2.05 (0.76)	.053		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	6.29 (3.26)	.000	6.24 (3.54)	.001	6.26 (3.14)	.000	6.25 (3.13)	.000
Single and living with others	1.32 (0.72)	.615	1.39 (0.81)	.569	1.45 (0.94)	.565	1.48 (0.96)	.542
0 to 6 family members (reference)								
7 to 11 family members	0.88 (0.49)	.812	0.83 (0.44)	.724	0.97 (0.49)	.957	0.94 (0.47)	.903

12 to 17 family members	1.16 (0.61)	.783	1.14 (0.58)	.798	1.38 (0.71)	.529	1.33 (0.68)	.574
18+ family members	1.41 (0.79)	.538	1.34 (0.73)	.592	0.64 (0.39)	.472	0.60 (0.37)	.412
Count of social activities	0.24 (0.07)	.000	0.24 (0.06)	.000	0.27 (0.09)	.000	0.27 (0.09)	.000
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.55 (0.21)	.116	0.54 (0.21)	.107	0.52 (0.21)	.112	0.52 (0.21)	.112
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.25 (0.70)	.693			1.63 (0.79)	.317		
Received more support than gave	1.89 (0.89)	.176			2.02 (0.97)	.144		

Interaction Term				
Gave and received an equal amount of support with no e4 allele (reference)				
Gave and received an equal amount of support with at least one e4 allele	1.34 (0.74)	.598	1.85 (1.13)	.315
Gave more support than received with no e4 allele	0.95 (0.50)	.920	1.45 (0.81)	.512
Gave more support than received with at least one e4 allele	2.93 (3.31)	.342	4.22 (3.11)	.051
Received more support than gave with no e4 allele	1.38 (0.77)	.567	2.12 (1.21)	.187
Received more support than gave with at least one e4 allele	4.64 (3.19)	.026	2.70 (2.00)	.181

Panel C. Alzheimer's Disease vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.47 (0.73)	.002			3.48 (1.14)	.000		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.95 (0.58)	.025	1.93 (0.57)	.026	0.84 (0.32)	.645	0.79 (0.31)	.542
Single and living with others	1.70 (0.73)	.216	1.70 (0.72)	.213	0.97 (0.46)	.942	0.96 (0.46)	.928
0 to 6 family members (reference)								
7 to 11 family members	0.91 (0.33)	.799	0.91 (0.33)	.787	1.50 (0.60)	.310	1.53 (0.62)	.289

12 to 17 family members	0.98 (0.36)	.956	0.98 (0.36)	.956	1.21 (0.53)	.664	1.20 (0.52)	.676
18+ family members	0.83 (0.33)	.627	0.83 (0.33)	.630	0.77 (0.36)	.583	0.76 (0.36)	.555
Count of social activities	0.33 (0.06)	.000	0.33 (0.06)	.000	0.56 (0.12)	.007	0.59 (0.13)	.013
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	1.14 (0.33)	.651	1.13 (0.33)	.668	1.09 (0.36)	.799	1.09 (0.36)	.782
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	0.40 (0.14)	.009			0.40 (0.18)	.037		
Received more support than gave	1.57 (0.49)	.147			0.99 (0.38)	.982		

Interaction Term				
Gave and received an equal amount of support with no e4 allele (reference)				
Gave and received an equal amount of support with at least one e4 allele	2.10 (0.93)	.092	4.50 (2.08)	.001
Gave more support than received with no e4 allele	0.41 (0.18)	.039	0.54 (0.30)	.274
Gave more support than received with at least one e4 allele	0.86 (0.45)	.769	1.16 (0.70)	.812
Received more support than gave with no e4 allele	1.40 (0.52)	.369	1.20 (0.55)	.689
Received more support than gave with at least one e4 allele	4.02 (1.73)	.001	2.49 (1.34)	.089

Note: Regression Models 3 and 4 were run with additional covariates for baseline cognitive status, CVD, physical activity, race/ethnicity, age, education, gender, proxy status, and time since baseline.

Loneliness Moderating Term

A dichotomous variable for each of the unique categories of feelings of loneliness and the dichotomous version of the APOE-e4 variable was added in Model 2 and Model 4 for self-respondents only (see **Table 5.15**). Regression results for Model 2 demonstrated that self-respondents who reported feelings of loneliness and who had at least one e4 allele were at greater risk of being diagnosed with CIND, non-Alzheimer's dementia, and Alzheimer's disease compared to self-respondents who did not report feeling lonely and had no e4 alleles (RRR=4.12 and p=.011; RRR=4.61 and p=.099; RRR=2.90 and p=.057 respectively). Self-respondents who did not feel lonely but had at least one e4 allele were also at greater risk of being diagnosed with Alzheimer's disease compared to those who did not report feelings of loneliness and had no e4 alleles (RRR=2.16 and p=.018). A Wald test demonstrated an improvement in model fit through the addition of the loneliness moderating effect terms in Model 2 for self-respondents only (Wald Statistic=0.0605).

Addition of the loneliness moderating effect terms in Model 4 demonstrated that self-respondents who felt lonely and had at least one e4 allele were at greater risk of being diagnosed with CIND rather than normal cognition when compared to self-respondents who did not feel lonely and did not have any e4 alleles (RRR=5.21 and p=.003). Self-respondents who did not feel lonely and those who reported feelings of loneliness who had at least one e4 allele were at greater risk of being diagnosed with Alzheimer's disease when compared to self-respondents who did not feel lonely and who did not have any e4 alleles (RRR=3.45 and p=.001; RRR=3.32 and p=.038 respectively). A Wald goodness of fit test demonstrated an improvement in model fit by the addition of

the loneliness moderating effect terms in Model 4 (Wald Statistic=0.0052). Overall, these findings seem to indicate that self-respondents who reported feelings of loneliness and who had at least one e4 allele were at greater risk of being diagnosed with CIND, non-Alzheimer's dementia, and Alzheimer's disease.

In sum, all of the social environment variables except for social engagement were shown to improve model fit and to have a moderating effect on the relationship between the APOE-e4 allele and cognitive diagnosis. Both the living arrangement and reciprocity moderating effect terms were found to improve model fit and to have a moderating effect on the APOE-e4 allele in the main effects model (Model 2) and the fully adjusted model (Model 4). When the moderating effect terms for family network size and perceived social support were added to Model 4, they were found to improve model fit and demonstrated a statistically significant moderating influence on the relationship between the APOE-e4 allele and cognitive diagnosis. Among self-respondents, the moderating effect terms for feelings of loneliness were found to improve model fit and to moderate the relationship between the APOE-e4 allele and cognitive diagnosis in both main effects and fully adjusted models.

Table 5.15. Results of Hierarchical Regression Models with Loneliness Moderating Effect Terms Among Self-Respondents Only (n=663)

Panel A. CIND vs. Normal Cognition

	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
Variable	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**	**RRR (se)**	**P-Value**
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	1.18 (0.35)	.587			1.41 (0.44)	.268		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.23 (0.37)	.497	1.23 (0.37)	.487	1.04 (0.36)	.905	1.05 (0.36)	.896
Single and living with others	1.45 (0.56)	.334	1.48 (0.56)	.298	1.42 (0.58)	.387	1.46 (0.60)	.354
0 to 6 family members (reference)								

7 to 11 family members	0.69 (0.23)	.272	0.70 (0.24)	.282	0.76 (0.28)	.452	0.77 (0.28)	.471
12 to 17 family members	0.66 (0.24)	.261	0.66 (0.24)	.257	0.72 (0.27)	.392	0.73 (0.28)	.396
18+ family members	0.72 (0.28)	.385	0.72 (0.28)	.390	0.64 (0.26)	.266	0.66 (0.27)	.299
Count of social activities	0.61 (0.10)	.003	0.62 (0.10)	.003	0.73 (0.13)	.078	0.74 (0.13)	.090
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.91 (0.25)	.732	0.92 (0.25)	.748	0.90 (0.26)	.707	0.91 (0.27)	.747
Did not feel lonely (reference)								
Felt lonely	2.19 (0.68)	.012			2.01 (0.64)	.027		
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.13 (0.34)	.683	1.09 (0.33)	.785	1.13 (0.36)	.705	1.08 (0.35)	.818

Received more support than gave	1.22 (0.43)	.576	1.21 (0.43)	.590	1.16 (0.43)	.682	1.15 (0.42)	.706
Interaction Term								
Did not feel lonely with no e4 allele (reference)								
Did not feel lonely with at least one e4 allele			0.91 (0.34)	.797			1.06 (0.40)	.881
Felt lonely with no e4 allele			1.73 (0.63)	.128			1.56 (0.57)	.227
Felt lonely with at least one e4 allele			4.12 (2.28)	.011			5.21 (2.90)	.003

Panel B. Non-Alzheimer's Dementia vs. Normal Cognition

Variable	Model 1 Main effects only; unadjusted		Model 2 Interaction effects; unadjusted		Model 3 Main effects only; fully adjusted		Model 4 Interaction effects; fully adjusted	
	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value	RRR (se)	P-Value
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	2.20 (1.22)	.155			2.21 (0.93)	.059		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	6.21 (3.78)	.003	6.27 (3.80)	.002	5.97 (3.49)	.002	5.99 (3.50)	.002
Single and living with others	1.58 (1.01)	.471	1.63 (1.04)	.444	2.42 (1.64)	.191	2.47 (1.70)	.189
0 to 6 family members (reference)								
7 to 11 family members	0.92 (0.56)	.888	0.97 (0.62)	.965	0.84 (0.47)	.753	0.85 (0.48)	.775

12 to 17 family members	1.18 (0.66)	.768	1.20 (0.69)	.756	1.28 (0.70)	.651	1.27 (0.69)	.657
18+ family members	0.71 (0.48)	.614	0.78 (0.54)	.718	0.37 (0.27)	.176	0.37 (0.29)	.201
Count of social activities	0.30 (0.09)	.000	0.30 (0.09)	.000	0.32 (0.11)	.001	0.32 (0.11)	.001
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	0.50 (0.21)	.105	0.49 (0.22)	.108	0.55 (0.25)	.183	0.55 (0.25)	.187
Did not feel lonely (reference)								
Felt lonely	1.26 (0.62)	.635			0.77 (0.37)	.575		
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	1.29 (0.83)	.686	1.23 (0.74)	.728	1.35 (0.72)	.568	1.33 (0.71)	.595

Received more support than gave	1.85 (0.95)	.227	1.86 (0.96)	.233	1.86 (0.92)	.209	1.86 (0.92)	.209
Interaction Term								
Did not feel lonely with no e4 allele (reference)								
Did not feel lonely with at least one e4 allele			1.48 (0.82)	.481			1.93 (1.08)	.239
Felt lonely with no e4 allele			0.83 (0.47)	.743			0.65 (0.37)	.440
Felt lonely with at least one e4 allele			4.61 (4.27)	.099			2.55 (1.90)	.207

Panel C. Alzheimer's Disease vs. Normal Cognition

Variable	Model 1 Main effects only; unadjusted RRR (se)	Model 1 P-Value	Model 2 Interaction effects; unadjusted RRR (se)	Model 2 P-Value	Model 3 Main effects only; fully adjusted RRR (se)	Model 3 P-Value	Model 4 Interaction effects; fully adjusted RRR (se)	Model 4 P-Value
Genetic Predisposition								
No e4 alleles (reference)								
At least one e4 allele	1.99 (0.59)	.020			3.02 (1.03)	.001		
Social Connectedness								
Married and living with others (reference)								
Single and living alone	1.92 (0.64)	.049	1.93 (0.65)	.048	0.82 (0.35)	.632	0.83 (0.35)	.652
Single and living with others	1.30 (0.57)	.555	1.30 (0.57)	.560	0.98 (0.48)	.968	0.99 (0.48)	.988
0 to 6 family members (reference)								
7 to 11 family members	1.07 (0.40)	.858	1.04 (0.38)	.915	1.40 (0.58)	.425	1.37 (0.57)	.452

12 to 17 family members	0.89 (0.35)	.760	0.88 (0.35)	.743	1.00 (0.46)	.996	1.05 (0.48)	.918
18+ family members	1.07 (0.45)	.876	1.04 (0.44)	.919	0.90 (0.43)	.828	0.87 (0.42)	.769
Count of social activities	0.42 (0.09)	.000	0.42 (0.09)	.000	0.64 (0.14)	.039	0.64 (0.14)	.037
Perceived Isolation								
No one other than spouse willing to provide care (reference)								
Has someone other than spouse willing to provide care	1.09 (0.33)	.778	1.09 (0.33)	.777	1.01 (0.36)	.981	1.01 (0.35)	.985
Did not feel lonely (reference)								
Felt lonely	1.48 (0.54)	.274			1.18 (0.46)	.672		
Reciprocity								
Gave and received an equal amount of support (reference)								
Gave more support than received	0.49 (0.18)	.056	0.50 (0.18)	.058	0.47 (0.21)	.085	0.48 (0.21)	.093
Received more support than gave	1.32 (0.45)	.418	1.31 (0.45)	.425	0.94 (0.36)	.880	0.96 (0.36)	.907

Interaction Term				
Did not feel lonely with no e4 allele (reference)				
Did not feel lonely with at least one e4 allele	2.16 (0.70)	.018	3.45 (1.33)	.001
Felt lonely with no e4 allele	1.62 (0.71)	.272	1.36 (0.64)	.519
Felt lonely with at least one e4 allele	2.90 (1.62)	.057	3.32 (1.92)	.038

Note: Regression Models 3 and 4 were run with additional covariates for baseline cognitive status, CVD, physical activity, race/ethnicity, age, education, gender, proxy status, and time since baseline.

CHAPTER 6

DISCUSSION

While research has demonstrated that the APOE-e4 allele is a risk factor for developing dementia, and Alzheimer's disease specifically, it is not a definitive cause. Twin studies have demonstrated discordance in the expression of disease symptoms between monozygotic twins who were genetically predisposed to the disease (Brandt, et al., 1993; Breitner, et al., 1995; Ryff & Singer, 2005). This would indicate that other factors, such as the environment, play a role in disease expression. The role of the environment in the manifestation of disease symptoms has been increasingly explored. Aspects of the social environment have been found to have an inconsistent relationship with cognitive decline in later life, once again demonstrating risk but not deterministic influences on cognitive difficulty. The mixed findings of the independent effects of genetic and environmental factors suggest there may be a connection between the two that influences the expression of disease symptoms.

Previous research studies have demonstrated a relationship between social factors and the APOE-e4 allele to Alzheimer's disease, although not consistently. Education (Seeman, et al., 2005; Wang, et al., 2012), SES (Zhao, etc., 2005), and social activity (Wang, et al., 2002) are all aspects of the environment that have been examined in relation to the APOE-e4 allele and Alzheimer's disease. A study that examined SES, as

measured by government job level, in relation to cognitive function did not find that the APOE-e4 allele moderated this relationship (Zhao, et al., 2005). Being socially active was associated with a decreased risk of dementia in respondents with and without the APOE-e4 allele (Wang, et al., 2002). Seeman and colleagues (2005) found that individuals who had achieved educational levels beyond eighth grade and who had at least one e4 allele experienced more drastic cognitive decline than those without any e4 alleles. Wang and colleagues (2012) found that education moderated the relationship of the e4 allele to dementia development.

This study further examined the relationship of genetic factors and aspects of the social environment to cognitive diagnosis. Previous research primarily used convenience and clinical samples in order to explore this relationship. This study contributed to the current body of knowledge in part by using the first U.S. nationally representative sample of cognitive well-being among older persons to explore this relationship and by including a wide range of social relationship measures.

Prevalence of APOE Genotypic Combinations

One of the research questions explored in this study was: *What is the prevalence of the APOE allele combinations in a U.S. nationally representative sample of older adults and how do the rates generated with these data compare to rates from other study samples?* The ADAMS sample was compared to convenience samples found in various studies that focused on sample groups from different regions or with specific chronic conditions. The prevalence rates of the most common and least common APOE alleles in the ADAMS sample were similar to those in the comparison samples reviewed in this

study, especially for samples drawn from regionally based groups. Overall, the e3/e3 genotypic combination was the most common found in the comparison studies and the HRS ADAMS sample. The e2/e2 was the least common among these groups and comprised less than 3% of any of the research samples. This finding was consistent with the existing literature that identified the e3/e3 combination to be the most common (Genin, et al., 2011) and the e3 allele itself to be the most prevalent worldwide. This might be expected since the study samples reviewed here were drawn primarily from countries that have historically had a stable food supply. A stable food supply has been associated with a higher prevalence of the e3 allele (Corbo & Scacchi, 1999).

The e4 allele has been associated with a greater risk of coronary artery disease (CAD) and Alzheimer's disease among individuals living in more developed countries. This is expected given the association of the e4 allele with lipid transport and cholesterol absorption and the hypothesized increased risk of CAD in developed countries. It has been suggested that since the e4 allele was associated with greater cholesterol absorption, it would be advantageous in an environment where there was a risk of cholesterol levels that were too low (e.g., an environment where food was not readily available). However, this advantage would become a risk factor for CAD in an environment where food was plentiful and dangerously low cholesterol was not a risk. The e4 allele has been found to be more common among populations that have had unstable food supplies and have in more recent history had a culture of foraging for food, such as the Pygmy population (Corbo & Scacchi, 1999). The ADAMS sample had similar prevalence rates of the e4 allele to the other sample groups examined. The highest prevalence of the e4 allele was found in samples that were examined based on a specific diagnosis of a disease, such as

CAD or Alzheimer's disease, and is likely due to the allele's relationship to cholesterol and lipid transport in the body.

In sum, the nationally representative sample from the ADAMS study did not vary greatly from non-U.S. samples on prevalence rates of the APOE genotypic combinations. This may be because the sample groups to which the ADAMS were compared were from developed countries and global comparisons have found prevalence rates to be similar among developed countries.

Comparison of Respondents with and without the APOE-e4 Allele

The second question this study sought to answer was: *Do people with the APOE-e4 allele differ from individuals without it on measures of demographic characteristics, health factors, or the social environment at baseline and the time of the ADAMS wave in a U.S. nationally representative sample of older adults?* Bivariate results demonstrated that respondents with and without the e4 allele did not differ on any aspects of the social environment. The groups did differ along the dimensions of race/ethnicity, age, baseline cognitive functioning, and physical activity. Overall, more non-Hispanic Black respondents had at least one e4 allele than respondents from each of the other race/ethnic groups identified in this study. This is consistent with previous findings that showed more African-American respondents had the e4 allele than their Caucasian counterparts (Borenstein, et al., 2006; Fillenbaum, et al., 2001). Respondents who had the e4 allele were younger than respondents without the e4 allele. This may be a selection effect and related to the increased risk of dementia and CAD associated with the e4 allele (Corbo &

Scacchi, 1999). Older respondents with the e4 allele may not have survived to older ages due to complications associated with dementia or CAD.

Most respondents who had at least one e4 allele were found to have low baseline cognitive functioning consistent with the greater risk of cognitive decline associated with the APOE-e4 allele (Alzheimer's Association, 2012; Bretsky, et al., 2003; Corbo & Scacchi, 1999; Corder, et al., 1993). A larger proportion of respondents who had the e4 allele were physically active when compared to the proportion of respondents without the e4 allele (39% vs. 30% respectively). This finding is interesting because the literature has found that physical activity is associated with a lower risk of Alzheimer's disease and other types of dementia (Larson, et al., 2006) and most of the respondents in this study with low baseline cognitive function also had the e4 allele. However, a previous study did not find exercise to be associated with a lower risk of incident dementia among individuals with the e4 allele (Podewils, et al., 2005). The higher proportion of individuals with the e4 allele who were physically active may be related to factors such as age or health. Respondents with the e4 allele were younger than those without any e4 alleles. Additionally, a larger proportion of respondents with the e4 allele reported having no CVD when compared to the proportion of respondents without any e4 alleles who reported not having a CVD. Thus respondents with the e4 allele may have been younger and healthier and more able to exercise than their counterparts without the e4 allele.

Only race/ethnicity and proxy status were found to have a significant relationship to the e4 allele in the 2002 wave. It would be expected that race/ethnicity would be significant in both waves since this is a feature that is consistent in individuals over time. Proxy status may have been significant since more respondents had a proxy at follow-up

than at baseline. It is likely that the increase in proxy respondents at follow-up was a reflection of declining health among study participants. In sum, respondents with and without the APOE-e4 allele did not differ greatly in the cross-sectional comparison. Only race/ethnic differences between individuals with and without the APOE-e4 allele were consistent over time.

Relationship of Genetic Predisposition and the Social Environment to Cognitive Diagnosis

This study evaluated whether the APOE-e4 allele and the social environment were associated with a greater risk of cognitive difficulty in a U.S. nationally representative sample of older adults. This section discusses the findings generated from examination of the following research question: *Is there a relationship between the APOE-e4 allele and a diagnosis of dementia or Alzheimer's disease in a U.S. nationally representative population-based sample? Is there a relationship between the social environment and a diagnosis of dementia or Alzheimer's disease in a U.S. nationally representative population-based sample?* Results from cross-sectional analyses are discussed first, then results from a change analysis are discussed.

The APOE-e4 allele was strongly associated with the risk of Alzheimer's disease, which is consistent with the existing literature (Alzheimer's Association, 2012; Bretsky, et al., 2003; Corder, et al., 1993). The relationship between CIND and non-Alzheimer's dementia and the e4 allele was less strong. Respondents with two e4 alleles were at greater risk of CIND, however having one e4 allele was associated with a greater risk of non-Alzheimer's dementia. This is consistent with previous findings that demonstrated a

relationship between the APOE-e4 allele and the risk of cognitive decline (Alzheimer's Association, 2012; Bretsky, et al., 2003; Corder, et al., 1993), MCI (Brainerd, et al., 2011), and non-Alzheimer's dementia (Myers, et al., 1996). The e4 allele has been found to be associated with more rapid progression of cognitive decline from normal functioning to MCI in the ADAMS sample. However, this relationship was not found to be significantly related to other types of CIND in at least one study (Brainerd, et al., 2013). The e4 allele has also been associated with a higher risk of converting from MCI to Alzheimer's disease (Landau, et al., 2010).

Results demonstrated a relationship between the three social environment constructs included in this study (social connectedness, perceived isolation, and reciprocity) and cognitive functioning. Aspects of social connectedness, as well as the social connectedness index, were found to have a positive association with cognitive functioning consistent with other research. Social connectedness was defined as family network size, type of living arrangement, and level of social engagement. The index was comprised of living arrangement, social engagement, and geographic proximity. This study found single respondents who live alone are at greater risk of cognitive difficulty. Other studies have also found that respondents who live alone and are unmarried are at greater risk of cognitive decline (Fratiglioni, et al., 2000). Being more socially connected was associated with a lower risk of CIND, Alzheimer's disease and non-Alzheimer's dementia. This is expected given the deleterious health and cognitive outcomes associated with being socially disconnected (Cornwell and Waite, 2009; Fratiglioni, et al., 2004).

Risk of CIND, non-Alzheimer's dementia, and Alzheimer's disease was lower among respondents who were more socially engaged. Socially engaged individuals were those who reported participating in volunteer activities, helping friends, or were working. This is consistent with previous findings that found an association between social engagement and better cognitive health (Alzheimer's Association, 2012; Middleton and Yaffe, 2010). It cannot be ascertained with these data whether being socially engaged served a protective role or whether respondents who were more socially engaged were also more cognitively intact due to the possibility of reciprocal causation; however, the relationship remained consistent for all three cognitive diagnoses.

Respondents who believed they had social support available to them were found to be at lower risk of non-Alzheimer's dementia than respondents who did not believe this support was available. This is consistent with previous findings suggesting that individuals who perceived they had social support available to them had better cognitive functioning (Yeh and Liu, 2003). A perceived lack of social support has been associated with negative outcomes such as depression, anxiety, and a higher prevalence of chronic conditions (Hawthorne, 2008; Moak and Agrawal, 2010).

The literature has identified equitable social relationships to be preferable among study participants (Rook as cited in Jung, 1990) and was associated with reduced anxiety (Griffith as cited in Jung, 1990) and greater well-being (Maton as cited in Jung, 1990). People reported withdrawing from social networks in which there was an inequitable exchange, both in instances where other network members did not reciprocate or if the individual was unable to reciprocate (Offer, 2012). Contrary to the reciprocity literature, this study found respondents who gave more support than they received had a lower risk

of being diagnosed with Alzheimer's disease. This finding is surprising and may be a reflection of an individual's cognitive ability rather than an effect of the non-reciprocal nature of the relationship. In other words, respondents who were more cognitively intact may have been more able and more likely to provide instrumental support to those around them. One study did find older adults who gave more support than they received reported higher levels of well-being (Thomas, 2010). The giving of support may be associated with the retention of a valued role (Sibert, et al. as cited in Thomas, 2010) and has been associated with less stress (Piferi & Lawler as cited in Thomas, 2010), apart from caregiving responsibilities (Garand, Dew, Eazor, DeKosky, & Reynolds as cited in Thomas, 2010; Pinquart & Sorensen as cited in Thomas, 2010). If the giving of support is associated with less stress, it is possible that this may be related to a decreased disruption of the HPA axis which may be associated with less hippocampal damage associated with cognitive difficulty.

In sum, all of the social environment variables included in this study, except for size of the family network, were found to be significantly related to cognitive diagnosis. It may be that the benefits derived from a large social network are salient to relationships that extend beyond the family, such as friends and confidants. A limitation of this measure is that the quality of the relationships could not be ascertained. It may be that the benefit of the social network is based on the quality of the relationship rather than the quantity of relationships. Perceived social support was marginally significant at the 10% level. This may be due to the measure used. Respondents were asked to report whether they believed they had someone other than a spouse who would be willing to provide care. As noted previously, this is not an ideal measure of perceived social support and it

may prove beneficial to use a more sensitive measure in the future in order to examine its relationship to cognitive diagnosis.

Change Analysis

A change analysis was conducted in order to ascertain whether a change in aspects of the social environment was related to cognitive diagnosis. Change variables were created by comparing differences in respondent answers to the survey questions from baseline to follow-up. This study found that a change in level of social engagement was associated with a greater risk of being diagnosed with non-Alzheimer's dementia or Alzheimer's disease. Respondents who became involved in more social activities (volunteering, helping friends, and working) were at lower risk of non-Alzheimer's dementia and Alzheimer's disease. This is consistent with previous findings that have demonstrated better cognitive functioning among individuals who were more socially engaged (Alzheimer's Association, 2012; Middleton and Yaffe, 2010). Interestingly, becoming less socially engaged was also associated with a lower risk of Alzheimer's disease. Cross-tabulations showed that 251 respondents who experienced no change in their level of social engagement were not socially engaged in both waves. This may have skewed the significance of becoming less engaged.

Self-respondents who felt lonely at follow-up who had not felt lonely at baseline were at greater risk of being diagnosed with non-Alzheimer's dementia or Alzheimer's disease compared to respondents who experienced no change in feelings of loneliness. This finding was consistent with previous research that found respondents who reported feeling lonely also demonstrated greater cognitive decline and were at greater risk of

being diagnosed with dementia (Hawkley and Cacioppo, 2010; Holwerda, et al., 2012; Wilson, et al., 2007). Findings also suggested that self-respondents who were no longer lonely at follow-up but who had been lonely at baseline were at greater risk of being diagnosed with non-Alzheimer's dementia compared to respondents who experienced no change in feelings of loneliness. This finding is unexpected. It may be that since the HRS asked whether respondents felt lonely in the week prior to the interview, the data do not reflect a long term sense of loneliness that respondents may have experienced. In other words, feelings of loneliness may have varied depending upon the immediate circumstances (such as a visit from family members or friends) and may not have captured a general feeling of loneliness experienced by some respondents.

Self-respondents who became depressed at follow-up were at greater risk of being diagnosed with CIND compared to respondents who did not experience a change in depressive symptomatology between waves. This makes sense given that the literature has found depression to be associated with later cognitive difficulty and dementia (Barnes, et al., 2007; Read, et al., 2008). Respondents with CIND may also have become depressed because they were aware of their cognitive decline and their powerlessness to change it.

In sum, genetic predisposition and a poor social environment (as measured by the social connectedness index, living arrangement, social engagement, perceived social support, and reciprocity) were found to be associated with a greater risk of later cognitive difficulty. Being more socially engaged and more socially connected was associated with a lower risk of cognitive difficulty. Changes in level of social engagement and feelings of loneliness were associated with an increased risk as well. However, it should be noted

that it could not be determined with these data what level of change may have been associated with the increased risk.

Moderating Effects of the Social Environment on Genetic Predisposition to Dementia

Last, this study examined whether aspects of the social environment moderated the relationship between genetic predisposition and cognitive well-being. Specifically, the following question was addressed: *Do characteristics of the social environment moderate the relationship of the APOE-e4 allele to cognitive diagnosis? From the perspective of examining the gene-environment relationship in dementia diagnosis, this study seeks to examine whether the genetic risks for developing Alzheimer's disease that have been associated with the APOE-e4 allele are moderated by the social environment.*

Results showed that some aspects of the social environment did moderate the relationship of the APOE-e4 allele with cognitive well-being. Being single and living alone was found to be associated with an increased risk of both Alzheimer's disease and other types of dementia among respondents with at least one e4 allele. Being single, regardless of living arrangement, was associated with an increased risk of Alzheimer's disease among respondents with at least one e4 allele. It may be that single respondents were more isolated, which is consistent with the literature that found single people to report feeling more isolated (Hawthorne, 2008). Isolation has been associated with an increase in stress hormones that adversely affect the hippocampus (Berkman, et al., 2000). The hippocampus has been found to be damaged in people with Alzheimer's disease and dementia (Fratiglioni, et al., 2004) and people with the e4 allele have been found to be at

greater risk for hippocampal damage (Soininen, & Riekkinen, 1996). These findings seem to indicate a need for further study into this relationship.

Compared to respondents with six or fewer family members, having more than six family members was associated with a greater risk of Alzheimer's disease and other types of dementia among respondents who had at least one e4 allele. This is unexpected given that larger social networks have been associated with better cognitive functioning in previous studies (Holtzman, et al., 2004; Middleton and Yaffe, 2010). The discrepancy in these findings with those reported in the literature may be related to the quality of the social relationships, which could not be ascertained with these data. The quality of social interactions has been found to have psychological ramifications. Negative social exchanges have been associated with deleterious effects on well-being (Newsom, et al., 2005), while individuals who had positive interactions with their social networks demonstrated a reduction in stress levels (Fratiglioni, et al., 2004). Thus the quality of the relationships rather than the network size may have a stronger moderating influence on the relationship of the e4 allele to dementia diagnosis. This study also focused on the family network and did not include additional social relationships, such as friendships or relationships with neighbors or coworkers. It may be that these other types of relationships were more likely to yield a negative relationship with cognitive decline.

Perceived social support demonstrated a moderating effect on the relationship between the APOE-e4 allele and cognitive well-being. The belief that social support was not available was associated with a greater risk of Alzheimer's disease and non-Alzheimer's dementia among respondents with at least one e4 allele. In the literature, the perception that social support was available was associated with lower stress levels

(Berkman, et al., 2000). Thus it might be expected that respondents who did not perceive social support was available to them may have also experienced higher stress levels. Stress hormones have been associated with permanent damage to the hippocampus (Berkman, et al., 2000) as well as with an increased risk of Alzheimer's disease (Wilson, Evan, Bienias, et al. as cited in Fratiglioni, et al., 2004).

When including a moderating term for reciprocity and the APOE-e4 allele, having an inequitable exchange of support (measured here by reciprocity of exchange) was associated with a greater risk of cognitive difficulty among respondents with at least one e4 allele. Overall, giving or receiving more support rather than giving and receiving an equal amount of support was associated with a greater risk of CIND, non-Alzheimer's dementia, and Alzheimer's disease among respondents with at least one e4 allele. This is congruent with the research that suggested that individuals who were engaged in reciprocal relationships demonstrated reduced levels of anxiety (Griffith as cited in Jung, 1990). Individuals who felt they had received more support than they provided were at greater risk of being depressed as were individuals who gave more support than they received (Ybema, et al., 2001). Depression has been associated with higher levels of cortisol, a stress hormone (Fratiglioni, et al., 2004). Sustained high levels of stress have been associated with hippocampal damage (Berkman, et al., 2000). It should be noted that this finding is an interesting departure from the findings in multivariate analyses without the moderating terms that found respondents who gave more than they received to be at less risk of Alzheimer's disease. It may be that the risk of Alzheimer's disease associated with the APOE-e4 allele is greater than any positive benefit that may be derived from the giving of support, such as greater well-being (Thomas, 2010), retention

of a valued social role (Sibert, et al. as cited in Thomas, 2010), or less stress (Piferi & Lawler as cited in Thomas 2010).

Loneliness was found to be associated with a greater risk of cognitive difficulty among self-respondents who had at least one e4 allele compared to those without the e4 allele. The literature has found loneliness to be associated with higher cortisol levels (stress hormones) as well as to decrease the production of genes that regulate the system in the body responsible for decreasing stress (Cacioppo and Hawkley, 2009; Cacioppo, et al., 2011; Hawkley and Cacioppo, 2010). In other words, loneliness may be related to an increase in stress hormones and a decrease in the body's ability to reduce stress. Loneliness has also been associated with cognitive decline, Alzheimer's disease, and other types of dementia (Hawkley and Cacioppo, 2010; Holwerda, et al., 2012). This finding indicates a need for further study into the mechanisms involved in the relationship of loneliness and the APOE-e4 allele in relation to cognitive functioning.

Study Limitations

The ADAMS was the first U.S. nationally representative dataset on dementia, which is a strength of these data. In depth clinical assessments were administered in order to assign a cognitive diagnosis. Genetic information about the APOE genotype was also collected from study participants. The study sample was drawn from the HRS and provides a unique opportunity to connect study participants back to the HRS data and enhance the information available for examination. This study connected the ADAMS sample to the HRS, providing the ability to analyze a wide range of social relationship

information about participants and to introduce a robust set of controls. While these are strengths of the HRS data, there are also limitations associated with the data.

Some details about the social environment could not be ascertained with the HRS-ADAMS data. For example, information about the family network was available, but the HRS did not collect information about the full extent of a respondent's social network, such as number of friends, coworkers, neighbors, and so forth. There was also no information available about the qualitative aspects of the social environment, such as the positive or negative nature of the social relationship.

Although much larger in size than many of the extant clinical studies employed to analyze cognitive decline, the size of the sample was relatively small, which resulted in some cases in a small number of events (especially, cases of dementia). However, the ADAMS was a relatively large sample for a dataset focused on cognitive decline and dementia (n=856). A power analysis was not conducted in part because the investigator had no capacity to increase the sample size based on a secondary analysis of the data.

Another limitation of the data is that the sample may have been biased since the healthiest individuals are the ones most likely to have survived from the 1998 sample, a common problem in this type of research. Individuals who did not survive or remain in the study after that time period would not have been included in the pool from which the ADAMS sample was drawn and were more likely to have cognitive decline in the change analysis. To partially evaluate this issue, individuals who were in the study in 1998 were compared to those who remained in the study in 2002. There were some differences found between the two waves on measures of the social environment and respondents tended to be in poorer cognitive and physical health in 2002.

These data and the analyses that were used in this study were able to identify correlational relationships only. Thus it should be noted that causation cannot be determined based on this study. Due to the timing of the HRS-ADAMS data collection strategy, this study was unable to follow these individuals over time and examine information about their social environment and its relationship to later cognitive diagnosis. Additionally, there were three waves of data collected for the ADAMS. This study used the first wave of the ADAMS data that was available due to its larger sample size because there was a substantial loss in sample size in the subsequent waves with the final wave having a sample of 217 respondents.

Future Research

Despite the limitations associated with these data, this study made a valuable contribution to the field. This study used a U.S. nationally representative sample of older adults with dementia to examine the moderating influence of the social environment on genetic predisposition and dementia development. This study found that aspects of the social environment moderated the relationship of the APOE-e4 allele to cognitive diagnosis. While the results are promising, future research is necessary in order to determine causation, the extent of the moderating influence, and the physiological mechanisms that play a role in the manifestation of cognitive decline and dementia.

This study identified correlational relationships, but experimental studies with randomization and the use of longitudinal data could serve to establish causation. However, designing such studies are extremely difficult due to concerns about human subjects well-being. Although the HRS is a longitudinal dataset, this study was unable to

take full advantage of the longitudinal nature of the HRS due to the limitations associated with the timing of the ADAMS data collection strategy. The ability to track information about the social environment over time and how this is related to the development of dementia among older people with a genetic predisposition would help to tease out causative influences on disease manifestation.

Future research would benefit from further exploring the mechanisms through which the social environment moderates the relationship of genetic predisposition to dementia development. Examination about whether the damage to the hippocampus is related to the social environment as suggested earlier and whether it is this damage in addition to the risk of damage to the hippocampus associated with the e4 allele that contribute to disease manifestation warrants further exploration.

It would be beneficial to determine the role that qualitative aspects of the social environment play in disease manifestation. This study did not find a larger family network to serve a protective role in the development of dementia or Alzheimer's disease specifically. This would seem to indicate that the quality of the relationships rather than the network size may have a stronger influence and should be examined. It would be interesting to observe whether a social network outside of the family network, such as close friends, may also play a role, and if so, to what extent.

While this study more broadly examined several aspects of the social environment, a more in-depth analysis of each of these areas in relation to genetic predisposition and dementia development and the physiological mechanisms involved would contribute to the field greatly. For example, having a reciprocal relationship was found to be beneficial in this study. Developing more expansive measures in order to examine the reciprocal

nature of social relationships would be interesting. Reciprocity could be examined beyond instrumental support to include emotional, appraisal, and informational support. Understanding if reciprocity is desired purely based on instrumental support or if emotional support might be considered an even exchange with instrumental support would be informative. Examining which type of support is related to cognitive functioning among individuals who are genetically predisposed compared to those who are not is another area that could be explored. It would also be beneficial to examine what are considered optimal levels of support or exchange and how these may differ based on the individual. For example, some individuals may be more inclined to provide support than others.

A more rigorous examination of perceived social support and loneliness would benefit the field. This study used a less than ideal measure of perceived social support and found it to moderate the relationship of the e4 allele to cognitive diagnosis. Developing specific measures to assess perceived social support and examining how this affects the relationship of the e4 allele to dementia development would help to inform the field. Similarly, this study was limited to examining feelings of loneliness among self-respondents only. More expansive measures that analyze loneliness among respondents with and without a proxy would help to inform the extent to which loneliness may moderate the relationship of genetic predisposition to cognitive functioning.

Policy Implications

The gene-environment relationship to cognitive functioning should be included as an area for research funding in accordance with the National Alzheimer's Project Act

(NAPA). NAPA was enacted by President Obama in 2012. The Act allocates $156 million towards combating the disease through research, caregiver support, provider training/education, and a public awareness campaign. Resources should be allocated towards research that further examines the gene-environment interaction and how this relates to cognitive disease manifestation.

Persons with Alzheimer's disease and other types of dementia often require the use of long-term services and supports (LTSS). Reports estimate that approximately 62% of LTSS is paid for by Medicaid and/or Medicare (Kaiser Commission on Medicaid and the Uninsured, 2009; The Scan Foundation, 2013). As more and more people reach older ages and develop conditions that require LTSS, the system is at risk of becoming overburdened and the economic costs are large. The demographic shift and lack of financial and human resources increases the risk of overburdening the LTSS system. Understanding aspects of the social environment that could help to delay the onset of disease symptoms has strong implications for both practice and policy. The ability to delay when a person requires support could provide a significant cost-savings to the LTSS system.

Policies should be implemented in order to support the development of programs that might enhance older adults' social lives, both before disease onset and after. More adult day centers that provide social opportunities for the individual and reprieve for the caregiver should be available. Transportation services for individuals with Alzheimer's disease and other types of dementia would also be beneficial. Many transportation services cannot be utilized by individuals with cognitive impairment. However, mobility would allow older adults with cognitive impairment, as well as those without cognitive

difficulty, to access social opportunities of their choosing, such as attending church or club events or visiting with friends. Adequate transportation services would enhance individuals' ability to be more socially engaged, which was found to be beneficial in this study and the extant literature.

There is a shift in the long-term care industry towards person-centered care. It would be a natural progression within this framework to put mechanisms in place to facilitate a strong and nurturing social environment among service recipients. For example, LTSS providers could create ways that allow individuals to reciprocate in their relationships that would serve to enhance this area of their social environment. In an LTSS facility, providers could engage residents' assistance in minor preparations for activities or meals or help them to identify another role that brings them fulfillment and would allow individuals to feel more equity in their social interactions. Further research could also examine whether the benefits derived from the social environment affect well-being or if they might serve to delay symptom onset or slow the progression of disease symptoms. The findings from this study are promising and warrant additional research. Better understanding of how the social environment moderates the relationship of genetic predisposition to cognitive functioning and the mechanisms involved could contribute greatly to delaying the onset and possible progression of this devastating disease.

Conclusion

This study contributed to the field by examining whether aspects of the social environment moderated the relationship of genetic predisposition to cognitive functioning in a nationally representative sample of U.S. older adults. The findings indicated that

being single and living alone, perceiving a lack of social support, engaging in inequitable exchanges of support, and self-reported loneliness did moderate this relationship. In the future, it will be important to determine the specific physiological mechanisms that are involved to enhance our understanding of the gene-environment relationship in connection to dementia development.

APPENDIX A
SAMPLE DESCRIPTION AND PRELIMINARY ANALYSIS

Table 1. Cross Tabulation of 4 Category Cognitive Diagnosis Variable by Living Arrangement

Cognitive Diagnosis	Married and Living with Someone		Single and Living Alone		Single and Living with Others		P-Value
	Num	Pct	Num	Pct	Num	Pct	
Non-Alzheimer's Dementia	24	6.4	32	12.1	12	8.5	.000
Alzheimer's Disease	76	20.3	84	31.8	43	30.5	
CIND	106	28.3	71	26.9	44	31.2	
Normal Cognition	168	44.9	77	29.2	42	29.8	
Total	374	99.9	264	100.0	141	100.0	

Table 2. Cross Tabulation of 4 Category Cognitive Diagnosis Variable by Family Network Size

Cognitive Diagnosis	0 to 6 Family Members		7 to 11 Family Members		12 to 17 Family Members		18+ Family Members		P-Value
	Num	Pct	Num	Pct	Num	Pct	Num	Pct	
Non-Alzheimer's Dementia	19	9.3	16	7.2	17	9.8	16	8.9	.246
Alzheimer's Disease	54	26.5	62	28.1	42	24.1	45	25.0	
CIND	62	30.4	56	25.3	40	23.0	63	35.0	
Normal Cognition	69	33.8	87	39.4	75	43.1	56	31.1	
Total	204	100.0	221	100.0	174	100.0	180	100.0	

Table 3. Cross Tabulation of 4 Category Cognitive Diagnosis Variable by Geographic Proximity

	No Friends or Relatives Live Close		At Least One Friend or Relative Lives Close		
Cognitive Diagnosis	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Non-Alzheimer's Dementia	16	9.9	52	8.4	
Alzheimer's Disease	40	24.7	163	26.4	
CIND	50	30.9	171	27.7	.755
Normal Cognition	56	34.6	231	37.4	
Total	162	100.1	617	99.9	

Table 4. Cross Tabulation of 4 Category Cognitive Diagnosis Variable by Social Engagement

Cognitive	**No Activities**		**1 Activity**		**2 Activities**		**3 Activities**		
Diagnosis	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Non-Alzheimer's Dementia	48	13.8	14	5.5	5	3.5	1	3.1	
Alzheimer's Disease	132	37.8	52	20.3	14	9.9	5	15.6	.000
CIND	97	27.8	86	33.6	34	23.9	4	12.5	
Normal Cognition	72	20.6	104	40.6	89	62.7	22	68.8	
Total	349	100.0	256	100.0	142	100.0	32	100.0	

Table 5. Cross Tabulation of 4 Category Cognitive Diagnosis Variable by Perceived Social Support

	No One Other than Spouse Willing to Provide Care		Has Someone Other than Spouse Willing to Provide Care		
Cognitive Diagnosis	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Non-Alzheimer's Dementia	32	10.1	36	7.8	.015
Alzheimer's Disease	64	20.2	139	30.1	
CIND	92	29.0	129	27.9	
Normal Cognition	129	40.7	158	34.2	
Total	317	100.0	462	100.0	

Table 6. Cross Tabulation of 4 Category Cognitive Diagnosis Variable by Loneliness (n=663)

	Did Not Feel Lonely		Felt Lonely		
Cognitive Diagnosis	**Num**	**Pct**	**Num**	**Pct**	**P-Value**
Non-Alzheimer's Dementia	32	6.6	17	9.6	.000
Alzheimer's Disease	106	21.9	41	23.0	
CIND	123	25.4	71	39.9	
Normal Cognition	224	46.2	49	27.5	
Total	485	100.1	178	100.0	

Note: Feelings of loneliness was only asked of self-respondents.

Table 7. Cross Tabulation of 4 Category Cognitive Diagnosis Variable by Reciprocity

Cognitive Diagnosis	Gave and Received an Equal Amount of Support		Gave More Support than Received		Received More Support than Gave		P-Value
	Num	Pct	Num	Pct	Num	Pct	
Non-Alzheimer's Dementia	24	10.8	17	8.1	27	7.8	.000
Alzheimer's Disease	88	39.5	28	13.3	87	25.2	
CIND	58	26.0	58	27.5	105	30.4	
Normal Cognition	53	23.8	108	51.2	126	36.5	
Total	223	100.1	211	100.1	345	99.9	

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