COGNITIVE DYSFUNCTION, GENDER, AND NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE

A Dissertation

by

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ABSTRACT

Alzheimer's disease (AD) is associated with progressive cognitive declines that classically affect memory in the mild stages of the disease and gradually impair all other cognitive functions. Although certain changes in cognitive abilities are known to be associated with AD, better characterization of how cognitive functions become impaired relative to each other is needed to improve our understanding of AD.

It is also vital to better understand how and why AD affects women differently than men. Almost two-thirds of individuals with AD in the United States are women, and several studies have shown that women are at higher risk of developing AD. Among those with AD, women seem to have worse cognitive deficits than men. It is unclear why women may be more vulnerable to AD than men.

The potential contribution of neuropsychiatric symptoms to the gender gap in AD has not been considered carefully. Neuropsychiatric symptoms (e.g., depression, anxiety) are commonly experienced by individuals with AD, but these emotional symptoms often differ between men and women. Furthermore, neuropsychiatric symptoms are associated with risk for AD and accelerated cognitive deterioration. Neuropsychiatric symptoms may mediate the gender gap in AD, but this hypothesis has not been analyzed.

Given these important, unanswered questions about the relationships among cognitive dysfunction, gender, and neuropsychiatric symptoms in AD, the current research (1) developed cross-sectional and longitudinal models of AD-associated

cognitive dysfunction, (2) analyzed gender differences in these models, (3) examined whether neuropsychiatric symptoms mediated any gender differences in AD-associated cognitive dysfunction, and (4) analyzed whether gender or neuropsychiatric symptoms predicted conversion from non-demented aging to AD.

Results indicated that individuals with AD experienced linear cognitive decline over a two-year period. Among individuals with AD, women had worse memory performance and exhibited faster rates of memory decline than men. Neuropsychiatric symptoms did not mediate these gender effects on AD-associated cognitive dysfunction, but they did increase odds of conversion from non-demented aging to AD. However, gender did not predict likelihood of converting to AD. Overall, this study suggested that AD-afflicted women may suffer from worse memory dysfunction than their male counterparts, even when controlling for dementia severity.

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NOMENCLATURE

AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive
ADNI	Alzheimer's Disease Neuroimaging Initiative
CDR	Clinical Dementia Rating Scale
CFA	Confirmatory Factor Analysis
CN	Cognitively Normal
DIF	Differential Item Functioning
IRT	Item Response Theory
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental Status Examination
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory-Questionnaire
RAVLT	Rey Auditory Verbal Learning Test
SEM	Structural Equation Modeling
SMC	Significant Memory Concerns

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INTRODUCTION AND LITERATURE REVIEW

Alzheimer's disease (AD) is a major health and societal concern that currently affects an estimated 5.3 million Americans (Alzheimer's Association, 2015). AD is the sixth leading cause of death in the United States and is projected to affect 13.8 million Americans over the age of 65 years by 2050 (Alzheimer's Association, 2015). Worldwide, AD is projected to affect 106.2 million older adults by 2050 (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Considering these staggering estimates and current lack of disease-modifying or preventative treatments, effective interventions and prevention are needed more than ever. Toward this end, research has been aimed at better understanding the disease as a whole, with a particular focus on characterizing early symptoms and predictors of future decline.

AD is conceptualized as a disease spectrum or continuum (Carrillo et al., 2012), rather than a static disease state. AD is not a consequence of normal or accelerated aging (Fjell et al., 2014; Nelson et al., 2011, 2012), but rather a distinct disease with insidious onset. AD advances progressively and spans a continuum across preclinical AD (Sperling et al., 2011), mild cognitive impairment (MCI; Albert et al., 2011; Petersen et al., 2001; Petersen, 2004), and dementia due to AD (McKhann et al., 2011). The preclinical stage is characterized by the development of disease pathology in the brain. Subjective memory concerns can also develop in this early stage, but objective cognitive performance is predominantly preserved. As the disease progresses, cognitive impairment becomes overt and measurable on neuropsychological assessment, such that individuals meet criteria for MCI. Cognitive declines gradually become more prominent

and affect one's capacity to care for oneself and complete important daily activities, at which point the person meets criteria for dementia due to AD.

It can be useful to consider these important clinical diagnostic stages along the AD continuum, but it is also essential to remember that the disease itself is progressive and so each of these stages represent a range of severity along a dimension (Backman, Jones, Berger, Laukka, & Small, 2005; Balsis, Miller, Benge, & Doody, 2011; Miller, Balsis, Lowe, Benge, & Doody, 2011). Although the emergence or increased severity of certain clinical symptoms, such as deterioration of cognition and ability to complete daily activities, is linked to conversion between diagnostic stages (e.g., conversion from MCI to dementia), the disease itself advances in a progressive manner rather than a stepwise, categorical manner.

As a neurodegenerative condition, AD is marked by a pattern of abnormalities within the brain that disrupt neurochemical and neuroanatomical integrity. Two of the earliest markers of AD are abnormal accumulation of amyloid-beta (Hardy & Higgins, 1992; Hardy & Selkoe, 2002) and pathological tau formation (Ballatore, Lee, & Trojanowski, 2007; Braak & Braak, 1995; Braak, Thal, Ghebremedhin, & Del Tredici, 2011), causing the development of amyloid plaques and neurofibrillary tangles, hallmark signs of AD (Ittner & Gotz, 2011; Risacher & Saykin, 2013). The plaques and tangles cause synaptic dysfunction and reduced regionalized cerebral activity, which can be measured by reduced glucose metabolism on functional neuroimaging (e.g., FDG-PET scans). Changes in neural activity parallel the pattern of neuroanatomical volumetric losses (Chen et al., 2010; Mosconi et al., 2008). Structural brain changes initially affect

the medial temporal lobe, specifically first in the entorhinal cortex, followed by thinning of the hippocampus and associated regions (Desikan et al., 2010; Devanand et al., 2012; Jiji, Smitha, Gupta, Pillai, & Jayasree, 2013; Johnson, Fox, Sperling, & Klunk, 2012; Schuff et al., 2009). As the disease progresses, ventricles expand and brain atrophy becomes globalized and severe (Scahill, Schott, Stevens, Rossor, & Fox, 2002; Whitwell et al., 2007).

Recent theoretical models have proposed a sequence of how key disease markers may change along the course of AD (Jack et al., 2010, 2013; Sperling et al., 2011). These models propose that markers of synaptic dysfunction emerge early in the disease, followed by indicators of cortical atrophy and later by cognitive decline. However, there is also evidence that suggests that hippocampal volume, synaptic dysfunction (measured by FDG-PET imaging), and global cognition may actually decline simultaneously (Bertens, Knol, Scheltens, Visser, & Alzheimer's Disease Neuroimaging Initiative, 2015). These models represent cognition as a single entity when there are numerous cognitive functions that have distinct trajectories in AD (e.g., Carter, Caine, Burns, Herholz, & Lambon Ralph, 2012). So while these theoretical models are useful for guiding future research efforts and promoting a broad, unified approach to analyzing AD, these disease models need to be validated and specific cognitive processes need to be integrated into the models.

Cognitive Declines in Alzheimer's Disease

As AD impairs neuronal function and brain structure, cognitive dysfunction develops beyond what is consistent with normal aging-related cognitive declines. Within

a healthy older adult population without cognitive impairment, normal cognitive aging patterns show steady declines in certain cognitive abilities, but improvements in other skills. Older adults show improvements in cognitive abilities, such as vocabulary and general knowledge, as they age (Park et al., 2002; Salthouse, 2004; Salthouse, Atkinson, & Berish, 2003). However, beginning in early adulthood (Salthouse, 2009b), there are nearly linear declines in processing speed, visuospatial abilities, executive functions, language skills, and verbal and visuospatial memory (Bopp & Verhaeghen, 2005; Caselli et al., 2014; Jacobs et al., 1995; Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012; Park et al., 2002; Salthouse, 2004, 2009a; Salthouse, Atkinson, & Berish, 2003; Salthouse & Meinz, 1995; Wilson et al., 2002).

While there are these steady cognitive declines in non-diseased aging, the declines are much more dramatic in AD. On cognitive assessment, individuals who develop AD can be differentiated from older adults who perform within expected limits for their age (and therefore are considered cognitively healthy or "normal"). Individuals with MCI and AD dementia perform significantly below their same-age peers on neuropsychological measures (e.g., Backman et al., 2005; Salthouse & Becker, 1998). There are also significant differences in baseline cognitive performance between older adults who remain cognitively healthy over time and those who were cognitively intact at baseline but eventually develop AD (Rubin et al., 1998; Tierney, Yao, Kiss, & McDowell, 2005).

Progressive declines in cognitive performance become increasingly evident with worsening AD severity, but subtle cognitive changes may develop earlier in the disease

process than previously thought (Schmid, Taylor, Foldi, Berres, & Monsch, 2013; Sperling et al., 2011). In fact, there is a large body of evidence that cognitive functions begin to change several years before clinical diagnosis (Backman et al., 2005; Elias et al., 2000; Linn et al., 1995; Salmon & Bondi, 2009; Saxton et al., 2004; Wilson et al., 2012).

One longitudinal study (Wilson et al., 2012) found that global cognitive function changed at a nonlinear rate and began to decline about 7.5 years prior to a diagnosis of dementia. Cognitive decline rapidly accelerated about 5.5 years later, approximately 2 years prior to dementia diagnosis, and continued to decline at this quick rate even beyond diagnosis of dementia. This is consistent with other longitudinal studies that showed a steady decline in global cognition (assessed by the Mini-Mental Status Examination; MMSE) for several years prior to dementia diagnosis (Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000), with accelerated decline in the three years prior to diagnosis (Amieva et al., 2008; Small & Backman, 2007). Other global measures of cognition, such as the Clinical Dementia Rating scale (CDR), MMSE, and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), have been shown to decline more quickly in individuals with MCI than in individuals with preclinical AD (Bertens et al., 2015). Even individuals with subjective memory concerns but no overt cognitive impairment at initial testing show disproportionate declines over time on measures of global cognition compared to healthy controls (Chamberlain et al., 2011). These early deficits in global cognition are supported by meta-analytic findings that individuals who were later diagnosed with AD had significantly lower baseline scores on tests of global

cognition (e.g., MMSE) than individuals who did not develop AD (Backman et al., 2005; Tierney et al., 2005).

Patterns of cognitive deterioration parallel the spread of AD throughout the brain. Just as AD initially affects the medial temporal lobe and then spreads throughout the brain, AD causes disproportionate declines in specific cognitive functions and is associated with a classic neuropsychological profile. Early cognitive declines reflect the impact of the disease on the medial temporal lobe, so early deficits develop in episodic memory (Buckner, 2004; Caselli et al., 2014; Linn et al., 1995; Mickes et al., 2007; Saxton et al., 2004), followed by difficulty in other areas of learning and memory. AD can also be marked by early declines in nonamnestic cognitive domains, such as complex executive or language functions (Albert et al., 2011; Sacuiu, Sjogren, Johansson, Gustafson, & Skoog, 2005; Salmon & Bondi, 2009). Declines in semantic memory, verbal fluency, and verbal concept formation have been shown as early as 10 to 12 years prior to diagnosis with dementia (Amieva et al., 2008). Individuals with MCI show faster rates of decline in executive and memory measures compared to individuals with preclinical AD who do not yet meet criteria for MCI or dementia due to AD (Bertens et al., 2015).

A recent study (Mura et al., 2014) examined how well various neuropsychological measures could detect cognitive change in individuals with MCI who either converted to AD within a three-year period or remained stable. The authors found that individuals with MCI who later converted to AD showed significant declines over time on tests of language, verbal episodic memory, and working memory compared

to individuals with MCI who did not convert to AD. Differences in annual change between the two groups were largest on tests of language and verbal episodic memory. There were smaller but still significantly different rates of annual change between the two groups on select measures of processing speed, visual memory, and working memory (measured by Trail Making Test Part A, Benton Visual Retention Test, and Serial Digit Ordering Test, respectively). Surprisingly, there were no significant group differences in terms of mean annual change for a classic executive measure of visual set shifting (i.e., Trail Making Test Part B), nor two measures of verbal abstraction and psychomotor speed (i.e., WAIS Similarities and WAIS Digit Symbol Test).

Furthermore, Mura and colleagues (2014) demonstrated that each of these neuropsychological tests had a different psychometric ability to measure cognitive ability. Since each of these neuropsychological tests had a different relationship to latent cognition, this finding also indicates that each test has differential sensitivity to measuring cognitive change. Based on these results, the researchers concluded that tests measuring verbal episodic memory and language were more sensitive to detecting cognitive change in MCI than tests of immediate visual memory, verbal concept abstraction, and executive function.

Backman and colleagues (2005) conducted an important meta-analysis to examine baseline differences in a wide range of cognitive functions between individuals who were later diagnosed with AD and individuals who did not later develop AD. The investigators found that at baseline, subjects with preclinical AD (i.e., those who were later diagnosed with AD) had significantly lower performance at baseline on numerous

cognitive tasks compared to control subjects (i.e., those who did not later develop AD). Specifically, the preclinical AD group showed significant deficits in episodic memory, verbal ability, visuospatial skill, attention, perceptual speed, and executive functioning at baseline. The effect sizes were large for perceptual speed (d = 1.11), executive functioning (d = 1.07), and episodic memory (d = 1.03). There were moderate but still noteworthy effect sizes for verbal ability (d = 0.79), visuospatial skill (d = 0.64), and attention (d = 0.62). The only cognitive domain that did not show significant differences between those who later developed AD versus those who did not was primary memory, consisting of tasks involving basic attention and sensory memory (e.g., WAIS Digit Span-Forward). As the authors note, these findings support the emergence of early declines in episodic memory, but they also indicate that numerous other cognitive functions are affected in preclinical AD. Effect sizes for episodic memory, executive functioning, and perceptual speed were virtually indistinguishable and had overlapping confidence intervals, suggesting that executive dysfunction and perceptual slowing may represent prominent cognitive declines on par with episodic memory difficulties in preclinical AD.

As AD severity intensifies, cognitive performance continues to decline in memory and across all other cognitive functions, including attention, executive, language, processing speed, and visuospatial abilities (Salmon & Bondi, 2009). As noted previously, in addition to memory dysfunction, early deficits may influence executive abilities (including mental manipulation of information, problem solving, and set shifting) and language (including deficits in verbal fluency and confrontation naming).

As the disease progresses, deficits in attention and visuospatial abilities become more evident (Saxton et al., 2004). Although impairment on complex attentional tasks may develop in early AD, basic attentional processes involved in focusing and sustaining attention do not decline until later in the disease (Weintraub, Wicklund, & Salmon, 2012). Cognitive functions continue to decline and may even deteriorate at an accelerated rate in the last few years prior to death (Wilson, Leurgans, Boyle, Schneider, & Bennett, 2010).

Although certain changes in cognitive abilities are known to be associated with AD, research continues to refine our understanding of how cognitive difficulties emerge consequent to the disease. We need more longitudinal studies that examine trajectories of change across a wide range of cognitive functions in AD. Better characterization of how cognitive functions are impaired and change across the course of the disease is needed to improve our understanding of AD.

Neuropsychiatric Symptoms in Alzheimer's Disease

In addition to cognitive dysfunction, individuals with AD frequently experience emotional and behavioral symptoms, often referred to as neuropsychiatric symptoms. Neuropsychiatric symptoms increase with dementia severity (Canevelli et al., 2013), so they are more common among individuals with MCI and AD relative to those with healthy cognitive functioning. In a population-based study, 27% of cognitively healthy older adults reported at least one neuropsychiatric symptom, whereas 51% of adults with MCI reported at least one neuropsychiatric symptom (Geda et al., 2008). Similarly, other studies report that between 35-85% of individuals with MCI experience at least one

neuropsychiatric symptom (Apostolova & Cummings, 2008; Gallagher et al., 2010; Van der Mussele et al., 2014). Individuals with AD dementia also commonly experience at least one neuropsychiatric symptom. Approximately 50% of patients with dementia experienced at least one neuropsychiatric symptom in a large population-based study (Peters et al., 2015) but prevalence rates were closer to 80-90% in another study (Nowrangi, Lyketsos, & Rosenberg, 2015).

Certain neuropsychiatric symptoms, such as depression, anxiety, apathy, and irritability, tend to be especially common in individuals with MCI and AD dementia. In a review of the literature, Apostolova and Cummings (2008) found that depression, apathy, and anxiety were consistently among the top four neuropsychiatric symptoms most frequently experienced by patients with MCI, with other common symptoms including irritability and agitation. Similarly, Geda and colleagues (2008) found that apathy, agitation, anxiety, irritability, and depression were approximately two to five times more prevalent among patients with MCI than older adults with normal cognition.

Apathy seems to increase with worsening AD severity so that it may be the most common neuropsychiatric symptom in AD dementia (Apostolova & Cummings, 2008). Drijgers and colleagues (2011) reported higher rates of apathy in patients with dementia (35.3%) versus patients with MCI (25.8%). However, Ramakers and colleagues (2010) reported that 70% of their sample with MCI endorsed symptoms of apathy.

Emotional (e.g., agitation, depression, anxiety) and behavioral (e.g., apathy, euphoria, disinhibition) symptoms increase with advancing dementia severity and remain more common than psychotic symptoms. According to a study by Canevelli and

colleagues (2013), among participants with mild AD (CDR = 1), approximately 46% had emotional and/or behavioral symptoms, whereas approximately 60% of older adults with moderate to severe AD (CDR = 2 or 3) had these symptoms. Gallagher and colleagues (2010) suggest that anxiety may be the most common neuropsychiatric symptom in MCI (52% of their MCI sample), but affective disturbances (37%) and aggression (32%) were also relatively common. In this study, other neuropsychiatric symptoms were less common but still present, including 23% of the sample with purposeless activity and 12% of the sample with delusions. Similarly, in the study by Canevelli and colleagues (2013), psychotic symptoms were less common than emotional or behavioral symptoms but still present and increased with dementia severity. In this study, approximately 12% of older adults with mild AD (CDR = 1) had psychotic symptoms, whereas almost 26% of older adults with moderate to severe AD (CDR = 2 or 3) had psychotic symptoms.

Neuropsychiatric symptoms and risk for Alzheimer's disease.

Neuropsychiatric symptoms are associated with higher risk for AD dementia (Rosenberg et al., 2013). Several studies have confirmed a link between depression and increased risk of developing dementia due to AD (e.g., Apostolova & Cummings, 2008; Brodaty et al., 2012; Byers & Yaffe, 2011; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Indeed, depressive symptoms increase prior to a diagnosis of AD (Gaugler et al., 2014). Both the presence and severity of depressive symptoms in MCI are independent predictors of progression to AD dementia (Van der Mussele et al., 2014). It should be noted that it is still controversial whether depression represents a risk factor for dementia

or prodromal symptoms of dementia. Regardless of the etiology, though, it has been established that symptoms of depression are linked to higher risk of AD.

Neuropsychiatric symptoms also may predict conversion to MCI and dementia. Symptoms of anxiety in cognitively healthy individuals predicted conversion to MCI over a two-year period (Brodaty et al., 2012). Furthermore, individuals who convert from MCI to AD dementia seem to experience more symptoms of anxiety compared to individuals who remain stable in MCI (Gallagher et al., 2010). Specifically, Gallagher and colleagues (2010) found that the combination of anxiety about future events and purposeless activity (e.g., pacing, repetitively putting on and taking off clothing) significantly predicted conversion from MCI to AD. However, this predictive relationship was not independent of performance on a brief neuropsychological battery (CAMCOG), so these neuropsychiatric symptoms actually may serve as a proxy of clinical severity rather than independent predictors. Furthermore, it is noteworthy that these neuropsychiatric symptoms were rated by informants rather than the participants themselves, so they represented behaviors that had become noticeable to observers.

Banks and colleagues (2014) also studied how neuropsychiatric symptoms may predict conversion to AD. Of their sample of 644 cognitively healthy older adults participating in the Alzheimer's Disease Cooperative Study Prevention Instrument Project, participant-reported presence of neuropsychiatric symptoms at baseline predicted conversion to MCI or AD over a four-year period. Those who converted reported higher levels of anxiety at baseline than those who did not convert. There were no differences in participant-reported levels of depression, apathy, or irritability at

baseline between those who progressed and those who did not. Among those participants who later converted to MCI or AD, their study partners more frequently reported symptoms of anxiety but also depression. Interestingly, however, total neuropsychiatric symptoms reported by partners at baseline did not predict decline to MCI or AD. As participants progressed to MCI or AD over time, partners reported increased levels of neuropsychiatric problems overall and anxiety and apathy specifically. These findings suggest that self-reported symptoms of anxiety and depression among cognitively healthy older adults may be risk factors of later conversion to MCI or AD. Caregivers are able to detect and report increasing levels of anxiety and apathy as patients' cognition worsens.

Other studies have found a link between apathy and increased risk of developing AD dementia (Apostolova & Cummings, 2008). A longitudinal study by Copeland and colleagues (2003) found higher rates of apathy at baseline among individuals who converted from normal aging to AD over a three-year period (27%) compared to control subjects who remained stable and cognitively normal (3%). Similarly, Balsis, Carpenter, and Storandt (2005) described increases in apathy prior to a diagnosis of AD for 24% of their sample who converted to dementia. Twenty-one percent of their sample with preclinical AD experienced increases in apathy prior to death.

Another recent study by Palmer and colleagues (2011) showed that symptoms of apathy were a strong predictor of conversion from amnestic MCI to AD; in fact, patients who had clinically relevant symptoms of apathy (i.e., an Apathy score of at least 2 on the Neuropsychiatric Inventory) in MCI had a fourfold chance of progressing to AD relative

to patients without symptoms of apathy. This same study did not find that depressive symptoms in MCI increased risk of converting to AD over a four-year period, which suggests that the presence of apathy in MCI may be a critical marker of AD risk, independent of depressive symptoms.

Finally, agitation has been suggested as a risk factor for AD. Copeland and colleagues (2003) reported higher rates of agitation at baseline among individuals who converted from MCI to AD over a three-year period (36%) relative to individuals who remained stable in MCI (18%) and individuals who remained cognitively normal over this period (6%). A separate study found that the severity of verbal agitation, in particular, was associated with higher risk of converting from MCI to AD (Van der Mussele et al., 2014).

Neuropsychiatric symptoms and cognitive deficits. In addition to elevating risk of diagnostic conversion, neuropsychiatric symptoms are associated with specific cognitive deficits. The presence of neuropsychiatric symptoms is associated with worse executive functioning, attention, and global cognition among older adults with normal cognition or MCI (Brodaty et al., 2012). Brodaty and colleagues also found several associations between specific neuropsychiatric symptoms and neuropsychological impairment. Depression was linked to impaired executive function; anxiety to impaired attention/processing speed, memory, visuospatial abilities, and global cognition; agitation to impaired memory, visuospatial abilities, and global cognition; and apathy to impaired visuospatial skills and global cognition. In a separate study, apathy was linked

with poorer executive functioning, particularly psychomotor speed in MCI and verbal fluency in MCI and AD (Drijgers et al., 2011).

In terms of longitudinal outcome, neuropsychiatric symptoms may accelerate cognitive decline. A few studies have analyzed this issue in samples of older adults with normal cognition, MCI, and AD. Among older adults without cognitive impairment, depressive symptoms may hasten decline in global cognition and episodic memory (Panza et al., 2009). Baseline anxiety and agitation were associated with declines in executive functions and language, respectively, over a two-year period for individuals with either MCI or normal cognition (Brodaty et al., 2012). Increases in euphoria, aberrant motor behavior, problematic eating behaviors, and worsening sleep quality have been linked to cognitive decline among individuals with MCI (Pocnet et al., 2015). Among individuals with moderate to severe AD, the presence of any behavioral symptoms (i.e., apathy, disinhibition, euphoria, and/or aberrant motor behavior) has been associated with more rapid cognitive decline (Canevelli et al., 2013). Furthermore, results from the Cache County Dementia Progression Study, a large population-based study, suggest that psychosis (i.e., delusions, hallucinations) and agitation/aggression are associated with faster progression to severe AD (Peters et al., 2015). Psychosis, affective symptoms (i.e., depression, anxiety, irritability), and agitation also were associated with earlier death in this study. Although only a handful of studies have examined the relationship between neuropsychiatric symptoms and cognitive change in elderly samples, it appears that neuropsychiatric symptoms are linked to more rapid deterioration of global and specific cognitive functions.

In sum, neuropsychiatric symptoms become more prevalent as cognition declines, particularly depression, apathy, anxiety, irritability, and agitation. These neuropsychiatric symptoms increase risk of converting from milder forms of cognitive impairment to dementia due to AD. Neuropsychiatric disturbances have been linked to poorer neuropsychological performance on executive, attentional, and global cognitive measures and may actually hasten cognitive deterioration over time. More research is needed to better understand the influence of neuropsychiatric symptoms on cognitive dysfunction in AD, especially over time and for important subgroups of patients, such as women and men. Neuropsychiatric symptoms often vary by men and women, so it may be important to examine their influence on cognitive functions for each gender. Furthermore, many of these aforementioned studies included gender as a covariate or confounding variable, rather than examining whether the relationship between neuropsychiatric symptoms and cognitive dysfunction in AD may vary across gender. This is an important empirical issue, especially considering the gender imbalance in AD.

Gender Gap in Alzheimer's Disease

There is a critical gender gap that exists in AD, with more women affected by the disease than men. Almost two-thirds of individuals with AD in the United States are women (Alzheimer's Association, 2015; Carter, Resnick, Mallampalli, & Kalbarczyk, 2012) and numerous studies have confirmed higher prevalence of AD in women than men (e.g., Brookmeyer et al., 2007; Plassman et al., 2007; Tschanz et al., 2011; Zhang et al., 1990). Prevalence rates of AD tend not to be adjusted to account for differences in base rates of women and men in the general older adult population. Among the broader

population of adults 65 years and older, approximately 56% are women, but after the age of 85 years women outnumber men almost 2 to 1 (Administration on Aging, Administration for Community Living, & U.S. Department of Health and Human Services, 2015).

Only a couple studies have analyzed prevalence rates of AD within women and men separately to account for this base rate difference. In a Chinese sample of older adults with AD and other dementias, prevalence rates were significantly higher in women than men (Zhang et al., 1990). In the Aging, Demographics, and Memory Study, a population-based study of older Americans, 11.48% of women and 7.05% of men over the age of 71 years had AD (Plassman et al., 2007). These findings suggest that even after controlling for differences in the proportion of women to men in the older adult population, women are more likely to have AD.

It also is useful to consider gender differences in incidence rates of AD, or the number of new cases of AD that are diagnosed within a given time period. Gender differences in incidence rates contrast women's risk of developing AD compared to men's risk, whereas gender differences in prevalence rates describe the relative proportion of women to men who have AD at a given time. Although many studies have found similar incidence rates of AD in women and men (e.g., Bachman et al., 1993; Barnes et al., 2003; Ganguli, Dodge, Chen, Belle, & DeKosky, 2000; Hebert, Scherr, McCann, Beckett, & Evans, 2001; Mielke, Vemuri, & Rocca, 2014), other studies have suggested that women are actually at greater risk of developing AD. In De Deyn and colleagues' (2011) study of Belgian older adults between the ages of 75 to 80 years,

incidence rates of dementia over a three-year period were almost 1.5 times greater for women (41.53 per 1000 women) relative to men (28.85 per 1000 men). Although a large proportion of this sample converted to AD, many participants did convert to other forms of dementia. Studies specific to AD incidence rates have confirmed increased vulnerability to the disease for women. In an early study of sex-specific incidence rates of AD between the ages of 75 to 85 years (Aronson et al., 1990), women were 2.7 times as likely as men to develop AD. In a meta-analysis conducted by Gao and colleagues (1998), women had an incidence rate of AD that was 1.56 times the incidence rate for men.

Fratiglioni and colleagues (1997, 2000) found that among European samples of older adults, incidence rates were significantly higher for women than men at every age. Furthermore, incidence rates continued to increase for women past the age of 85, whereas incidence rates plateaued for men after the age of 85. Ruitenberg and colleagues (2001) examined sex differences in AD incidence rates in a large, longitudinal, population-based study of adults 55 years and older in the Netherlands. Incidence rates were similar for men and women until the age of 90 years, after which women's incidence rates continued to increase whereas men's incidence rates declined. These studies suggest that women not only have higher incidence rates of AD than men, but that this gender gap becomes more pronounced late in life, after the approximate ages of 85 to 90 years.

Data from the Cache County Study, a large longitudinal study of older adults between the ages of 65 to 100-plus years, suggest a nonlinear relationship between age

and incidence that varies slightly across gender. Controlling for education and APOE ε4 genetic risk, Zandi and colleagues (2002) found that men and women had similar incidence rates of AD between the ages of 65 to 80, after which women were approximately twice as likely as men to develop AD. In both men and women, incidence rates continued to increase up to a certain age and then decelerated thereafter (Miech et al., 2002). This finding is consistent with other studies that have found a deceleration of the increase in incidence rates with advancing age (Gao et al., 1998). However, Miech and colleagues found a significant gender difference in when this deceleration occurred. For men, the critical age was 93 years, but incidence rates did not decline for women until after the age of 97 years. Overall, these studies showed that women's risk of AD is substantially higher than men's after the age of 85, and that although incidence rates for both sexes may decelerate late in life, this deceleration happens later for women than for men.

Gender differences in cognition: Cross-sectional findings. In addition to sex differences in prevalence and incidence rates of AD, there are gender differences in the cognitive profile of AD. The literature on cognitive differences between men and women with AD is relatively sparse, but it does suggest that women tend to show worse cognitive deficits than men.

Among healthy adults, women tend to slightly outperform men on tasks of verbal ability (including verbal episodic memory and verbal fluency), whereas men tend to have better visuospatial abilities (de Frias, Nilsson, & Herlitz, 2006; Voyer, Voyer, & Bryden, 1995; Weiss, Kemmler, Desenhammer, Fleischhacker, & Delazer, 2003). In

healthy older adults, men seem to retain their visuospatial advantage (Millet et al., 2009) and women seem to retain their advantage on tests of verbal memory. Barnes and colleagues (2003) examined cross-sectional sex differences in cognitive abilities in participants from the Religious Orders Study who were cognitively healthy and free of dementia at baseline. They found that women performed better than men on tasks of verbal episodic memory and perceptual speed, but worse than men on semantic memory (including tasks of verbal fluency, naming, and vocabulary). Women and men had equivalent performances on working memory, visuoperceptual skills, and nonverbal reasoning. Similarly, Munro and colleagues (2012) found that women performed better than men on tasks of psychomotor speed and verbal episodic memory. However, in this study, women performed worse than men on tasks of visuoconstruction and visual perception and equivalent to men on tests of verbal fluency and executive functioning.

The reliable pattern of stronger verbal skills in cognitively healthy women seems to change with the development of AD. Pusswald and colleagues (2015) found consistent deficits in verbal memory for women with AD relative to men with AD, but no sex differences in nonverbal memory or executive functions. This sex difference in verbal memory remained even after controlling for dementia stage and educational attainment. Chapman and colleagues (2011) also found that men with AD outperformed women with AD for verbal episodic learning and memory, although among healthy control participants, women performed better than men on these tasks.

Beinhoff and colleagues (2008) studied sex differences in verbal and visuospatial episodic memory among a sample of German participants diagnosed with AD dementia,

MCI, or healthy controls. Although women performed better than men on tasks of verbal episodic memory in the healthy control and MCI groups, there was no sex difference in verbal episodic memory in the AD condition. Men performed better than women in visuospatial episodic memory in the AD group, but there were no sex differences in visuospatial memory in the MCI or healthy control groups. Furthermore, the authors found that men with MCI and AD had a distinct pattern of visuospatial delayed recall that was stronger than verbal delayed recall. In contrast, women performed equally poor for both types of memory (verbal vs. visuospatial). There were no gender differences in any of the diagnostic groups on cognitive tasks of verbal fluency and naming. Again, this pattern of sex differences was independent of dementia severity (measured by the MMSE) and intelligence (measured by a German vocabulary test).

These studies suggest that women lose their verbal advantage with the development of AD. Men, on the other hand, may retain their visuospatial advantage and even performed better than women on verbal tasks in some studies. Other studies suggest that there are no sex differences in certain cognitive abilities in AD, but overall the findings are mixed and somewhat inconsistent. To analyze trends across various samples, Irvine and colleagues (2012) published a meta-analysis of 15 studies of AD patients. Their results revealed small but consistent deficits across all cognitive domains examined for women relative to men. These cognitive domains included verbal, visuospatial, memory, semantic, and nonsemantic abilities, with effect sizes ranging from $d = 0.14$ to $d = 0.27$. Males had an advantage and performed significantly better than female participants in all these cognitive domains. This pattern was independent of

global dementia severity (measured by the MMSE), age, or educational attainment. Although there may be inconsistencies in patterns of sex differences between individual studies, this meta-analysis argues for a distinct female deficit in cognitive performance among individuals with AD.

Gender differences in cognition: Longitudinal findings. It is also important to consider how cognitive functions change over time for women compared to men. Not enough research has analyzed this issue, and among the studies that do exist, there are inconsistent findings regarding sex differences in cognitive trajectories.

Even among older adults who are cognitively healthy, there is not a clear consensus of how men and women experience cognitive change. A systematic review of 13 studies of healthy older adults (Ferreira, Santos, Ferri, & Galduroz, 2014) did not find evidence of sex differences in rates of cognitive decline between the ages of 60-80 years. Rather, the authors indicated that age was the biggest predictor of rate of cognitive change, with decline becoming faster in older individuals. Barnes et al. (2003) also found that men and women who were cognitively healthy at baseline had similar rates of cognitive change over an eight-year period. These findings are in contrast with a large epidemiological study of 6476 healthy older adults born before 1924 (Karlamangla et al., 2009), which found that global cognitive decline was faster in women than men across a nine-year period. Proust-Lima and colleagues (2009) also found slightly steeper cognitive decline in healthy older females relative to healthy older men.

For individuals on the AD spectrum, we simply do not have enough information about sex differences in cognitive trajectories, but preliminary evidence suggests that

women experience steeper cognitive decline than men. Holland and colleagues (2013) found that women with MCI had faster rates of decline over a 36-month period than men on two global measures of severity, the CDR-SB and ADAS-Cog. Men and women with AD dementia declined at similar rates on these global measures. In contrast, Tschanz and colleagues (2011) found that in a sample of individuals diagnosed with AD, females declined faster than men on the MMSE, a measure of global cognitive dysfunction. The former study utilized clinical trial data from the Alzheimer's Disease Neuroimaging Initiative, whereas the latter study used population-based data, which may explain the discrepant findings.

There are no studies that have examined sex differences in specific areas of cognitive change (in contrast to change on measures of global severity) among individuals with MCI or AD. Given the worse cognitive performance that women demonstrate in cross-sectional studies, it is critical to analyze how cognitive functions change over time in women versus men.

In sum, we do not yet fully understand just how AD influences cognitive functions in women relative to men. There are few studies that consider either cross-sectional or longitudinal sex differences in cognitive abilities in an AD sample. We need more information about how a broad range of cognitive functions change across the course of AD to fill in our understanding of this important issue.

It is also important to consider what drives these sex differences in cognition in AD. Does AD affect women differently than men? Do women's cognitive abilities deteriorate at a faster rate than men's? On the other hand, perhaps the measures

themselves assess cognitive abilities differently for men than for women on the AD spectrum. These issues remain unclear. It is essential to examine whether there might be a gender bias in the tests that would explain why women perform worse than men, or whether there are other factors that might account for these sex differences in cognition. Furthermore, once we better understand this issue at the cross-sectional level, it is critical to understand how cognitive functions deteriorate over time in women relative to men with AD.

Explaining the Gender Gap in Alzheimer's Disease

There are several theories about why women seem to be more vulnerable to AD than men. Traditionally, the gender gap in prevalence rates has been attributed to women's longer life expectancy, since advancing age is the greatest risk factor for developing AD (Hebert et al., 2001; Plassman et al., 2007). There is also some evidence that men are more likely than women to die of cardiovascular disease in mid-life, so those men who survive into late life may have better cardiovascular health than women and thus lower risk of dementia (Chene et al., 2013). Among those who do develop AD, studies have found that men have higher mortality rates and more medical comorbidities relative to women (Gambassi et al., 1999; Sinforiani et al., 2010), so clinical outcomes, particularly survival duration, may vary between sexes. These factors may partially explain gender differences in prevalence rates.

It is essential also to consider why women may have a higher risk of developing AD (i.e., higher incidence rates). In the current older adult cohort, men are more likely than women to have higher cognitive reserve (e.g., greater educational and occupational

attainment), which has been shown to reduce risk for AD (Stern, 2012). There is also evidence that apolipoprotein E, a well-known genetic risk factor for AD, actually puts women at higher risk than men for developing AD (Damoiseaux et al., 2012; Ungar, Altmann, & Greicius, 2014).

In addition, changes in estrogen may play a key role in the gender gap, considering that women experience a dramatic decline in estrogen levels at menopause. Estrogen has been shown to have a neuroprotective effect against damage to the brain caused by beta-amyloid and tau (Dye, Miller, Singer, & Levine, 2012). Declines in estrogen due to menopause have been linked to risk of AD (Dye et al., 2012; Paganini-Hill & Henderson, 1994; Zandi et al., 2002) and cognitive impairment (Rocca, Grossardt, & Maragnore, 2008b). Interestingly, reductions in estrogen levels after bilateral oophorectomy (i.e., surgical removal of both ovaries) have also been linked to higher long-term risk of depressive and anxious symptoms compared to women who experienced natural menopause (Rocca et al., 2008a), which suggests that there may be a relationship between estrogen and affective symptoms.

While these factors contribute to the gender gap in AD, they may not completely explain women's vulnerability to AD, both in terms of higher incidence rates and worse cognitive performance. For example, Irvine and colleagues (2012) found that women with AD had consistent cognitive deficits relative to men with AD even after controlling for educational attainment, an indicator of cognitive reserve. Changes in estrogen are clearly associated with risk of AD, but it is uncertain whether these hormonal changes directly cause neurocognitive impairment or may be mediated by another mechanism

(e.g., affective symptoms). There is likely a complex web of interacting factors that drive gender differences in the development and clinical expression of AD. There are likely other factors beyond those already discussed that place women at greater risk for AD-associated deteriorations.

The potential contribution of neuropsychiatric symptoms to the gender gap in AD has not been considered carefully. Women are far more likely than men to experience affective disorders like depression and anxiety throughout their lifetime (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008; McLean & Anderson, 2009; Seeman, 1997). In fact, women are approximately twice as likely as men to suffer from depression or generalized anxiety disorders (Kessler, 2003; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Vesga-Lopez et al., 2008). Depressed older adults are also more likely to be female, both in the absence of overt cognitive impairment (Apostolova & Cummings, 2008; Luppa et al., 2012) and in MCI and dementia (Cerejeira, Lagarto, & Mukaetova-Ladinska, 2012; Van der Mussele et al., 2014). Self-reported sleep problems are linked with higher risk of developing AD in men (Benedict et al., 2014). In a recent study by Brodaty and colleagues (2015), women were more likely to be depressed whereas men were more likely to experience apathy, agitation, disinhibition, irritability, and delusions–although it should be noted that this was within a mixed sample of adults with various types of dementia. In a related study of nursing home patients with mixed forms of dementia, men were more likely to exhibit apathy while women were more likely to experience depression and anxiety (Zuidema, de Jonghe, Verhey, & Koopmans, 2009). In a large study of nursing home residents with AD (Buchanan, Wang, Ju, &

Graber, 2004), women were more likely to exhibit depressive and anxious behaviors, whereas men were likely to wander and demonstrate repetitive movements, like pacing and fidgeting.

In general, research is scarce that examines sex differences in neuropsychiatric symptoms experienced by individuals on the AD spectrum. We need this information, not only to better understand how men and women are affected by emotional/behavioral symptoms as part of AD but also to examine whether neuropsychiatric symptoms may contribute to the overall gender gap in AD (Li & Singh, 2014). Women's elevated lifetime risk of affective symptoms such as depression and anxiety may contribute to an increased vulnerability to AD. For example, depression has been linked to cerebral atrophy and glucose hypermetabolism in numerous cortical regions in older adults (Smith et al., 2009), including hippocampal volume loss (Naismith, Norrie, Mowszowski, & Hickie, 2012). Psychiatric symptoms could cause an accumulation of detrimental effects over time. Because women are at higher risk of these affective symptoms, then this psychiatric-related neurological damage could mediate the gender gap in the development and clinical expression of AD. However, this hypothesis needs to be analyzed.

Aims of the Proposed Research

Given these important, unanswered questions about the relationships among cognitive dysfunction, gender, and neuropsychiatric symptoms in AD, the current study had the following goals within four broad aims:

Aim 1: Model cognitive dysfunction in AD. Cross-sectional and longitudinal models of AD-associated cognitive dysfunction are needed to improve our understanding of how cognitive functions are impaired and decline across the course of the disease.

Goal A: Develop a cross-sectional model of AD-associated cognitive dysfunction. This study modeled the relative impairment of cognitive functions across the continuum of AD-associated cognitive dysfunction based on participants' performance at baseline (i.e., their first evaluation). Cognitive functions that were examined included memory, language, visuospatial abilities, and executive functions/processing speed (measured by neuropsychological assessment). The research produced statistical models that describe the relationship between neuropsychological tests/indicators and latent variables of AD-associated cognitive dysfunction (i.e., latent variables of memory, language, visuospatial abilities, executive/processing speed, and overall cognitive dysfunction).

Goal B: Model longitudinal change in AD-associated cognitive dysfunction. This provides important information about the relative rate at which specific cognitive functions change and become impaired over time along the AD continuum. This information will refine what we know about the neuropsychological profile of AD. These AD-associated cognitive trajectories were compared to patterns of cognitive change in the control subjects.

Aim 2: Analyze gender differences in AD-associated cognitive dysfunction. There is mixed information about whether women and men experience different

neuropsychological profiles of AD. This needs to be analyzed cross-sectionally and longitudinally for a range of cognitive functions.

Goal A: Analyze cross-sectional gender differences in AD-associated cognitive dysfunction. The research examined the generalizability of the baseline measurement model of cognitive dysfunction across gender. Sex differences in this baseline model would suggest differences in structure, sensitivity, or relative impairment of cognitive markers between men and women. Results were compared between participants with a diagnosis of AD within the first two years of their ADNI enrollment and a non-demented sample.

Goal B: Analyze gender differences in AD-associated cognitive trajectories. The study examined whether there were gender differences in longitudinal cognitive change. This sheds light on whether men and women experience similar trajectories of cognitive decline in AD or whether there are key gender differences in the progression of cognitive deterioration. Again, results were compared between the AD sample and the non-demented sample.

Aim 3: Examine whether neuropsychiatric symptoms mediate potential effects of gender on AD-associated cognitive dysfunction. Neuropsychiatric symptoms increase with dementia severity, have been associated with higher risk for AD and faster cognitive deterioration, and often differ in prevalence between women and men. It may be that neuropsychiatric symptoms contribute to the overall gender gap in AD, but this needs to be analyzed.

Goal A: Examine whether neuropsychiatric symptoms mediate potential gender differences in cross-sectional AD-associated cognitive dysfunction. The study examined whether neuropsychiatric symptoms might explain any cross-sectional gender differences in AD-associated cognitive dysfunction.

Goal B: Examine whether neuropsychiatric symptoms mediate potential gender differences in AD-associated cognitive change. The research also examined whether neuropsychiatric symptoms were a mechanism for any gender differences in longitudinal trajectories of AD-associated cognitive dysfunction.

Aim 4: Analyze whether gender or neuropsychiatric symptoms predict odds of conversion to AD. Finally, the research examined conversion from non-demented aging to AD, an important medical milestone. Specifically, the research analyzed whether conversion rates differed by gender and/or neuropsychiatric symptoms. Are women more or less likely to convert from MCI to AD than men? Does the presence or severity of neuropsychiatric symptoms influence likelihood of conversion? This aim provided key information about whether gender and/or neuropsychiatric symptoms predicted likelihood of converting from healthy aging or MCI to AD.

METHOD

The Alzheimer's Disease Neuroimaging Initiative (ADNI) database was analyzed for this study. ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations as a public-private partnership. The initial phase, ADNI1, was followed by two extensions, ADNI-GO and ADNI2. To date, ADNI has recruited over 1600 adults, ages 55 to 90 years, from across the United States to participate in the research. These participants represent the continuum of AD, from cognitively normal individuals to those with clinical diagnoses of MCI and AD. Participants are followed longitudinally and participate in comprehensive evaluations, including thorough neuropsychological and neuropsychiatric assessment. The ADNI database provided a unique opportunity to analyze a wide spectrum of cognitive and neuropsychiatric functions–key disease-related variables–for a large sample of individuals who are followed longitudinally. Because of this, the ADNI database was ideal for analyzing the questions for the current research.

Participants

ADNI has enrolled participants that represent a wide range of diagnoses along the AD spectrum, including normal aging, subjective memory concerns, MCI, and AD. According to ADNI protocol, cognitively normal (CN) participants serve as the controls and show no signs of MCI, dementia, or significant depression. CN participants have normal cognition (defined as CDR = 0, MMSE between 24-30, and WMS-R Logical

Memory II subscale score above education-adjusted cutoffs) and neither the participants nor their study partners report memory concerns.

Beginning in ADNI2, participants with significant memory concerns (SMC) were enrolled. SMC participants have normal cognition (defined the same as for CN participants), but there is significant concern about memory (either reported by the participant, study partner, or clinician) coupled with a significant memory concern based on the Cognitive Change Index, a self-report scale.

MCI participants have been enrolled since ADNI1, but in ADNI-GO and ADNI2, MCI participants were defined as either having early MCI or late MCI. Overall for an MCI diagnosis, subjects must have a subjective memory concern and exhibit significant amnestic dysfunction (defined by CDR = 0.5 plus an abnormal score on the WMS-R Logical Memory II subscale). However, MCI subjects have sufficiently preserved functional abilities and global cognition (MMSE score between 24-30), such that they do not meet criteria for AD. The determination of early MCI versus late MCI is based on severity of impairment on the WMS-R Logical Memory II subscale, a measure of delayed recall for auditory information presented in story format.

Participants were diagnosed with AD if they met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD (McKhann et al., 1984). At time of ADNI diagnosis, AD participants demonstrated deficits in their global cognition (based on MMSE scores between 20-26 plus CDR scores of 0.5 or 1), abnormal memory functioning (based on scores on the WMS-R Logical Memory II

subscale), and significant concerns with memory (reported by the participant, study partner, or clinician).

For the current research study, participants were selected from across all three ADNI phases, ADNI1, ADNI-GO, and ADNI2. At the initial baseline appointment, 1662 participants had completed all 15 cognitive tests of interest for the present study. Of these 1662 participants, 749 were female (45%) and 913 were male (55%). Participants ranged in age from 48 to 91 years old (M = 73.81, SD = 7.18 years) and were highly educated (M = 15.94, SD = 2.83 years). The majority of participants identified their race as White/Caucasian (n = 1537). Approximately one-third had a diagnosis of either CN or SMC (N = 511, 31%), half had a diagnosis of MCI (N = 852, 51%), and the remainder had a diagnosis of AD (N = 299, 18%).

Due to attritional factors and differences in timing of ADNI enrollment, the sample size decreased at subsequent follow-up visits (see Table 1), with notable drop-off after month 24. Across all time-points, males made up over half of the sample, and percentage of participants with AD did not exceed one-quarter. Although the sample size decreased, the sample characteristics did not change significantly across time points.

We used this sample of 1662 participants to maximize power for estimating the cross-sectional, statistical models of AD-associated cognitive dysfunction (Aim 1a). For the other analyses, we used a slightly smaller sample of 1054 participants who had completed neuropsychological testing at baseline, month 12, and month 24 (see Table 2). This sample did not significantly differ from the larger baseline sample of 1662 participants in terms of age, education, proportion of females, or diagnostic breakdown

Table 1. Longitudinal demographic statistics for all participants with cognitive data.

		Age at Baseline		Education		Gender		Diagnosis		
						Female	Male	CN/SMC	MCI	AD
Visit	***N***	***M***	***SD***	***M***	***SD***	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Baseline	1662	73.83	7.15	15.94	2.83	749 (45%)	913 (55%)	511 (31%)	852 (51%)	299 (18%)
Month 6	1543	73.85	7.06	15.96	2.83	691 (45%)	852 (55%)	486 (32%)	748 (49%)	309 (20%)
Month 12	1390	73.89	7.08	15.99	2.80	605 (44%)	785 (56%)	415 (30%)	660 (48%)	315 (23%)
Month 18	312	74.58	7.20	15.84	2.92	110 (35%)	202 (65%)	10 (3%)	217 (70%)	84 (27%)
Month 24	1100	73.72	7.04	16.09	2.77	481 (44%)	619 (56%)	370 (34%)	462 (42%)	268 (24%)
Month 36	574	73.94	6.91	16.04	2.73	248 (43%)	326 (57%)	193 (34%)	258 (45%)	123 (21%)
Month 48	283	74.62	6.50	16.05	2.78	116 (41%)	167 (59%)	107 (38%)	108 (38%)	67 (24%)
Month 60	200	74.50	5.89	16.04	2.87	78 (39%)	122 (61%)	93 (47%)	65 (33%)	42 (21%)
Month 72	204	74.83	5.97	15.95	2.89	83 (41%)	121 (59%)	95 (47%)	65 (32%)	44 (22%)
Month 84	163	74.60	5.47	15.88	2.87	69 (42%)	94 (58%)	73 (45%)	63 (39%)	27 (17%)
Month 96	92	74.53	5.73	16.07	2.89	32 (35%)	60 (65%)	43 (47%)	33 (36%)	16 (17%)

Note. Percentages may not add to 100% due to rounding. CN = cognitively normal. SMC = subjective memory concerns. MCI = mild cognitive impairment. AD = Alzheimer's disease.

Table 2. Demographic statistics for 1045 participants with cognitive data at baseline, month 12, and month 24.

		Age at Baseline		Education		Gender		Diagnosis		
						Female	Male	CN/SMC	MCI	AD
Visit	***N***	***M***	***SD***	***M***	***SD***	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Baseline	1045	73.71	7.04	16.11	2.76	455 (44%)	590 (57%)	339 (32%)	610 (58%)	96 (9%)
Month 12	1045	--	--	--	--	--	--	353 (34%)	532 (51%)	160 (15%)
Month 24	1045	--	--	--	--	--	--	354 (34%)	442 (42%)	249 (24%)

Note. Percentages may not add to 100% due to rounding. CN = cognitively normal. SMC = subjective memory concerns. MCI = mild cognitive impairment. AD = Alzheimer's disease.

Table 3. Diagnostic conversion rates relative to baseline diagnosis for men and women.

		Stable			Conversion			Reversion	
Visit	***N***	**CN/SMC**	**MCI**	**AD**	**CN/SMC to MCI**	**MCI to AD**	**CN/SMC to AD**	**MCI to CN/SMC**	**AD to MCI**
Baseline	1045	**339 (32%)**	**610 (58%)**	**96 (9%)**	--	--	--	--	--
Female	455	161 (35%)	252 (55%)	42 (9%)	--	--	--	--	--
Male	590	178 (30%)	358 (61%)	54 (9%)	--	--	--	--	--
Month 12	1045	**330 (32%)**	**521 (50%)**	**94 (9%)**	**9 (1%)**	**66 (6%)**	**--**	**23 (2%)**	**2 (0%)**
Female	455	157 (35%)	210 (46%)	42 (9%)	4 (1%)	27 (6%)	--	15 (3%)	--
Male	590	173 (29%)	311 (53%)	52 (9%)	5 (1%)	39 (7%)	--	8 (1%)	2 (0%)
Month 24	1045	**321 (31%)**	**424 (41%)**	**94 (9%)**	**16 (2%)**	**153 (15%)**	**2 (0%)**	**33 (3%)**	**2 (0%)**
Female	455	153 (34%)	177 (39%)	41 (9%)	7 (2%)	60 (13%)	1 (0%)	15 (3%)	1 (0%)
Male	590	168 (29%)	247 (42%)	53 (9%)	9 (2%)	93 (16%)	1 (0%)	18 (3%)	1 (0%)

Note. Conversion rates are relative to baseline diagnosis. Percentages represent percentage of relevant sample; that is, percentage of overall sample, percentage of females, or percentage of males. CN = cognitively normal. SMC = subjective memory concerns. MCI = mild cognitive impairment. AD = Alzheimer's disease.

at baseline. Of these 1054 participants, 455 were female (44%) and 590 were male (57%). The mean age was 73.71 years (*SD* = 7.04), and the sample was still highly educated (*M* = 16.11, *SD* = 2.76 years). At baseline, 339 had a diagnosis of either CN or SMC (32%), 610 had a diagnosis of MCI (58%), and 96 had a diagnosis of AD (9%). By month 24, almost one-quarter of the sample had a diagnosis of AD (*N* = 249, 24%). Between baseline and month 24, two of the participants with a baseline diagnosis of AD reverted to MCI, but 153 converted from MCI to AD and two converted from CN to AD (see Table 3).

Neuropsychological Battery

All ADNI participants completed a battery of cognitive testing at baseline and regular follow-up appointments. The schedule of testing varied slightly depending on whether their baseline diagnosis was AD, MCI, SMC, or CN. All participants were scheduled to complete follow-up cognitive testing at months 6, 12, and ongoing annual visits. The core ADNI neuropsychological battery that has been administered across all ADNI phases includes the following tests: the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog; Mohs, Rosen, & Davis, 1983), Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), Category Fluency Test (adapted from the CERAD Verbal Fluency test; Morris et al., 1989), Clock Drawing Test (Goodglass & Kaplan, 1983), Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), and Trail Making Test (Reitan, 1958; Reitan & Wolfson, 1985).

The current research analyzed 15 indicators from these neuropsychological tests that assess memory, language, executive functions, processing speed, and visuospatial

abilities. The ADAS-Cog assesses a variety of cognitive abilities, including memory (e.g., Delayed Recall and Word Recognition subtests), language (e.g., Naming subtest), visuoconstruction (e.g., Construction subtest), and processing speed (e.g., Number Cancellation subtest). The Boston Naming Test measures confrontation naming abilities, or a participant's ability to retrieve names for a series of 30 objects when presented with two-dimensional line drawings of those objects. The Category Fluency Test, a measure of verbal fluency, includes an Animals condition, in which participants are given one minute to generate as many names of animals as they can. The Clock Drawing Test is a measure of visuoconstruction abilities. There are two conditions: in the first "command" condition (Clock command), participants are asked to draw a clock with the hands set to a specified time, whereas in the second "copy" condition (Clock copy), participants are asked to copy a drawing of a clock that is provided to them. The RAVLT assesses immediate, delayed, and recognition aspects of verbal learning and memory; the present study examined list learning over five trials (RAVLT Learning), short-delay recall on trial 6, 30-minute delayed recall, and recognition memory after a 30-minute delay. Finally, the Trail Making Test measures psychomotor speed (Trail Making A) and executive functions (Trail Making B).

Neuropsychiatric Assessment

The Neuropsychiatric Inventory (NPI; Cummings et al., 1994), a structured clinical interview, was administered to a study partner/caregiver who knew the participant well in order to assess the participant's neuropsychiatric functioning. The NPI was developed to assess various forms of psychopathology in individuals with AD

and other dementias. The NPI measures a range of neuropsychiatric symptoms, including depression, anxiety, apathy, irritability, euphoria, agitation/aggression, delusions, hallucinations, disinhibition, aberrant motor behavior, disordered sleep and nighttime behaviors, and changes in appetite and eating. The study partner/caregiver was asked to indicate whether the participant had demonstrated these any of these 12 behaviors in the previous four weeks. For any behavior that the caregiver indicated was present in the past four weeks, the caregiver was then asked to rate severity of the behavior, frequency of the behavior, and amount of distress that the behavior caused the caregiver. The full NPI has only been administered during the ADNI2 phase.

The NPI-Questionnaire (NPI-Q; Kaufer et al., 2000) is an abbreviated version of the NPI that has been administered throughout the entirety of ADNI. As with the full NPI, study partners/caregivers were administered screening questions and asked to indicate whether any of the 12 behaviors had been present in the participant over the past four weeks. If the study partner indicated "yes" to any of the screening questions, the study partner was then asked to evaluate severity of the behavior. Severity ratings were made on a 3-point scale, where 1 is Mild ("noticeable, but not a significant change"), 2 is Moderate ("significant, but not a dramatic change"), and 3 is Severe ("very marked or prominent, a dramatic change"). If the behavior was rated as not present in the past month, then the Severity rating was 0. All of the Severity ratings were summed to produce the Total NPI-Q score.

Although the NPI-Q has been used throughout all ADNI phases, participants have either NPI or NPI-Q data at any given timepoint; no participants have data for both

scales. For example, of the 1045 participants with cognitive data at baseline, month 12, and month 24, 410 (39%) had NPI data while the other 635 (61%) had NPI-Q data at baseline. To increase statistical power and utilize the entire sample, an NPI severity composite score was created based on the severity ratings on the NPI and NPI-Q. This NPI severity composite score represents overall severity of neuropsychiatric symptoms for participants, regardless of whether they had NPI or NPI-Q data. This NPI severity composite score was used for all analyses.

Statistical Analyses

Statistical analyses were conducted largely within item response theory (IRT; Embretson & Reise, 2000; Hambleton, Swaminathan, & Rogers, 1991; Samejima, 1969) and structural equation modeling (SEM; Brown, 2015; Little, 2013) frameworks. These frameworks statistically factor out measurement error to permit analysis of how observed data (e.g., test scores) relate to latent constructs, such as latent cognition and latent neuropsychiatric disturbance.

IRT requires categorical data, whereas SEM can analyze continuous data. Because the neuropsychological indicators are continuous and spanned ranges of 5 (e.g., ADAS-Cog Naming) to 300 (e.g., Trail Making B), they were placed into categories for IRT analyses. The range of these variables was determined in the dataset at baseline evaluation. Values for each variable were then placed into five equal-width categories (0 through 4) using SPSS interval binning procedures.

As described below, repeated-measures ANOVAs were conducted for longitudinal analyses. Linear regressions were computed for mediation analyses, and

binary logistic regressions were conducted to examine whether gender or neuropsychiatric symptoms predicted odds of conversion to AD.

Aim 1, Goal A: Develop a cross-sectional model of AD-associated cognitive dysfunction. Confirmatory factor analysis (CFA) was conducted to analyze the structure of cognitive abilities. A second-order CFA model was hypothesized to fit the data, with a higher-order latent factor of global AD-associated cognitive dysfunction and four lower-order latent factors of discrete cognitive domains: memory, language, visuospatial, and executive/processing speed. The clustering of neuropsychological measures into these four lower-order cognitive domains and single higher-order factor was guided by test content and a previously published factor analysis of the ADNI1 neuropsychological battery (Park et al., 2012).

Within an IRT framework, Samejima's graded response model (Samejima, 1969) was used to estimate each cognitive marker's sensitivity or ability to measure latent AD-associated cognitive dysfunction (i.e., the *a* parameter) and discriminate between degrees of latent cognitive dysfunction (i.e., the *b* parameter). This produced a model that placed each cognitive marker's discriminative ability on a common scale so that they could be directly compared to one another. This enabled examination of how well and at what degree of disease severity different areas of cognitive dysfunction yielded information about AD. This cross-sectional model provided information both at the level of cognitive domains and at the level of specific tests. In other words, developing this model provided information about how the four cognitive domains (e.g., memory, language, visuospatial, executive/processing speed) related to one another across the continuum of

AD-associated cognitive dysfunction, but also about how specific tests (e.g., each of the memory tests examined) related to one another across this spectrum.

Aim 1, Goal B: Model longitudinal change in AD-associated cognitive dysfunction. Cognitive change between baseline, month 12, and month 24 was examined for all cognitive domains (i.e., memory, language, visuospatial, executive/processing speed, and global cognitive dysfunction). Repeated-measures ANOVAs were computed for each cognitive domain. Within-subjects polynomial contrasts were used to test linear versus quadratic rates of change from baseline to month 12 and month 24. Because age and education are known correlates of cognitive performance (e.g., Ardila, Ostrosky-Solis, Rosselli, & Gomez, 2000; van Hooren et al., 2007), they were entered as covariates in the models. In addition, clinical diagnostic status at month 24 was entered as a between-subjects factor. The diagnostic status variable represented whether the patient had a diagnosis of AD or was non-demented at month 24 of their ADNI enrollment. This binary variable was included as a moderating variable to test whether rate of cognitive change differed between an AD group and a non-demented group, as would be expected. Gender was also entered as a between-subjects factor in this model to test whether rate of change differed by gender for Aim 2B, described below.

Aim 2, Goal A: Analyze cross-sectional gender differences in AD-associated cognitive dysfunction. This goal was analyzed using an IRT framework. Differential item functioning (DIF) was used, which allows one to analyze whether items function differently or may be biased against one group compared to another. For the current

study, DIF techniques were harnessed to analyze whether the cross-sectional model of AD-associated cognitive dysfunction was equivalent in women and men, specifically whether any of the cognitive domains or 15 cognitive tests functioned significantly differently for women relative to men.

Aim 2, Goal B: Analyze gender differences in AD-associated cognitive trajectories. Potential gender differences were analyzed within the repeated-measures ANOVA models. Gender was entered as a between-subjects factor. This allowed us to test whether there was a main effect of gender on the average cognitive score across baseline, month 12, and month 24 for each cognitive domain. More interestingly, it enabled us to examine whether there was a significant time by gender interaction, which would suggest that women had a different pattern of cognitive change than men. Diagnostic status was also entered as a between-subjects factor to compare whether the effects of gender differed between the AD group and the non-demented group.

Aim 3, Goal A: Examine whether neuropsychiatric symptoms mediate potential gender differences in cross-sectional AD-associated cognitive dysfunction. We conducted a series of regressions (one set for each cognitive domain) according to the Baron and Kenny (1986) approach to test whether severity of neuropsychiatric symptoms mediated a gender effect on cognitive dysfunction. Age and education were entered as covariates in each of the steps. First, we analyzed whether gender significantly predicted cognitive dysfunction. Second, we examined whether gender predicted neuropsychiatric symptoms (i.e., the NPI severity composite). Third, we analyzed whether neuropsychiatric symptoms predicted cognitive dysfunction

controlling for gender. Fourth, we examined whether gender still significantly predicted cognitive dysfunction after controlling for neuropsychiatric symptoms. In order to demonstrate mediation, the effect of gender on cognitive dysfunction in step one would be significant, but it would become non-significant in step four after controlling for neuropsychiatric symptoms. These regressions testing for mediation were first conducted in the overall sample. They were then conducted in the AD sample and non-demented samples separately to examine whether diagnostic status served as a moderator for any mediation effect.

Aim 3, Goal B: Examine whether neuropsychiatric symptoms mediate potential gender differences in AD-associated cognitive change. To examine whether neuropsychiatric symptoms mediated any effects of gender on cognitive change, we re-ran the repeated measures ANOVA models as described above, but entered the NPI severity composite score as a covariate. Again, gender and diagnostic status were entered as between-subjects factors, age and education were entered as covariates (in addition to the NPI severity composite score), and each latent cognitive score was entered as a dependent variable in turn. Conducting these repeated-measures ANOVAs allowed us to examine whether any significant effects of gender from previous analyses (aim 2, goal B) became non-significant after controlling for neuropsychiatric symptoms.

Aim 4: Analyze whether gender or neuropsychiatric symptoms predict odds of conversion to AD. A binary logistic regression was conducted to analyze whether gender or neuropsychiatric symptoms predicted odds of conversion to AD. In the model, a binary variable representing conversion from CN or MCI to AD (0 = no, 1 = yes) was

entered as the dependent variable. Gender and the baseline NPI severity composite score were entered as covariates in the model.

RESULTS

Descriptive Statistics

Tables 4 and 5 display mean scores on raw cognitive tests at baseline, month 12, and month 24 for the overall sample of 1045 participants, as well as mean cognitive scores for the AD sample and the non-demented sample. As expected, participants with AD had worse cognitive performance than non-demented participants. In addition, participants with AD showed a deterioration of their cognitive scores over the two-year period, whereas non-demented participants' cognitive scores remained relatively stable.

Neuropsychiatric scores also increased over the two-year period for the entire sample, including greater frequency of each individual neuropsychiatric symptom (see Table 6). Individuals with AD had higher mean neuropsychiatric scores than the non-demented participants at each time point (see Table 7). Correspondingly, these demented participants also endorsed each neuropsychiatric symptom at a higher frequency than the non-demented participants (see Table 8 and Figure 1). Between 73-82% of the AD sample reported at least one neuropsychiatric symptom across the two-year time period, in contrast to 41-47% of the non-demented sample. The top five endorsed symptoms for the AD sample were irritability/lability (32-37%), depression/dysphoria (31-35%), anxiety (28-37%), apathy/indifference (24-37%), and agitation/aggression (24-31%). For the non-demented sample, the most frequent symptoms were almost identical but rates of these symptoms were lower. The top five endorsed symptoms for the non-demented sample were irritability/lability (17-20%), depression/dysphoria (15-19%), sleep problems (14-17%), agitation/aggression (9-13%), and anxiety (9-11%).

Table 4. Raw cognitive scores at baseline, month 12, and month 24.

	M (SD)		
Cognitive Test	**Baseline**	**Month 12**	**Month 24**
Memory			
RAVLT Learning	4.57 (2.65)	4.44 (2.80)	4.31 (2.86)
RAVLT Short-Delay Recall	5.98 (4.08)	6.00 (4.33)	5.91 (4.57)
RAVLT Delayed Recall	4.86 (4.28)	4.80 (4.64)	4.66 (4.75)
RAVLT Recognition	11.14 (3.52)	10.87 (3.92)	10.65 (4.16)
ADAS-Cog Delayed Recall	4.81 (2.77)	4.84 (3.05)	5.01 (3.17)
ADAS-Cog Recognition	3.54 (2.71)	3.56 (3.09)	3.99 (3.23)
Language			
Animals	18.28 (5.48)	18.10 (5.89)	17.42 (6.37)
Boston Naming Test	26.40 (3.86)	26.62 (4.43)	26.24 (5.03)
ADAS-Cog Naming	.17 (.44)	.16 (.45)	.21 (.55)
Visuospatial			
Clock command	4.42 (.87)	4.43 (.90)	4.35 (.99)
Clock copy	4.75 (.57)	4.77 (.52)	4.68 (.69)
ADAS-Cog Construction	.44 (.54)	.46 (.57)	.48 (.59)
Executive/Processing Speed			
Trail Making A	38.79 (16.60)	39.14 (18.42)	40.70 (23.66)
Trail Making B	106.32 (61.74)	110.55 (71.03)	116.48 (78.22)
ADAS-Cog Number Cancellation	.65 (.85)	.63 (.93)	.89 (1.08)

Note. N = 1054. Tests are grouped by cognitive domain. RAVLT = Rey Auditory Verbal Learning Test. ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive. Clock = Clock Drawing Test.

Table 5. Raw cognitive scores at baseline, month 12, and month 24 for AD and non-demented samples.

AD			
	M (SD)		
Cognitive Test	**Baseline**	**Month 12**	**Month 24**
Memory			
RAVLT Learning	2.71 (2.01)	2.16 (1.78)	1.88 (1.55)
RAVLT Short-Delay Recall	2.37 (2.09)	1.98 (1.93)	1.38 (1.75)
RAVLT Delayed Recall	1.22 (1.90)	.70 (1.52)	.32 (.94)
RAVLT Recognition	8.24 (3.89)	7.38 (4.07)	6.56 (4.36)
ADAS-Cog Delayed Recall	7.59 (2.08)	8.10 (1.90)	8.63 (1.77)
ADAS-Cog Recognition	5.58 (2.77)	6.27 (3.25)	7.10 (3.04)
Language			
Animals	15.07 (4.52)	13.75 (5.18)	11.88 (5.12)
Boston Naming Test	24.15 (5.04)	23.41 (6.01)	21.94 (6.88)
ADAS-Cog Naming	.35 (.61)	.39 (.69)	.54 (.83)
Visuospatial			
Clock command	3.86 (1.12)	3.76 (1.20)	3.49 (1.32)
Clock copy	4.57 (.74)	4.55 (.72)	4.31 (1.03)
ADAS-Cog Construction	.58 (.56)	.68 (.67)	.80 (.69)
Executive/Processing Speed			
Trail Making A	48.76 (21.92)	51.51 (24.82)	58.94 (33.13)
Trail Making B	156.18 (80.19)	175.81 (89.29)	195.76 (96.69)
ADAS-Cog Number Cancellation	1.10 (1.03)	1.26 (1.21)	1.78 (1.27)
NON-DEMENTED			
	M (SD)		
Cognitive Test	**Baseline**	**Month 12**	**Month 24**
Memory			
RAVLT Learning	5.15 (2.56)	5.15 (2.67)	5.07 (2.75)
RAVLT Short-Delay Recall	7.11 (3.89)	7.26 (4.10)	7.32 (4.25)
RAVLT Delayed Recall	6.01 (4.18)	6.08 (4.54)	6.02 (4.65)
RAVLT Recognition	12.04 (2.85)	11.96 (3.15)	11.93 (3.15)
ADAS-Cog Delayed Recall	3.94 (2.36)	3.81 (2.58)	3.88 (2.63)
ADAS-Cog Recognition	2.90 (2.36)	2.72 (2.51)	3.01 (2.62)
Language			
Animals	19.28 (5.37)	19.46 (5.43)	19.16 (5.69)
Boston Naming Test	27.10 (3.10)	27.62 (3.21)	27.58 (3.30)
ADAS-Cog Naming	.12 (.35)	.08 (.32)	.11 (.37)
Visuospatial			
Clock command	4.60 (.70)	4.63 (.66)	4.61 (.67)
Clock copy	4.81 (.50)	4.84 (.42)	4.79 (.49)
ADAS-Cog Construction	.40 (.52)	.39 (.52)	.38 (.52)
Executive/Processing Speed			
Trail Making A	35.67 (13.08)	35.27 (13.80)	35.00 (16.00)
Trail Making B	90.72 (44.48)	90.13 (48.86)	91.68 (50.34)
ADAS-Cog Number Cancellation	.51 (.73)	.43 (.72)	.61 (.84)

Note. AD n *= 249. Non-demented* n *= 796. Tests are grouped by cognitive domain. RAVLT = Rey Auditory Verbal Learning Test. ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive. Clock = Clock Drawing Test.*

Table 6. Neuropsychiatric scores at baseline, month 12, and month 24.

Neuropsychiatric Indicator	**Baseline**		**Month 12**		**Month 24**	
	N	***M(SD)***	***N***	***M(SD)***	***N***	***M(SD)***
NPI Severity Composite	1045	1.48 (2.49)	1043	1.92 (2.81)	1042	2.08 (3.13)
NPI Total	410	2.92 (5.61)	506	4.04 (7.06)	506	4.57 (8.04)
NPI-Q Total	635	1.57 (2.62)	543	2.11 (3.01)	536	2.28 (3.35)
Symptom Endorsement	**Y (%)**		**Y (%)**		**Y (%)**	
Delusions	11 (1%)		26 (2%)		31 (3%)	
Hallucinations	6 (1%)		11 (1%)		19 (2%)	
Agitation/Aggression	134 (13%)		164 (16%)		178 (17%)	
Depression/Dysphoria	197 (19%)		226 (22%)		225 (22%)	
Anxiety	141 (13%)		170 (16%)		173 (17%)	
Elation/Euphoria	18 (2%)		21 (2%)		27 (3%)	
Apathy/Indifference	120 (11%)		160 (15%)		173 (17%)	
Disinhibition	74 (7%)		92 (9%)		103 (10%)	
Irritability/Lability	216 (21%)		250 (24%)		243 (23%)	
Aberrant Motor Behavior	38 (4%)		52 (5%)		72 (7%)	
Sleep	154 (15%)		194 (19%)		195 (19%)	
Appetite and Eating Disorders	76 (7%)		107 (10%)		134 (13%)	
Any Symptom	509 (49%)		578 (55%)		576 (55%)	

Note. N = 1054. The NPI Severity Composite represents average severity ratings across NPI and NPI-Q. NPI = Neuropsychiatric Index. NPI-Q = Neuropsychiatric Index Questionnaire.

Table 7. Participants with AD have higher levels of neuropsychiatric symptoms than non-demented participants at baseline, month 12, and month 24.

	Non-Demented		AD		*t*-test		
Neuropsychiatric Indicator	***N***	***M(SD)***	***N***	***M(SD)***	***t(df)***	***p***	**Cohen's *d***
Baseline							
NPI Severity Composite	796	1.11 (2.01)	249	2.68 (3.34)	-7.04 (306.21)	<.001	-.57
NPI Total	341	2.40 (4.93)	69	5.52 (7.72)	-3.23 (79.59)	<.01	-.48
NPI-Q Total	455	1.11 (2.01)	180	2.72 (3.50)	-5.82 (227.41)	<.001	-.56
Month 12							
NPI Severity Composite	794	1.42 (2.34)	249	3.53 (3.50)	-8.89 (320.09)	<.001	-.71
NPI Total	432	3.24 (6.44)	74	8.68 (8.64)	-5.17 (87.41)	<.001	-.71
NPI-Q Total	368	1.44 (2.32)	175	3.53 (3.73)	-6.81 (239.70)	<.001	-.67
Month 24							
NPI Severity Composite	793	1.40 (2.32)	249	4.23 (4.21)	-10.12 (296.75)	<.001	-.83
NPI Total	432	3.37 (6.36)	74	11.57 (12.24)	-5.63 (79.87)	<.001	-.84
NPI-Q Total	361	1.38 (2.34)	175	4.15 (4.25)	-8.06 (226.59)	<.001	-.81

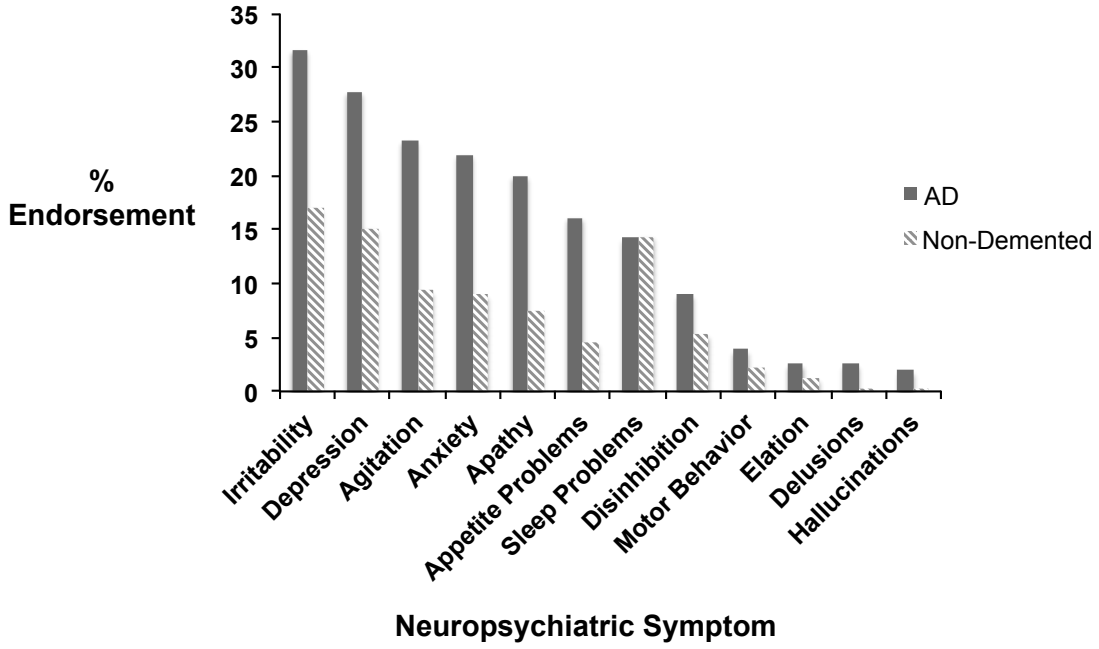
Note. The NPI Severity Composite represents average severity ratings across NPI and NPI-Q. NPI = Neuropsychiatric Index. NPI-Q = Neuropsychiatric Index Questionnaire. Diagnostic status of AD or non-demented is based on month 24 diagnosis.

Table 8. Neuropsychiatric symptoms differ for AD versus non-demented participants.

AD			
Symptom Endorsement: Y (%)	**Baseline**	**Month 12**	**Month 24**
Delusions	10 (4%)	21 (8%)	24 (10%)
Hallucinations	5 (2%)	9 (4%)	15 (6%)
Agitation/Aggression	60 (24%)	69 (28%)	77 (31%)
Depression/Dysphoria	76 (31%)	79 (32%)	86 (35%)
Anxiety	70 (28%)	81 (33%)	91 (37%)
Elation/Euphoria	8 (3%)	7 (3%)	14 (6%)
Apathy/Indifference	60 (24%)	88 (35%)	92 (37%)
Disinhibition	32 (13%)	47 (19%)	55 (22%)
Irritability/Lability	79 (32%)	90 (36%)	91 (37%)
Aberrant Motor Behavior	20 (8%)	31 (12%)	51 (20%)
Sleep	40 (16%)	60 (24%)	69 (28%)
Appetite and Eating Disorders	40 (16%)	49 (20%)	63 (25%)
Any Symptom	181 (73%)	205 (82%)	204 (82%)
NON-DEMENTED			
Symptom Endorsement: Y (%)	**Baseline**	**Month 12**	**Month 24**
Delusions	1 (0%)	5 (1%)	7 (1%)
Hallucinations	1 (0%)	2 (0%)	4 (1%)
Agitation/Aggression	74 (9%)	95 (12%)	101 (13%)
Depression/Dysphoria	121 (15%)	147 (19%)	139 (18%)
Anxiety	71 (9%)	89 (11%)	82 (10%)
Elation/Euphoria	10 (1%)	14 (2%)	13 (2%)
Apathy/Indifference	60 (8%)	72 (9%)	81 (10%)
Disinhibition	42 (5%)	45 (6%)	48 (6%)
Irritability/Lability	137 (17%)	160 (20%)	152 (19%)
Aberrant Motor Behavior	18 (2%)	21 (3%)	21 (3%)
Sleep	114 (14%)	134 (17%)	126 (16%)
Appetite and Eating Disorders	36 (5%)	58 (7%)	71 (9%)
Any Symptom	328 (41%)	373 (47%)	372 (47%)

Note. AD n = *249. Non-demented* n = *796. These ratings represent frequency of endorsement of each symptom across the Neuropsychiatric Index and Neuropsychiatric Index Questionnaire.*

Figure 1. Baseline endorsement of neuropsychiatric symptoms differs between AD and non-demented samples.



Note. AD n = *249, Non-demented* n = *796. These ratings represent frequency of endorsement of each symptom across the Neuropsychiatric Index and Neuropsychiatric Index Questionnaire.*

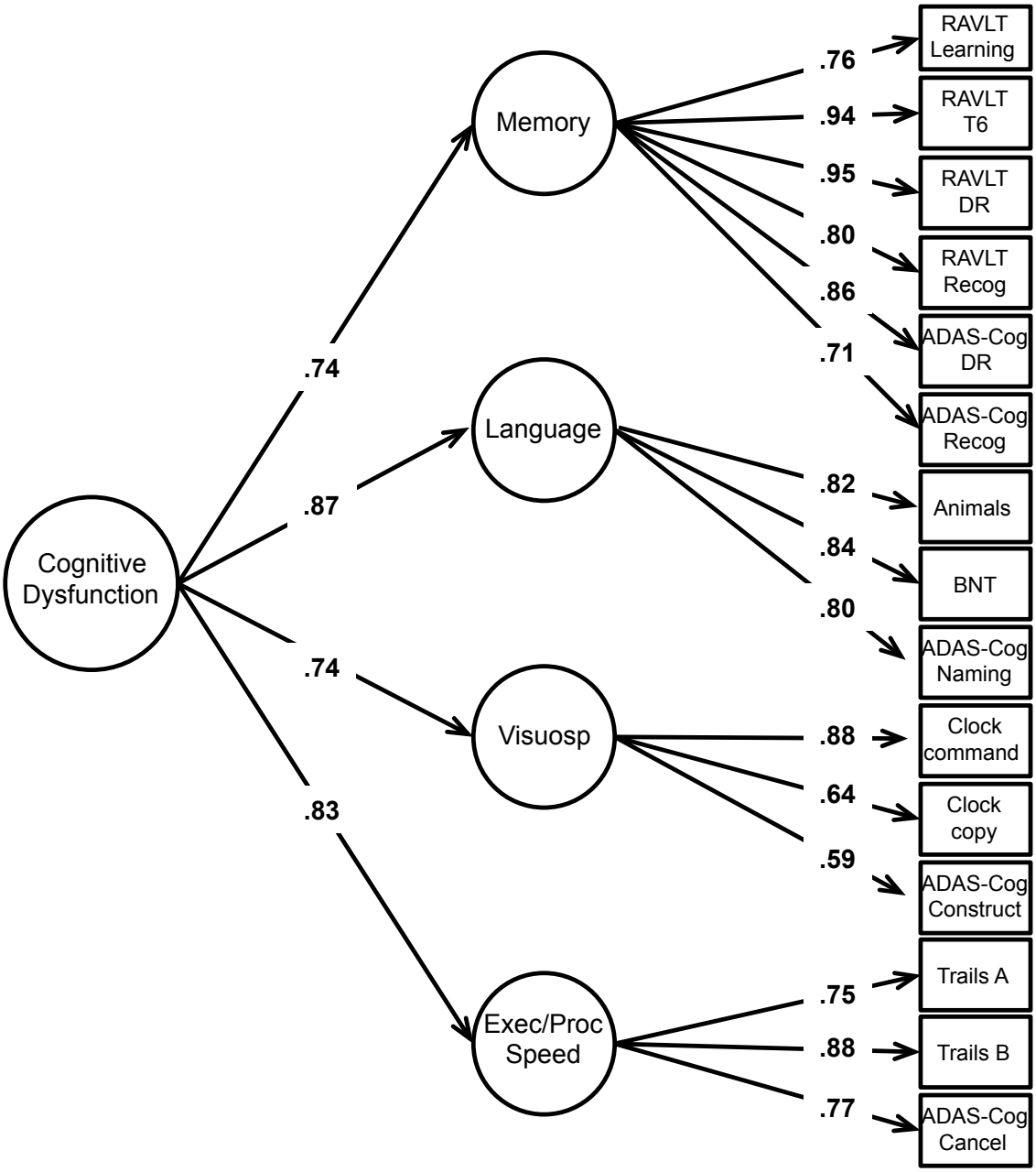
Aim 1, Goal A: Develop a cross-sectional model of AD-associated cognitive dysfunction.

A CFA was conducted to test a second-order factor structure of the neuropsychological measures. The 15 neuropsychological indicators were hypothesized to reflect four latent cognitive domains (memory, language, visuospatial, and executive/processing speed). These four latent factors in turn were hypothesized to reflect a single higher-order latent factor of AD-associated cognitive dysfunction (see Figure 2).

Using Weighted Least Squares Means and Variance Adjusted estimation, this second-order CFA had excellent fit: RMSEA = 0.04, CFI = 0.99, TLI = 0.99. These results support a single latent dimension (i.e., AD-associated cognitive dysfunction) common to the ADNI neuropsychological measures. Although the 15 neuropsychological measures indicate four distinct cognitive domains, these four domains covary strongly enough with one another that they represent a higher-order dimension of cognitive dysfunction. All 15 neuropsychological tests loaded moderately to extremely strongly onto their respective cognitive domains, and each of the cognitive domains loaded strongly onto the higher-order factor of AD-associated cognitive dysfunction (see Figure 2).

IRT analyses were then conducted to determine how these four neuropsychological factors function across the spectrum of AD-associated cognitive dysfunction. As illustrated in Table 9 and Figure 3, all four cognitive factors were

Figure 2. Higher-order structural model of ADNI neuropsychological tests.



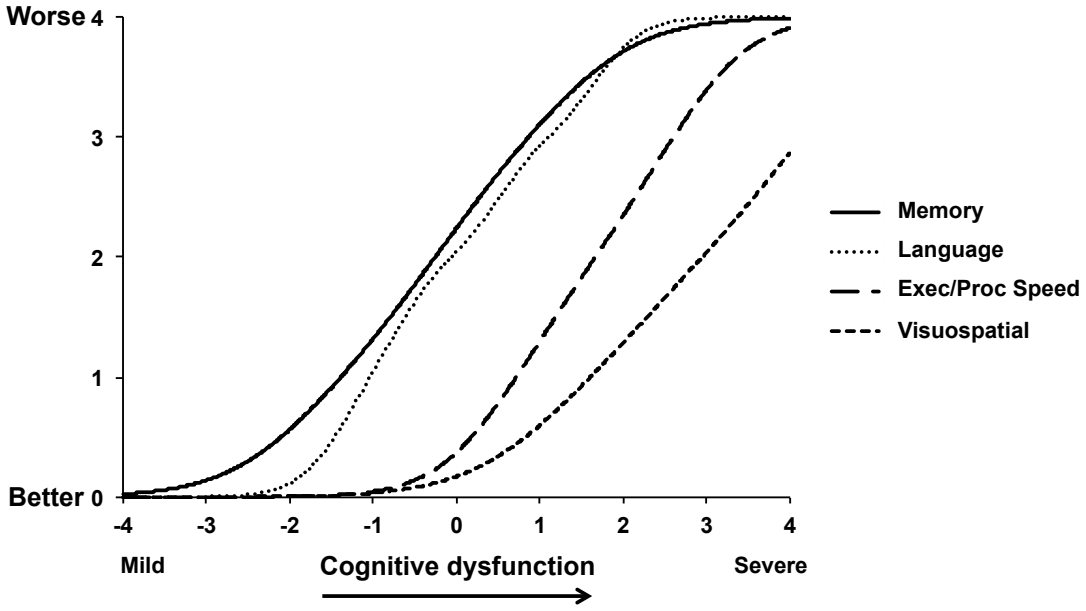
Note. RMSEA = 0.04, CFI = 0.99, TLI = 0.99. Visuosp = Visuospatial. Exec/Proc Speed = Executive/Processing Speed. RAVLT = Rey Auditory Verbal Learning Test. RAVLT Learning = number of words learned between trial 1 and trial 5 on the RAVLT. RAVLT T6 is a measure of short-delay free recall of words on trial 6. DR = Delayed Recall. Recog = Recognition. BNT = Boston Naming Test, and represents the numbers of words spontaneously and correctly produced. ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive. Clock = Clock Drawing Test; both the command and copy conditions are represented. ADAS-Cog Construc = ADAS-Cog Construction subtest. ADAS-Cog Cancel = ADAS-Cog Number Cancellation subtest.

Table 9. Item parameter estimates for cognitive domains and tests.

Cognitive Indicator	*a*	*b*1	*b*2	*b*3	*b*4
Memory Composite	1.79	-1.90	-0.69	0.18	1.36
RAVLT Learning (Trial 5-Trial 1)	2.62	-4.04	-2.23	-0.91	0.19
RAVLT Short-Delay Recall (Trial 6)	6.30	-1.53	-0.87	-0.30	0.35
RAVLT 30-Minute Delayed Recall	6.50	-1.69	-1.02	-0.53	-0.01
RAVLT Recognition	2.93	-0.29	0.50	1.20	1.80
ADAS-Cog Delayed Recall	4.55	-0.86	-0.22	0.39	0.97
ADAS-Cog Recognition	2.39	-0.41	0.42	1.36	1.93
Language Composite	2.04	0.10	1.88	3.27	3.82
Animals	7.95	-2.32	-1.03	0.11	1.64
Boston Naming Test	6.08	0.56	1.49	2.10	2.69
ADAS-Cog Naming	2.75	2.41	3.13	3.44	3.74
Visuospatial Composite	1.66	1.05	2.27	3.74	4.44
Clock command	4.92	0.15	1.01	1.57	2.15
Clock copy	2.52	0.89	1.98	2.76	3.33
ADAS-Cog Construction	1.15	0.05	3.44	5.64	--
Executive/Processing Speed Composite	2.30	0.37	1.14	2.20	2.92
Trail Making A	3.12	-0.61	1.27	2.00	2.47
Trail Making B	6.18	-1.06	0.40	0.90	1.18
ADAS-Cog Number Cancellation	3.34	0.91	1.69	2.27	2.82

Note. RAVLT = Rey Auditory Verbal Learning Test. ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive. Animals = Category Fluency-Animals. Clock = Clock Drawing Test.

Figure 3. Differential relationships between four cognitive domains and latent AD-associated cognitive dysfunction.



Note. Exec/Proc Speed = Executive/Processing Speed.

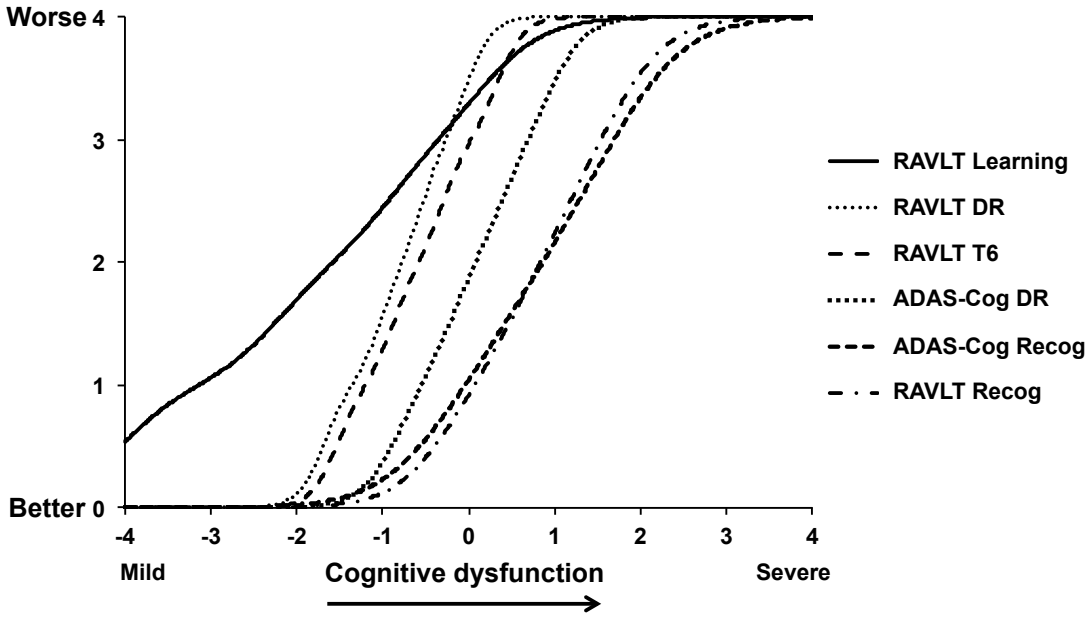
moderately to strongly related (Baker, 2001) to the higher-order latent factor (*a* parameters ranged from 1.66 to 2.30). The four cognitive factors differed in their relative impairment across the range of AD-associated cognitive dysfunction, as reflected by the range of *b* parameters. The latent dimension of AD-associated cognitive dysfunction was represented by a mean of 0 and a standard deviation of 1; lower scores represented milder degrees of cognitive dysfunction, whereas higher scores represented more severe levels of AD-associated cognitive dysfunction. At the mildest end of the spectrum, corresponding to no overt cognitive impairment, the four cognitive domains were all relatively intact. However, the curves began to separate between -3 to -0.5 standard deviations, suggesting that these distinct cognitive functions optimally discriminated and became impaired at different degrees of AD-associated cognitive dysfunction. Difficulties with memory were first evident around -3 standard deviations, and difficulties with language initially were evident around -2 standard deviations. By around -1 standard deviation, the memory and language curves were relatively similar, suggesting that language dysfunction "caught up" to memory dysfunction, as assessed by the ADNI cognitive measures. Both executive/processing speed and visuospatial functions were intact until approximately -0.5 standard deviation, after which the executive/processing speed curve had a steeper slope (similar to the slopes of the memory and language curves) relative to the visuospatial curve. This finding indicates that the visuospatial tests were less discriminating between degrees of AD-associated cognitive dysfunction than the memory, language, and executive/processing speed tests.

We also examined how the 15 individual neuropsychological measures functioned across the spectrum of AD-associated cognitive dysfunction. To do so, we used the item parameters for the four cognitive factors (memory, language, visuospatial, and executive/processing speed) as "anchors" to define the latent continuum of AD-associated cognitive dysfunction. Using IRT software (IRT-LR-DIF), we then determined the extent to which the 15 cognitive tests indicate that latent continuum. We used the initial parameter estimates that were calculated.

As illustrated in Table 9 and Figures 4 to 7, the cognitive tests were generally moderately to strongly related to the latent continuum of AD-associated cognitive dysfunction (*a* parameters ranged from 1.15 to 7.95). Among the memory items, indicators of free recall had a stronger relationship to the latent continuum than indicators of learning or recognition: RAVLT Short-Delay Recall (*a* = 6.30), RAVLT Delayed Recall (*a* = 6.50), and ADAS-Cog Delayed Recall (*a* = 4.55). Among the language items, both Animals (*a* = 7.95) and Boston Naming Test (*a* = 6.08) were very strongly related to the latent continuum. Among the executive/processing speed items, Trail Making B (*a* = 6.18), which involves divided attention, was more strongly related to the latent continuum than the other two items (i.e., Trail Making A and ADAS-Cog Number Cancellation), which involve more basic visual attention and graphomotor speed. ADAS-Cog Construction, a simple visuospatial measure, had the weakest relationship to the latent continuum (*a* = 1.15).

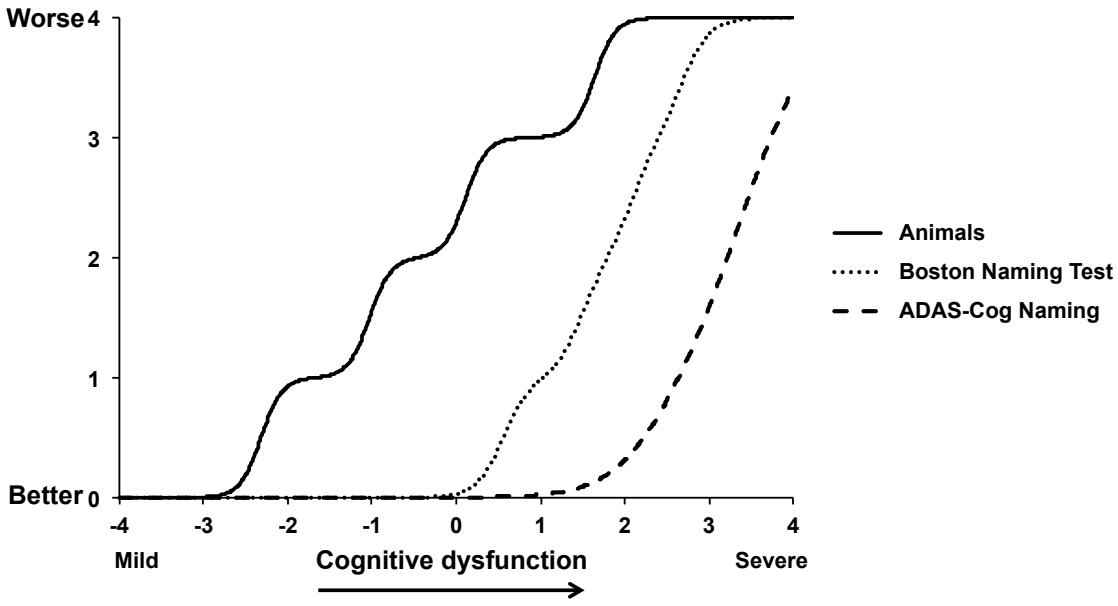
All 15 cognitive tests also differed in their ability to discriminate between degrees of AD-associated cognitive dysfunction (see Table 9 and Figures 4 to 7). Among

Figure 4. Relationships between memory measures and latent AD-associated cognitive dysfunction.



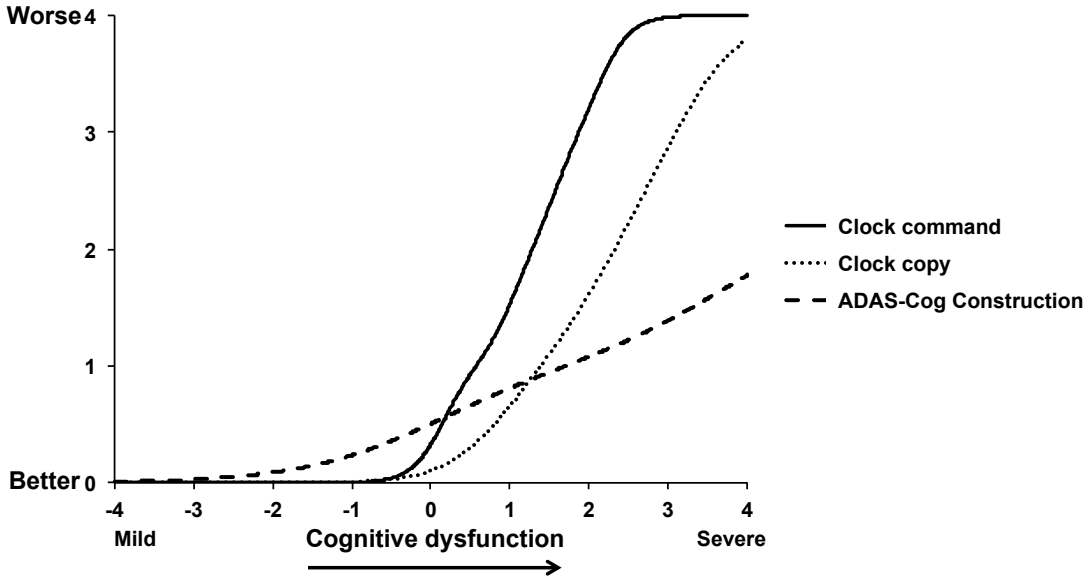
Note. RAVLT = Rey Auditory Verbal Learning Test. DR = Delayed Recall. ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive. Recog = Recognition. RAVLT Learning is number of words recalled on trial 5 minus number of words recalled on trial 1. RAVLT T6 = number of words recalled on trial 6, a measure of short-delay free recall.

Figure 5. Relationships between language measures and latent AD-associated cognitive dysfunction.



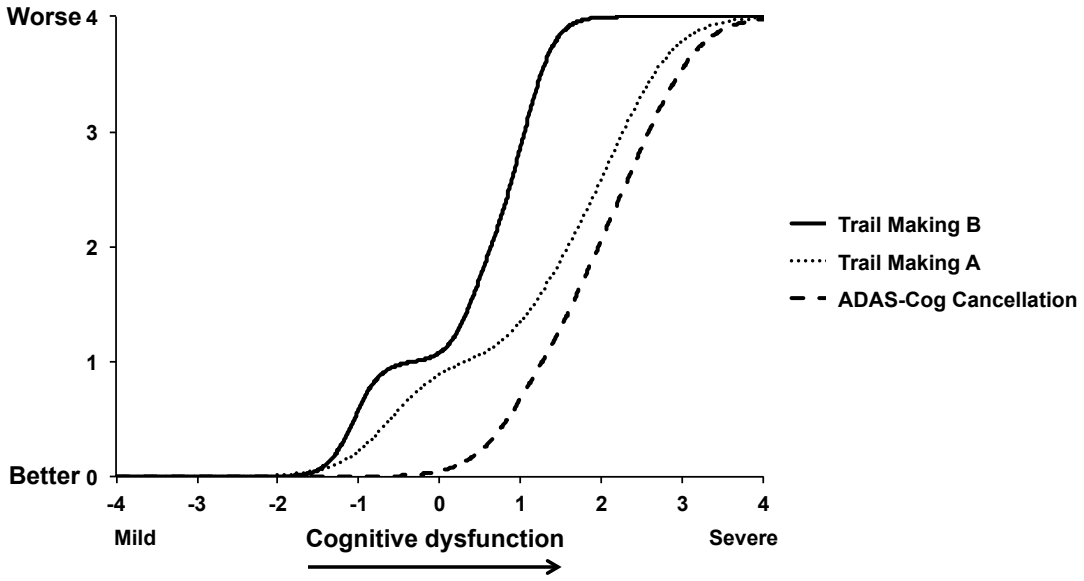
Note. Animals = Category Fluency-Animals subtest. Boston Naming Test = number of spontaneously correct words. ADAS-Cog Naming = Alzheimer's Disease Assessment Scale-cognitive Naming subtest.

Figure 6. Relationships between visuospatial measures and latent AD-associated cognitive dysfunction.



Note. Clock command = Clock Drawing Test command condition. Clock copy = Clock Drawing Test copy condition. ADAS-Cog Construction = Alzheimer's Disease Assessment Scale-cognitive Construction subtest.

Figure 7. Relationships between executive/processing speed measures and latent AD-associated cognitive dysfunction.



Note. Trail Making A and B are from the Trail Making Test, parts A and B. ADAS-Cog Cancellation = Alzheimer's Disease Assessment Scale-cognitive Number Cancellation subtest.

the memory measures, RAVLT Learning was most sensitive to mild degrees of cognitive dysfunction, whereas the other tests could better discriminate between moderate degrees of cognitive dysfunction. Among the language measures, Animals was sensitive to mild-to-moderate degrees of cognitive dysfunction, whereas ADAS-Cog Naming was intact until moderate-to-severe levels of cognitive dysfunction. The visuospatial measures as a whole remained intact until moderate degrees of cognitive impairment, after which both Clock Drawing Test conditions showed good discriminative ability; in contrast, ADAS-Cog Construction had poor ability to discriminate between degrees of cognitive dysfunction. Finally, all three of the executive/processing speed measures could best discriminate between moderate degrees of cognitive dysfunction, but Trail Making B was optimally sensitive to measuring cognitive impairment approximately one standard deviation earlier (milder) than ADAS-Cog Number Cancellation.

Lastly, we calculated baseline cognitive theta values for each participant using item parameters for the four cognitive factors and 15 cognitive tests. This yielded scores for each participant on the latent continuum of AD-associated cognitive dysfunction, as well as the four latent cognitive domains (i.e., memory, language, visuospatial, and executive/processing speed). Cognitive theta values were significantly different between the three diagnostic groups (i.e., cognitively intact, MCI, and AD) for all five factors, Fs(2, 1042) > 54.92, ps < .001 (see Table 10). Tukey post-hoc analyses indicated that all three diagnostic groups were significantly different from one another for all cognitive theta values, ps < .05. This confirms the expected pattern: latent cognitive dysfunction

Table 10. Latent cognitive scores are significantly different between diagnostic groups at baseline.

	M(SD)			**ANOVA**	
Cognitive Domain	**CN/SMC** *N = 339*	**MCI** *N = 610*	**AD** *N = 96*	***F*(2, 1042)**	***p***
Global	-.59 (.53)	-.02 (.66)	.81 (.60)	216.92	<.001
Memory	-.72 (.59)	.00 (.74)	.89 (.52)	249.69	<.001
Language	-.52 (.74)	-.09 (.72)	.49 (.77)	81.92	<.001
Visuospatial	-.20 (.53)	.09 (.66)	.54 (.75)	54.92	<.001
Exec/Proc Speed	-.45 (.64)	-.09 (.73)	.67 (.68)	100.46	<.001

Note. CN = cognitively normal. SMC = subjective memory concern. MCI = mild cognitive impairment. AD = Alzheimer's disease. Exec/Proc Speed = Executive/Processing Speed. Cognitive scores are latent theta scores derived from item response theory analyses for each cognitive domain.

was mildest for cognitively normal participants, worse for participants with MCI, and most severe for participants with AD.

Aim 1, Goal B: Model longitudinal change in AD-associated cognitive dysfunction.

We used baseline item parameters for the four cognitive domains and 15 cognitive tests to estimate theta values for cognitive scores at month 12 and month 24. Consistent with the pattern in raw cognitive scores (see Table 4), latent cognitive scores (i.e., theta values) were relatively stable for the non-demented group but became worse for the participants with AD between baseline to month 24 (see Table 11).

Repeated-measures ANOVAs revealed a significant linear trend over time for global cognitive theta for the entire sample, $F(1, 1039) = 4.07$, $p < .05$ (see Table 12). There was not a significant linear or quadratic trend over time for the other latent cognitive scores for the whole sample. However, all five cognitive domains had a significant within-subjects interaction between time and diagnostic status (see Tables 12-16): global ($F[1, 1039] = 197.52$, $p < .001$), memory ($F[1, 1039] = 117.33$, $p < .001$), language ($F[1, 1039] = 82.02$, $p < .001$), visuospatial ($F[1, 1039] = 30.04$, $p < .001$), and executive/processing speed ($F[1, 1039] = 64.37$, $p < .001$). These interactions were significant for a linear trend, but not a quadratic trend. The AD participants showed steady, linear cognitive decline over the two-year period, whereas the non-demented participants had a relatively flat slope, indicating stable cognitive performance (see Figures 8-12).

Table 11. Longitudinal latent cognitive scores for AD and non-demented participants.

Participant Subgroup	Visit	*N*	*M (SD)*				
			Global	**Memory**	**Language**	**Visuospatial**	**Executive**
Full Sample	Baseline	1045	-.13 (.73)	-.15 (.82)	-.18 (.79)	.04 (.66)	-.14 (.76)
	Month 12		-.11 (.83)	-.12 (.92)	-.16 (.83)	.03 (.68)	-.13 (.83)
	Month 24		-.00 (.93)	-.07 (.98)	-.08 (.93)	.10 (.74)	-.07 (.92)
AD	Baseline	249	.59 (.59)	.68 (.54)	.30 (.73)	.46 (.74)	.43 (.72)
	Month 12		.80 (.66)	.86 (.56)	.48 (.75)	.53 (.79)	.57 (.82)
	Month 24		1.10 (.77)	1.06 (.55)	.73 (.90)	.74 (.88)	.80 (.88)
Non-Demented	Baseline	796	-.35 (.62)	-.41 (.71)	-.33 (.74)	-.10 (.58)	-.32 (.68)
	Month 12		-.40 (.66)	-.42 (.78)	-.36 (.75)	-.13 (.56)	-.36 (.71)
	Month 24		-.35 (.68)	-.42 (.81)	-.33 (.78)	-.10 (.56)	-.34 (.76)

Note. The AD group includes participants who were either enrolled with a diagnosis of AD or converted to AD by month 24. The non-demented group includes participants with diagnoses of either cognitively normal or mild cognitive impairment at month 24. Cognitive scores are latent theta scores derived from item response theory analyses for each cognitive domain.

Table 12. Global cognitive dysfunction: repeated-measures ANOVA within-subjects contrasts.

Source	**Time**	***F*(1, 1039)**	***p***
time	Linear	4.07	**.04**
	Quadratic	1.46	.23
time*age	Linear	.76	.38
	Quadratic	1.65	.20
time*education	Linear	.03	.88
	Quadratic	.88	.35
time*gender	Linear	.73	.39
	Quadratic	.54	.46
time*dx	Linear	197.52	**<.001**
	Quadratic	.10	.75
time*gender*dx	Linear	.25	.62
	Quadratic	.67	.41

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. Results significant at p < .05 are bolded.

Table 13. Memory dysfunction: repeated-measures ANOVA within-subjects contrasts.

Source	**Time**	***F*(1, 1039)**	***p***
time	Linear	2.37	.12
	Quadratic	.04	.85
time*age	Linear	.01	.91
	Quadratic	.01	.93
time*education	Linear	1.80	.18
	Quadratic	.36	.55
time*gender	Linear	.59	.44
	Quadratic	3.54	.06
time*dx	Linear	117.33	**<.001**
	Quadratic	.28	.60
time*gender*dx	Linear	.01	.91
	Quadratic	5.86	**.02**

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. Results significant at p < .05 are bolded.

Table 14. Language dysfunction: repeated-measures ANOVA within-subjects contrasts.

Source	**Time**	***F*(1, 1039)**	***p***
time	Linear	2.14	.14
	Quadratic	1.05	.31
time*age	Linear	.21	.65
	Quadratic	.77	.38
time*education	Linear	.25	.62
	Quadratic	.06	.81
time*gender	Linear	.00	.97
	Quadratic	.05	.83
time*dx	Linear	82.02	**<.001**
	Quadratic	.09	.76
time*gender*dx	Linear	.09	.77
	Quadratic	.00	.96

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. Results significant at p < .05 are bolded.

Table 15. Visuospatial dysfunction: repeated-measures ANOVA within-subjects contrasts.

Source	**Time**	***F*(1, 1039)**	***p***
time	Linear	.95	.33
	Quadratic	.06	.81
time*age	Linear	.58	.45
	Quadratic	.05	.83
time*education	Linear	.15	.70
	Quadratic	.19	.67
time*gender	Linear	.67	.42
	Quadratic	.38	.54
time*dx	Linear	30.04	**<.001**
	Quadratic	.84	.36
time*gender*dx	Linear	.16	.69
	Quadratic	.02	.88

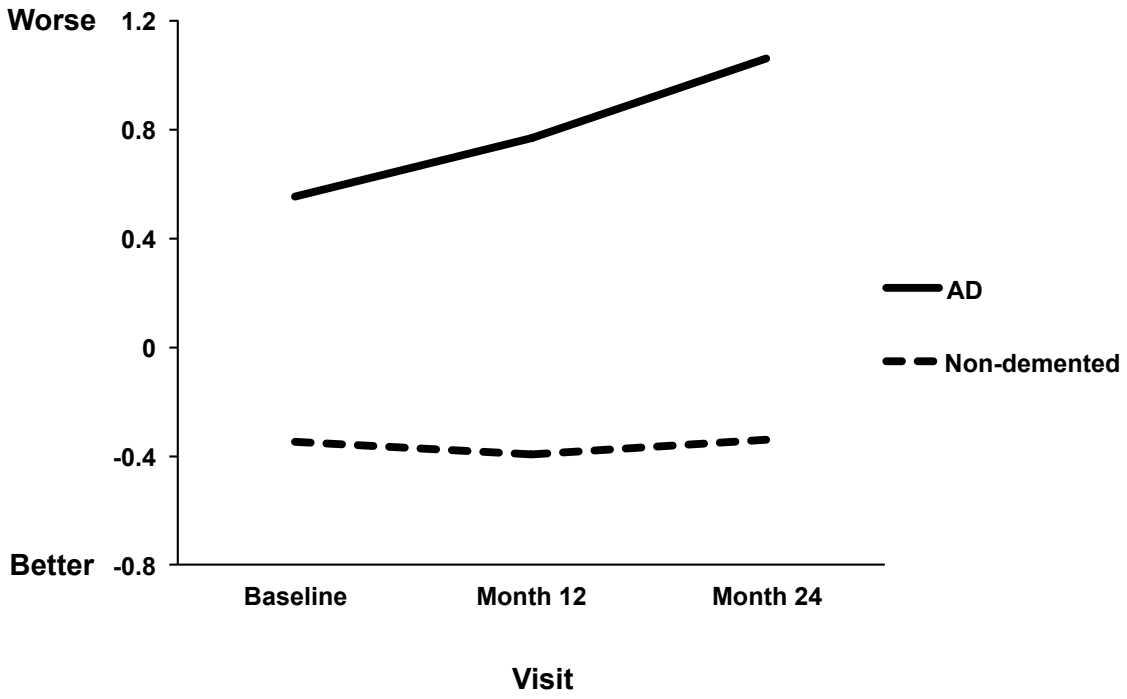
Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. Results significant at p < .05 are bolded.

Table 16. Executive/processing speed dysfunction: repeated-measures ANOVA within-subjects contrasts.

Source	**Time**	***F*(1, 1039)**	***p***
time	Linear	.03	.86
	Quadratic	1.45	.23
time*age	Linear	.79	.38
	Quadratic	1.77	.18
time*education	Linear	.05	.82
	Quadratic	.37	.54
time*gender	Linear	.01	.91
	Quadratic	.02	.89
time*dx	Linear	64.37	**<.001**
	Quadratic	.34	.56
time*gender*dx	Linear	.03	.87
	Quadratic	1.11	.29

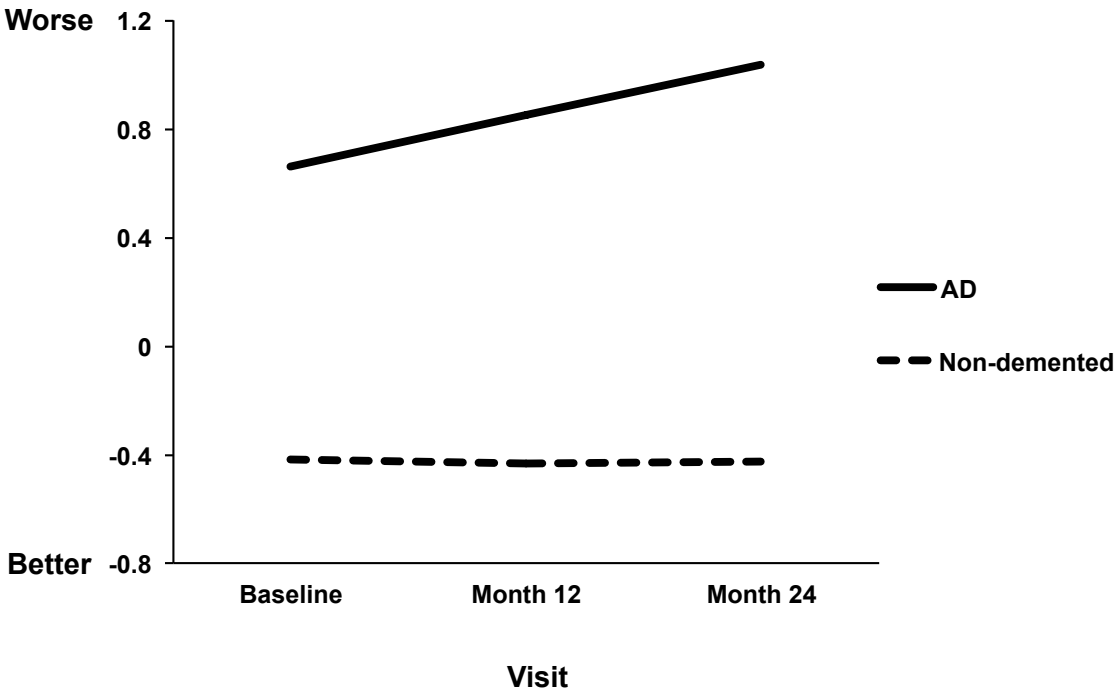
Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. Results significant at p < .05 are bolded.

Figure 8. Changes in global cognitive dysfunction depend on diagnostic status.



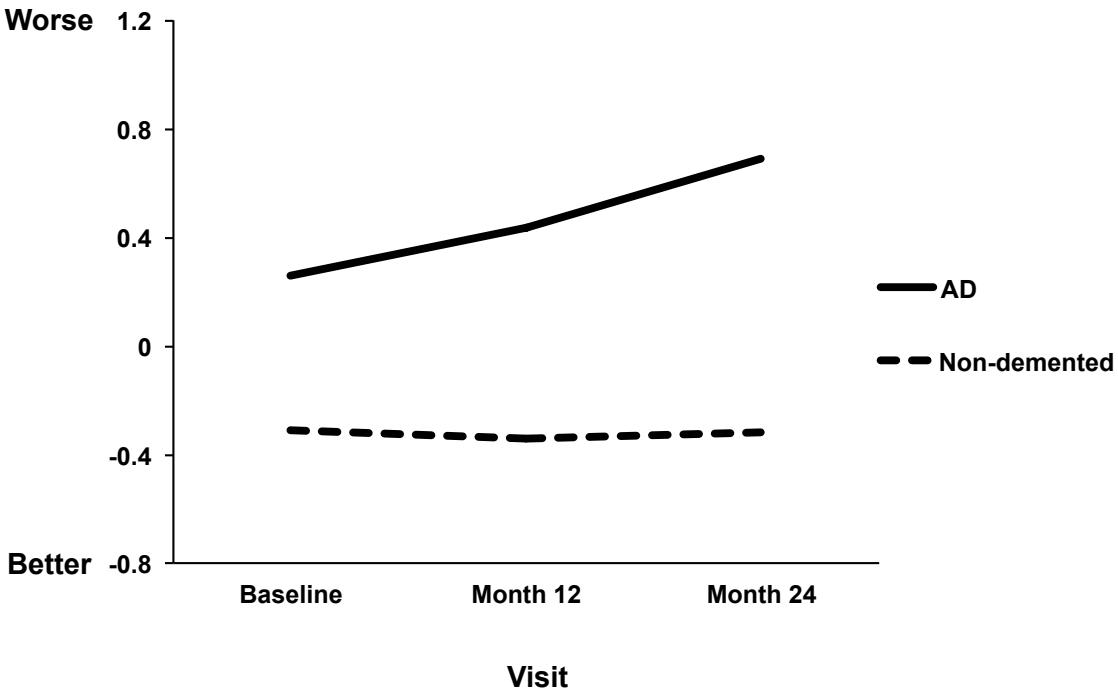
Note. AD n = *249, Non-demented* n = *796. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Figure 9. Changes in memory dysfunction depend on diagnostic status.



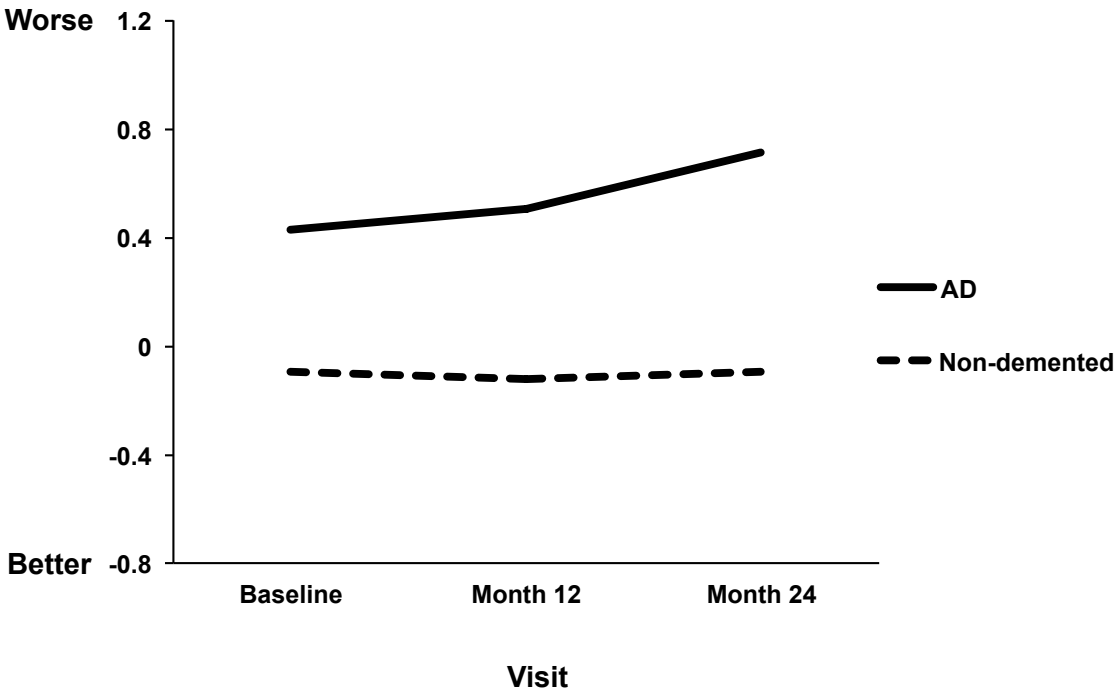
Note. AD n = *249, Non-demented* n = *796. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Figure 10. Changes in language dysfunction depend on diagnostic status.



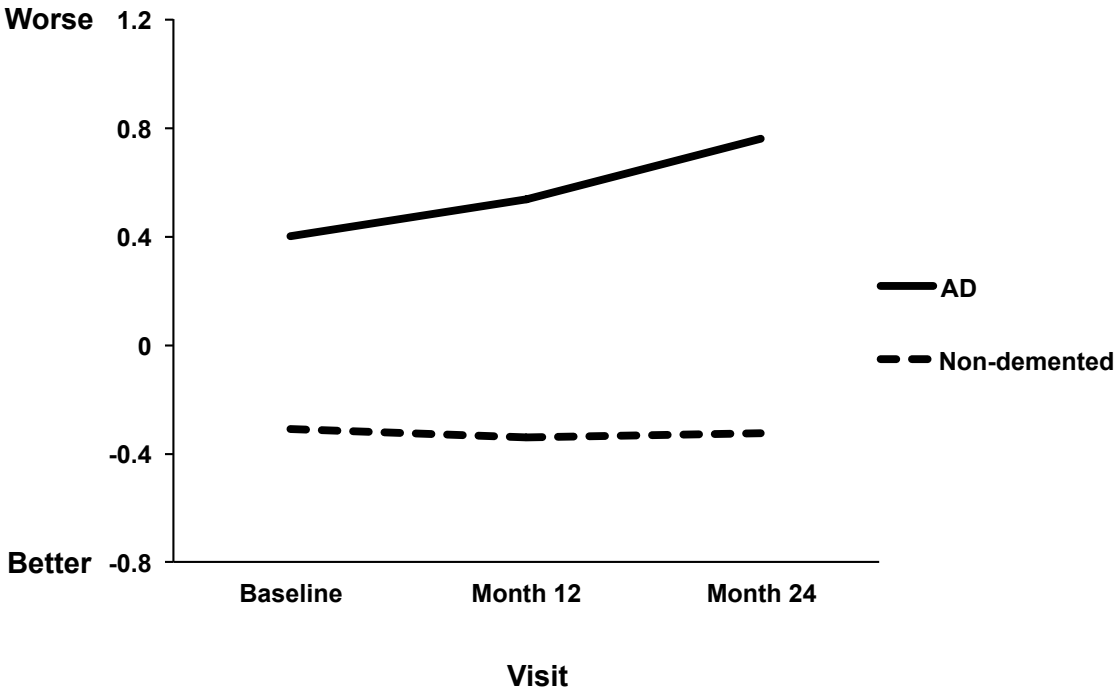
Note. AD n = *249, Non-demented* n = *796. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Figure 11. Changes in visuospatial dysfunction depend on diagnostic status.



Note. AD n = *249, Non-demented* n = *796. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Figure 12. Changes in executive/processing speed dysfunction depend on diagnostic status.



Note. AD n = *249, Non-demented* n = *755. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Aim 2, Goal A: Analyze cross-sectional gender differences in AD-associated cognitive dysfunction.

A series of *t*-tests revealed significant gender differences at baseline for latent global, $t(916.68) = 3.19$, $p < .01$, and memory scores, $t(891.07) = 4.63$, $p < .01$ (see Table 17). There was a trend for a significant gender difference at baseline for latent visuospatial scores, $t(1005.19) = 1.71$, $p = .09$. Effect sizes were fairly small for these gender differences (Cohen's *d*s = .11-.29). Men had higher scores than women in all three domains, indicating slightly worse cognitive functioning at baseline.

When the sample was split by diagnostic status (AD versus non-demented at month 24), these gender differences at baseline only remained significant for the non-demented group for latent global, $t(794) = 4.30$, $p < .01$, and memory scores, $t(794) = 6.27$, $p < .01$ (see Table 18). Among individuals with AD, women had slightly worse cognitive scores than men for global, memory, language, and executive domains. Effect sizes for these gender differences were small (Cohen's *d*s ranged from .11 to .21) and not statistically significant at baseline.

We next used IRT DIF analyses to examine whether the cross-sectional model of AD-associated cognitive dysfunction was invariant across gender. First, we conducted DIF analyses on the four cognitive domains (memory, language, visuospatial, executive/processing speed), with men serving as the reference group. Results indicated that none of these four cognitive factors were invariant across gender. This approach was akin to an "omnibus" test for DIF, so it was necessary to next examine for invariance across gender for the 15 cognitive tests.

Table 17. Gender differences in latent cognitive scores at baseline, month 12, and month 24.

Cognitive Domain	Visit	*M (SD)*		*t*-test		
		Female	**Male**	***t*(*df*)**	***p***	**Cohen's *d***
Global	Baseline	-.21 (.78)	-.06 (.69)	3.19 (916.68)	<.01	-.20
	Month 12	-.18 (.89)	-.06 (.78)	2.22 (904.86)	<.05	-.14
	Month 24	-.07 (.99)	.05 (.89)	2.01 (920.25)	<.05	-.13
Memory	Baseline	-.29 (.88)	-.05 (.75)	4.63 (891.07)	<.001	-.29
	Month 12	-.23 (1.01)	-.03 (.83)	3.52 (863.26)	<.001	-.22
	Month 24	-.19 (1.06)	.02 (.91)	3.39 (890.40)	<.01	-.21
Language	Baseline	-.16 (.78)	-.19 (.79)	-.62 (1043)	.53	.04
	Month 12	-.15 (.85)	-.16 (.82)	-.24 (1043)	.81	.01
	Month 24	-.07 (.97)	-.09 (.90)	-.35 (1043)	.73	.02
Visuospatial	Baseline	-.00 (.64)	.07 (.68)	1.71 (1005.19)	.09	-.11
	Month 12	.01 (.68)	.05 (.68)	.89 (1043)	.37	-.06
	Month 24	.08 (.75)	.12 (.74)	.99 (1043)	.32	-.05
Exec/Proc Speed	Baseline	-.16 (.77)	-.12 (.75)	.82 (1043)	.41	-.05
	Month 12	-.15 (.83)	-.12 (.84)	.48 (1043)	.63	-.04
	Month 24	-.10 (.94)	-.04 (.91)	.96 (1043)	.34	-.06

Note: Female N = *455, Male* N = *590. Cognitive scores are latent theta scores derived from item response theory analyses for each cognitive domain. Exec/Proc Speed = Executive/Processing Speed.*

Table 18. Gender differences in longitudinal cognitive theta scores vary by clinical diagnosis.

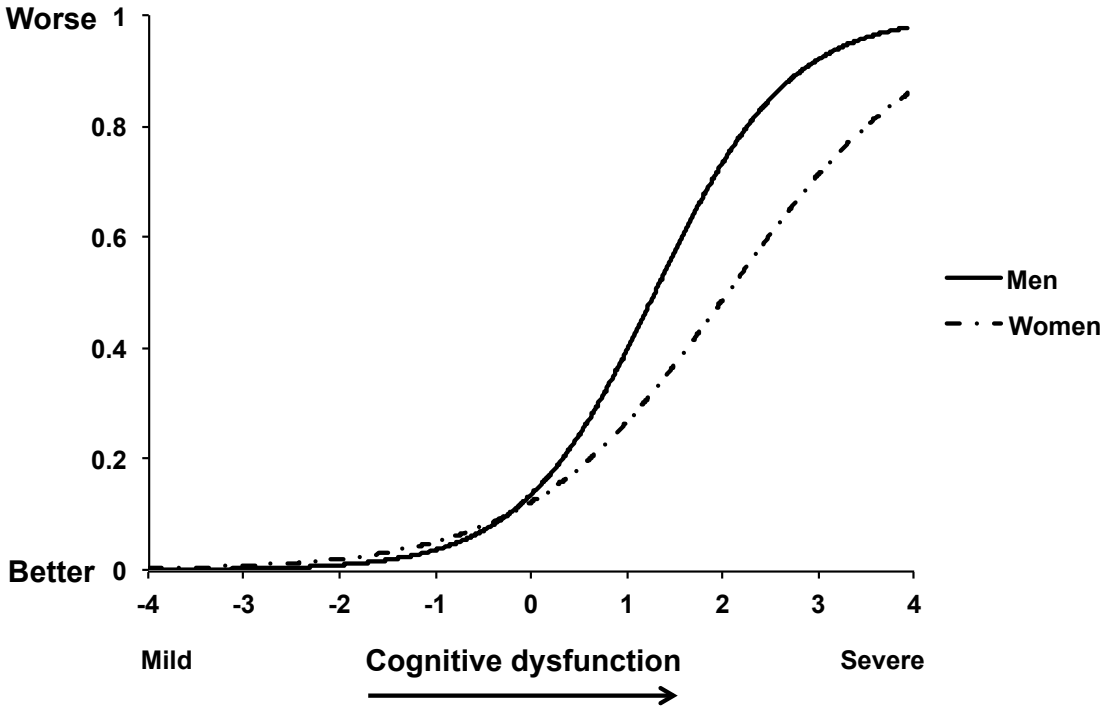
AD						
		M (SD)		*t*-test		
Cognitive Domain	**Visit**	**Female**	**Male**	***t*(*df*)**	***p***	**Cohen's *d***
Global	Baseline	.64 (.61)	.55 (.57)	-1.16 (247)	.25	.15
	Month 12	.89 (.66)	.74 (.66)	-1.72 (247)	.09	.23
	Month 24	1.16 (.75)	1.05 (.78)	-1.05 (247)	.30	.14
Memory	Baseline	.75 (.55)	.64 (.54)	-1.58 (247)	.12	.20
	Month 12	1.01 (.55)	.76 (.54)	-3.45 (247)	<.01	.46
	Month 24	1.14 (.48)	1.00 (.59)	-2.12 (240.68)	<.05	.26
Language	Baseline	.35 (.74)	.27 (.72)	-.87 (247)	.39	.11
	Month 12	.53 (.81)	.45 (.71)	-.85 (247)	.40	.11
	Month 24	.80 (.90)	.69 (.90)	-.91 (247)	.36	.12
Visuospatial	Baseline	.43 (.73)	.49 (.74)	.59 (247)	.56	-.08
	Month 12	.53 (.80)	.53 (.80)	-.04 (247)	.97	0
	Month 24	.74 (.93)	.74 (.85)	-.07 (247)	.95	0
Exec/Proc Speed	Baseline	.52 (.73)	.37 (.70)	-1.62 (247)	.11	.21
	Month 12	.64 (.81)	.53 (.83)	-1.02 (247)	.31	.13
	Month 24	.87 (.83)	.74 (.91)	-1.15 (247)	.25	.15
NON-DEMENTED						
		M (SD)		*t*-test		
Cognitive Domain	**Visit**	**Female**	**Male**	***t*(*df*)**	***p***	**Cohen's *d***
Global	Baseline	-.46 (.63)	-.27 (.60)	4.30 (.794)	<.001	-.31
	Month 12	-.49 (.69)	-.33 (.62)	3.37 (714.30)	<.01	-.24
	Month 24	-.43 (.73)	-.29 (.63)	2.84 (700.30)	<.01	-.21
Memory	Baseline	-.58 (.72)	-.27 (.67)	6.27 (794)	<.001	-.45
	Month 12	-.59 (.81)	-.29 (.73)	5.44 (714.10)	<.001	-.39
	Month 24	-.57 (.85)	-.30 (.75)	4.70 (704.16)	<.001	-.34
Language	Baseline	-.31 (.73)	-.34 (.76)	-.67 (794)	.50	.04
	Month 12	-.35 (.76)	-.37 (.75)	-.35 (794)	.73	.03
	Month 24	-.32 (.84)	-.35 (.73)	-.53 (794)	.60	.04
Visuospatial	Baseline	-.13 (.55)	-.07 (.60)	1.38 (778.17)	.17	-.10
	Month 12	-.14 (.55)	-.11 (.56)	.74 (794)	.46	-.05
	Month 24	-.12 (.56)	-.08 (.57)	.87 (794)	.39	-.07
Exec/Proc Speed	Baseline	-.36 (.66)	-.28 (.70)	1.49 (794)	.14	-.12
	Month 12	-.38 (.68)	-.34 (.72)	.71 (794)	.48	-.06
	Month 24	-.38 (.77)	-.30 (.75)	1.39 (794)	.17	-.11

Note. AD: Female N = *102, Male* N = *147. Non-demented: Female* N = *353, Male* N = *442. Cognitive scores are latent theta scores derived from item response theory analyses for each cognitive domain. Exec/Proc Speed = Executive/Processing Speed.*

There were missing data for several cells when examined within gender (e.g., men had missing data for response category "2" on ADAS-Cog Naming, women had missing data for response category "4" on ADAS-Cog Construction). Consequently, we recoded the data into dichotomous variables, such that response categories of "0" or "1" were recoded to a "0" and response categories of "2," "3," or "4" were recoded to a "1." This dichotomous recoding represents mild-to-minimal problems (new response category "0") or moderate-to-marked problems (new response category "1") on any given cognitive test.

Using these newly recoded 15 cognitive indicators, we then proceeded with constructing a set of anchor items that were invariant across gender. We iteratively removed a single item with the smallest amount of DIF from the larger set of cognitive items to add to the set of anchor items. We proceeded with this until the smallest DIF value for the remaining candidate items was statistically significant ($p < .05$). This procedure resulted in a set of eight anchor items that were invariant across gender: RAVLT Learning, RAVLT Recognition, ADAS-Cog Delayed Recall, ADAS-Cog Recognition, ADAS-Cog Naming, ADAS-Cog Number Cancellation, ADAS-Cog Construction, and Clock copy. The remaining seven items were candidate items: RAVLT Short-Delay Recall, RAVLT Delayed Recall, Animals, Boston Naming Test, Clock command, Trail Making A, and Trail Making B. Of these candidate items, Clock command had small but significant DIF across gender in both *a* and *b* parameters (see Figure 13). When not constraining item parameters to be equal in men and women, this item was more strongly related to the latent continuum in men ($a = 1.42$) than women (*a*

Figure 13. Clock Drawing Test–command has differential item functioning for men and women.



Note. Item parameters for women: a = 0.95, b = 2.10. Item parameters for men: a = 1.42, b = 1.33.

= 0.95). In addition, the Clock command item discriminated differently between degrees of severity along the latent continuum for men than women, based on DIF in the *b* parameter. Clock command discriminated in relatively milder degrees of AD-associated cognitive dysfunction for men ($b = 1.33$) than women ($b = 2.10$). The remaining six candidate items did not show significant DIF in *a* or *b* parameters.

Although the "omnibus" DIF test indicated a violation of invariance for the cognitive domains, the only cognitive test that showed significant DIF was the Clock command condition. This test was slightly more sensitive to AD-associated cognitive dysfunction for men than women. None of the other 14 cognitive tests had significant DIF. Therefore, although there were significant gender differences in mean cognitive scores, the cognitive tests as a whole seemed to function equivalently as measurements of cognitive dysfunction for men and women.

Aim 2, Goal B: Analyze gender differences in AD-associated cognitive trajectories.

The pattern of gender differences in cognitive scores at baseline generally remained constant at month 12 and month 24 (see Table 17). For the overall sample, there was still a significant gender difference for global theta at month 12, $t(904.86) = 2.22$, $p < .05$, and month 24, $t(920.25) = 2.01$, $p < .05$. There was also still a significant gender difference for memory theta at month 12, $t(863.26) = 3.52$, $p < .001$, and month 24, $t(890.40) = 3.39$, $p < .01$. For global and memory theta scores, men had worse cognitive performance than women at month 12 and month 24.

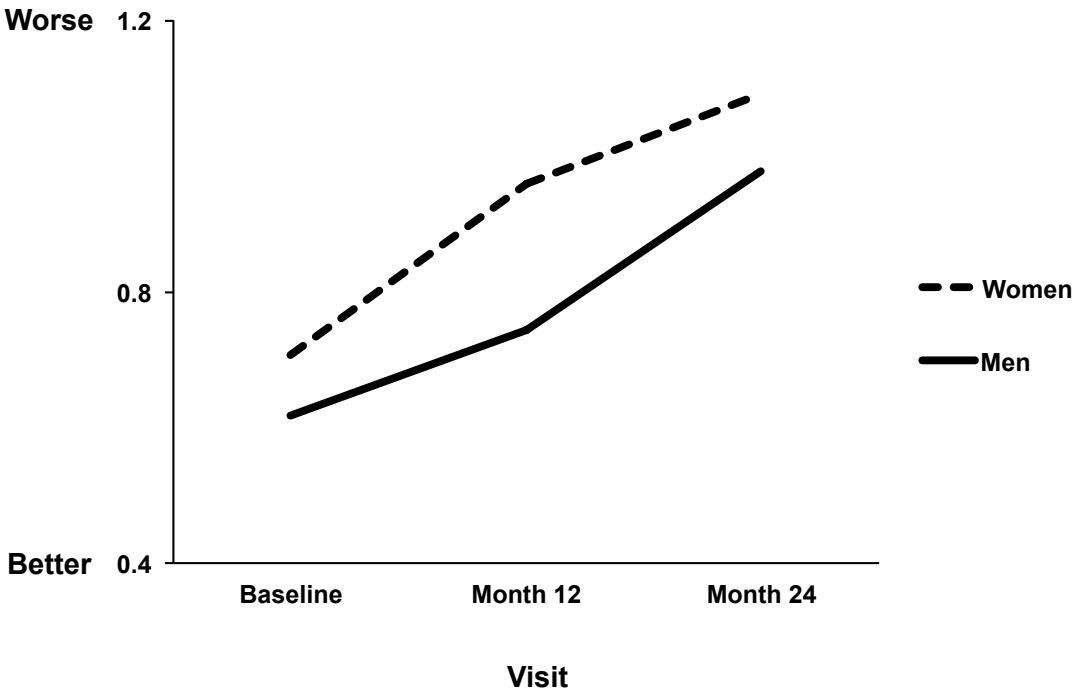
There was the same pattern of gender differences in global and memory theta scores at month 12 and month 24 for the non-demented sample (see Table 18), with men

performing worse than women at each of these two time points. However, among those with AD, women had significantly worse memory performance than men at month 12, $t(247) = 3.45$, $p < .01$, and month 24, $t(240.68) = 2.12$, $p < .05$. There was also a trend for women to perform worse than men for global theta at month 12, $t(247) = 1.72$, $p = .09$. These effect sizes ranged from small to medium strength (Cohen's ds = .23-.46).

As noted earlier, gender was entered as a between-subjects factor in the repeated-measures ANOVAs. This allowed us to examine whether women had different rates of cognitive change than men between baseline and month 24. There was a significant within-subjects interaction between time, gender, and diagnostic status for memory, $F(1, 1039) = 5.86$, $p < .05$ (see Table 13). This interaction was significant for a quadratic trend. Among participants with AD, women had a steep rate of decline from baseline to month 12, with decelerating but continuing decline from month 12 to month 24 (see Figure 14). In contrast, men with AD had a less steep rate of decline from baseline to month 12 but had accelerating decline from month 12 to month 24. Among non-demented participants, both men and women had relatively flat rates of cognitive change from baseline to month 24, but men had worse cognitive performance than women (see Figure 15).

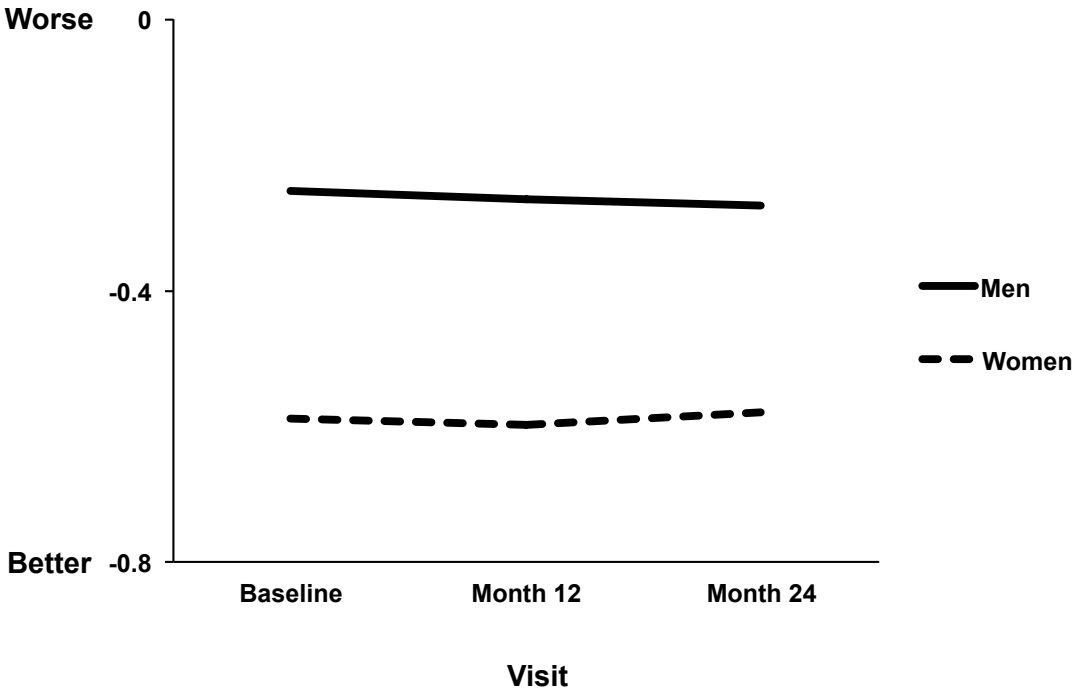
There were no significant within-subjects interactions between time and gender or between time, gender, and diagnostic status for latent global, language, visuospatial, or executive/processing speed scores (see Tables 13, 15-17). However, there was a significant between-subjects interaction between gender and diagnostic status for global theta averaged across the three time points, $F(1, 1039) = 11.06$, $p < .01$. After controlling

Figure 14. Women have different rates of memory decline than men in the AD group.



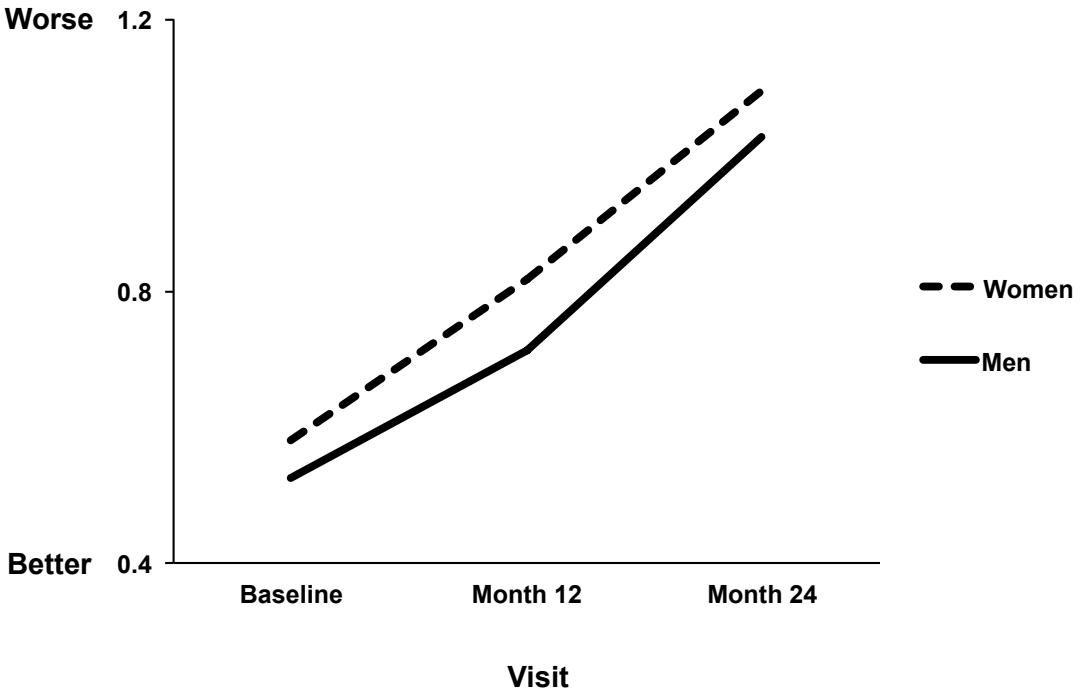
Note. Women n = *102, Men* n = *147. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Figure 15. Men have worse memory dysfunction than women in the non-demented group.



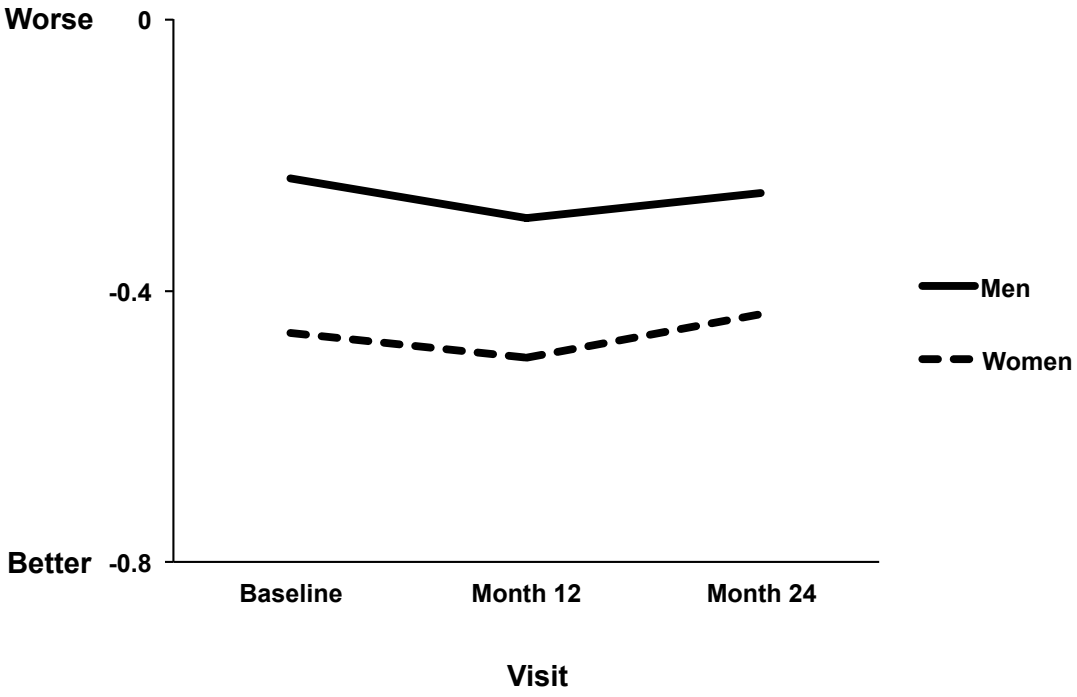
Note. Women n = *353, Men* n = *443. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Figure 16. Women have worse average global cognitive dysfunction than men in the AD group.



Note. Women n = *102, Men* n = *147. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

Figure 17. Men have worse average global cognitive dysfunction than women in the non-demented group.



Note. Women n = *353, Men* n = *443. Covariates were entered in the model at the following values: Age at baseline = 73.71, Education = 16.11.*

for age and education, men had worse average global cognitive performance than women in the non-demented group, but among the participants with AD, women had worse average global cognitive performance than men (see Figures 16 and 17). There were also marginally significant between-subjects effects of gender on average memory, $F(1, 1039) = 3.59$, $p = .06$, and average visuospatial dysfunction, $F(1, 1039) = 2.98$, $p = .09$. Because the majority of the sample was non-demented, this overall gender effect was driven by the non-demented men performing worse than the non-demented women.

Aim 3, Goal A: Examine whether neuropsychiatric symptoms mediate potential gender differences in cross-sectional AD-associated cognitive dysfunction.

As reported previously, at baseline in the overall sample, we found significant gender differences for mean global and memory theta scores, with a trend for a gender difference in mean visuospatial scores. Furthermore, there was a significant gender difference for neuropsychiatric symptoms in the overall sample (see Tables 19 and 20). Men had significantly higher scores on the NPI severity composite than women at baseline, $t(1039.88) = 3.36$, $p < .01$, month 12, $t(1037.14) = 3.89$, $p < .001$, and month 24, $t(1004.06) = 2.20$, $p < .05$. These gender differences had small effect sizes (Cohen's *d*s = .14-.24). This pattern of men having higher levels of neuropsychiatric symptoms than women was true for the non-demented participants as well as those with AD. In addition, men had notably higher rates of specific neuropsychiatric symptoms (see Table 20 and Figure 18). The neuropsychiatric symptoms with the greatest gender gap in endorsement rates included irritability/lability (26-30% of men vs. 14-18% of women),

Table 19. Men have higher levels of neuropsychiatric symptoms than women at baseline, month 12, and month 24.

	Women		Men		*t*-test		
Neuropsychiatric Indicator	***N***	***M(SD)***	***N***	***M(SD)***	***t(df)***	***p***	**Cohen's *d***
Baseline							
NPI Severity Composite	455	1.20 (2.03)	590	1.70 (2.78)	3.36 (1039.88)	<.01	-.21
NPI Total	190	2.36 (5.07)	220	3.41 (6.01)	1.91 (407.80)	.06	-.19
NPI-Q Total	265	1.23 (1.97)	370	1.81 (2.99)	2.94 (629.11)	<.01	-.23
Month 12							
NPI Severity Composite	454	1.55 (2.47)	589	2.21 (3.02)	3.89 (1037.14)	<.001	-.24
NPI Total	232	3.05 (5.12)	274	4.88 (8.27)	3.04 (463.70)	<.01	-.27
NPI-Q Total	224	1.71 (2.89)	319	2.40 (3.07)	2.67 (497.52)	<.01	-.23
Month 24							
NPI Severity Composite	454	1.84 (3.00)	588	2.26 (3.21)	2.20 (1004.06)	.03	-.14
NPI Total	232	4.18 (8.06)	274	4.90 (8.01)	1.01 (504)	.31	-.09
NPI-Q Total	222	2.01 (3.20)	314	2.48 (3.45)	1.62 (496.65)	.11	-.14

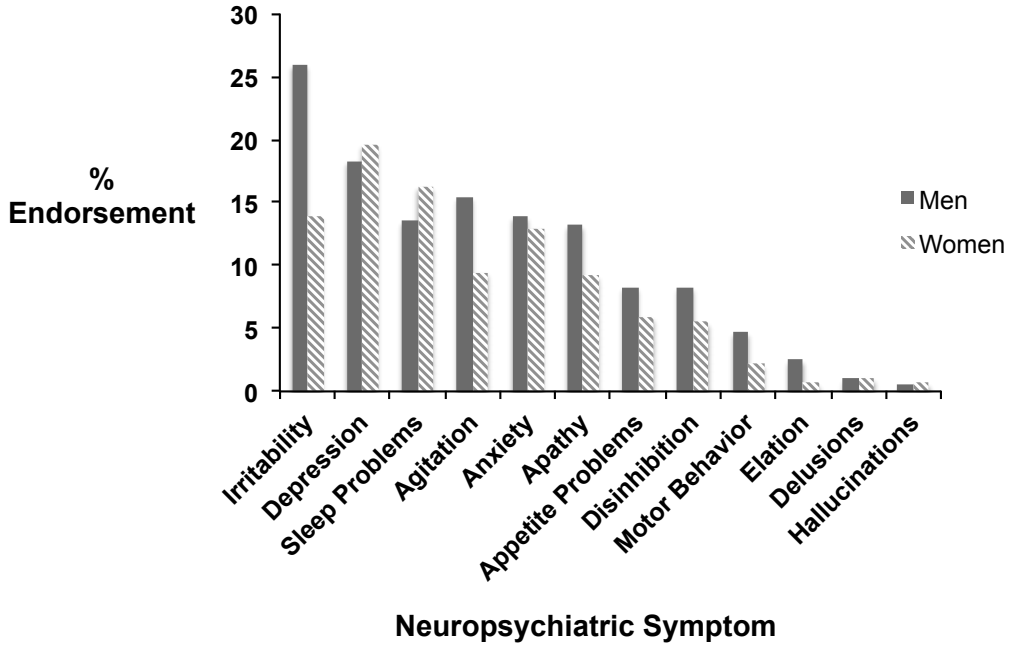
Note. The NPI Severity Composite represents average severity ratings across NPI and NPI-Q. NPI = Neuropsychiatric Index. NPI-Q = Neuropsychiatric Index Questionnaire.

Table 20. Neuropsychiatric symptoms differ by gender.

WOMEN			
Symptom Endorsement: Y (%)	**Baseline**	**Month 12**	**Month 24**
Delusions	5 (1%)	12 (3%)	16 (4%)
Hallucinations	3 (1%)	4 (1%)	12 (3%)
Agitation/Aggression	43 (9%)	43 (9%)	60 (13%)
Depression/Dysphoria	89 (20%)	95 (21%)	103 (23%)
Anxiety	59 (13%)	65 (14%)	72 (16%)
Elation/Euphoria	3 (1%)	5 (1%)	6 (1%)
Apathy/Indifference	42 (9%)	54 (12%)	63 (14%)
Disinhibition	25 (5%)	27 (6%)	32 (7%)
Irritability/Lability	63 (14%)	71 (16%)	84 (18%)
Aberrant Motor Behavior	10 (2%)	16 (4%)	25 (5%)
Sleep	74 (16%)	85 (19%)	82 (18%)
Appetite and Eating Disorders	27 (6%)	40 (9%)	56 (12%)
Any Symptom	207 (45%)	231 (51%)	235 (52%)
MEN			
Symptom Endorsement: Y (%)	**Baseline**	**Month 12**	**Month 24**
Delusions	6 (1%)	14 (2%)	15 (3%)
Hallucinations	3 (1%)	7 (1%)	7 (1%)
Agitation/Aggression	91 (15%)	121 (21%)	118 (20%)
Depression/Dysphoria	108 (18%)	131 (22%)	122 (21%)
Anxiety	82 (14%)	105 (18%)	101 (17%)
Elation/Euphoria	15 (3%)	16 (3%)	21 (4%)
Apathy/Indifference	78 (13%)	106 (18%)	110 (19%)
Disinhibition	49 (8%)	65 (11%)	71 (12%)
Irritability/Lability	153 (26%)	179 (30%)	159 (27%)
Aberrant Motor Behavior	28 (5%)	36 (6%)	47 (8%)
Sleep	80 (14%)	109 (18%)	113 (19%)
Appetite and Eating Disorders	49 (8%)	67 (11%)	78 (13%)
Any Symptom	302 (51%)	345 (58%)	338 (57%)

Note. Women n = *455, men* n = *590. These ratings represent frequency of endorsement of each symptom across the Neuropsychiatric Index and Neuropsychiatric Index Questionnaire.*

Figure 18. Baseline endorsement of neuropsychiatric symptoms differs between men and women.



Note. Women n = 455, men n = 590. These ratings represent frequency of endorsement of each symptom across the Neuropsychiatric Index and Neuropsychiatric Index Questionnaire.

agitation/aggression (15-20% of men vs. 9-13% of women), apathy/indifference (13-19% of men vs. 9-14% of women), disinhibition (8-12% of men vs. 5-7% of women), and elation/euphoria (3-4% of men vs. 1% of women). Men and women had similar rates of the other specific neuropsychiatric symptoms. We conducted a series of regressions to test whether neuropsychiatric symptoms mediated any gender effect on cognitive dysfunction. There was only evidence of cross-sectional mediation for the executive/processing speed domain (see Table 25). After controlling for age and education, the effect of gender on executive dysfunction was marginally significant, b = -.08, p = .09. After controlling for neuropsychiatric symptoms, the effect of gender on executive dysfunction was no longer significant, b = -.04, p = .35.

Gender significantly predicted other domains of cognitive dysfunction, but neuropsychiatric symptoms did not mediate this effect. After controlling for age and education, gender was a significant predictor of global cognitive dysfunction, b = -.20, p < .001, memory dysfunction, b = -.28, p < .001, and visuospatial dysfunction, b = -.12, p < .01 (see Tables 21-22, 24). However, gender was still a significant predictor after controlling for neuropsychiatric symptoms in each of these models: global cognitive dysfunction (b = -.16, p < .001), memory dysfunction (b = -.23, p < .001), and visuospatial dysfunction (b = -.10, p < .05). Men still had worse performance in each of these cognitive areas than women after controlling for age, education, and neuropsychiatric symptom severity. Gender did not significantly predict language dysfunction after controlling for age and education, b = -.03, p = .61 (see Table 23).

Table 21. Neuropsychiatric symptoms do not mediate the effect of gender on global cognitive dysfunction at baseline.

Order of Entry	**Predictors in Set**	**Model**			**Coefficients**			
		ΔR^2	**ΔF (df) for set**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Global Cognitive θ								
1	Age				.02 (.00)	.24	8.01	<.001
	Education	.11	65.05 (2, 1042)	<.001	-.06 (.01)	-.22	-7.61	<.001
2	Gender	.02	20.21 (1, 1041)	<.001	-.20 (.04)	-.13	-4.50	<.001
Step 2: DV = NPI severity score								
1	Age				-.02 (.01)	-.05	-1.68	.09
	Education	.01	5.18 (2, 1042)	<.01	-.08 (.03)	-.09	-2.85	.01
2	Gender	.02	17.15 (1, 1041)	<.001	-.65 (.16)	-.13	-4.14	<.001
Steps 3 & 4: DV = Global Cognitive θ								
1	Age				.02 (.00)	.24	8.01	<.001
	Education	.11	65.05 (2, 1042)	<.001	-.06 (.01)	-.22	-7.61	<.001
2	NPI severity score				.06 (.01)	.21	7.45	<.001
	Gender	.06	38.40 (2, 1040)	<.001	-.16 (.04)	-.11	-3.63	<.001

Note. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 22. Neuropsychiatric symptoms do not mediate the effect of gender on memory dysfunction at baseline.

Order of Entry	Predictors in Set	Model			Coefficients			
		ΔR^2	ΔF (df) for set	*p*	*b* (s.e.)	β	*t*	*p*
Step 1: DV = Memory θ								
1	Age				.02 (.00)	.16	5.19	<.001
	Education	.05	25.07 (2, 1042)	<.001	-.04 (.01)	-.14	-4.50	<.001
2	Gender	.03	30.36 (1, 1041)	<.001	-.28 (.05)	-.17	-5.51	<.001
Step 2: DV = NPI severity score								
1	Age				-.02 (.01)	-.05	-1.68	.09
	Education	.01	5.18 (2, 1042)	<.01	-.08 (.03)	-.09	-2.85	.01
2	Gender	.02	17.15 (1, 1041)	<.001	-.65 (.16)	-.13	-4.14	<.001
Steps 3 & 4: DV = Memory θ								
1	Age				.02 (.00)	.16	5.19	<.001
	Education	.05	25.07 (2, 1042)	<.001	-.04 (.01)	-.14	-4.50	<.001
2	NPI severity score				.08 (.01)	.24	8.15	<.001
	Gender	.08	49.34 (2, 1040)	<.001	-.23 (.05)	-.14	-4.60	<.001

Note. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 23. Neuropsychiatric symptoms do not mediate the effect of gender on language dysfunction at baseline.

Order of		**Model**			**Coefficients**			
Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df) for set**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Language θ								
1	Age				.02 (.00)	.19	6.42	<.001
	Education	.10	56.33 (2, 1042)	<.001	-.07 (.01)	-.24	-8.04	<.001
2	Gender	.00	.26 (1, 1041)	.61	-.03 (.05)	-.02	-.51	.61
Step 2: DV = NPI severity score								
1	Age				-.02 (.01)	-.05	-1.68	.09
	Education	.01	5.18 (2, 1042)	<.01	-.08 (.03)	-.09	-2.85	.01
2	Gender	.02	17.15 (1, 1041)	<.001	-.65 (.16)	-.13	-4.14	<.001
Steps 3 & 4: DV = Language θ								
1	Age				.02 (.00)	.19	6.42	<.001
	Education	.10	56.33 (2, 1042)	<.001	-.07 (.01)	-.24	-8.04	<.001
2	NPI severity score				.04 (.01)	.12	4.16	<.001
	Gender	.02	8.79 (2, 1040)	<.001	.00 (.05)	.00	.02	.98

Note. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 24. Neuropsychiatric symptoms do not mediate the effect of gender on visuospatial dysfunction at baseline.

Order of Entry	Predictors in Set	Model			Coefficients			
		ΔR^2	ΔF (df) for set	*p*	*b* (s.e.)	β	*t*	*p*
Step 1: DV = Visuospatial θ								
1	Age				.01 (.00)	.13	4.26	<.001
	Education	.06	30.06 (2, 1042)	<.001	-.05 (.01)	-.19	-6.20	<.001
2	Gender	.01	7.70 (1, 1041)	<.01	-.12 (.04)	-.09	-2.78	<.01
Step 2: DV = NPI severity score								
1	Age				-.02 (.01)	-.05	-1.68	.09
	Education	.01	5.18 (2, 1042)	<.01	-.08 (.03)	-.09	-2.85	.01
2	Gender	.02	17.15 (1, 1041)	<.001	-.65 (.16)	-.13	-4.14	<.001
Steps 3 & 4: DV = Visuospatial θ								
1	Age				.01 (.00)	.13	4.26	<.001
	Education	.06	30.06 (2, 1042)	<.001	-.05 (.01)	-.19	-6.20	<.001
2	NPI severity score				.03 (.01)	.11	3.71	<.001
	Gender	.02	10.77 (2, 1040)	<.001	-.10 (.04)	-.07	-2.30	.02

Note. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 25. Neuropsychiatric symptoms mediate the effect of gender on executive dysfunction at baseline.

Order of Entry	**Predictors in Set**	**Model**			**Coefficients**			
		ΔR^2	**ΔF (df) for set**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Executive θ								
1	Age				.03 (.00)	.25	8.71	<.001
	Education	.12	67.65 (2, 1042)	<.001	-.06 (.01)	-.21	-7.17	<.001
2	Gender	.00	2.82 (1, 1041)	.09	-.08 (.05)	-.05	-1.68	.09
Step 2: DV = NPI severity score								
1	Age				-.02 (.01)	-.05	-1.68	.09
	Education	.01	5.18 (2, 1042)	<.01	-.08 (.03)	-.09	-2.85	.01
2	Gender	.02	17.15 (1, 1041)	<.001	-.65 (.16)	-.13	-4.14	<.001
Steps 3 & 4: DV = Executive θ								
1	Age				.03 (.00)	.25	8.71	<.001
	Education	.12	67.65 (2, 1042)	<.001	-.06 (.01)	-.21	-7.17	<.001
2	NPI severity score				.05 (.01)	.17	5.97	<.001
	Gender	.03	19.27 (2, 1040)	<.001	-.04 (.05)	-.03	-.94	.35

Note. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Diagnostic status moderated the mediation of executive/processing speed. Neuropsychiatric symptoms only mediated the effect of gender on executive/processing speed for the non-demented participants, but not for individuals with AD (see Table 30). Neuropsychiatric symptoms did not mediate the effect of gender for any of the other cognitive domains for participants with AD or for non-demented participants (see Tables 26-29).

We also tested whether the baseline NPI severity composite score would mediate the effect of gender on cognitive dysfunction at month 24. The same findings emerged: neuropsychiatric symptoms mediated the effect of gender on executive/processing speed dysfunction, but only for non-demented participants. In this non-demented sample, after controlling for age and education, the effect of gender on executive/processing speed dysfunction was marginally significant, b = -.10, p = .06 (see Table 35). After entering the baseline NPI severity composite score as a predictor into the regression model, the effect of gender on executive dysfunction was no longer significant, b = -.08, p = 13. There was not evidence that the baseline NPI severity composite mediated any other gender effect for any of the other cognitive domains at month 24 (see Tables 31-35).

Aim 3, Goal B: Examine whether neuropsychiatric symptoms mediate potential gender differences in AD-associated cognitive change.

Although there was not strong evidence of neuropsychiatric symptoms mediating the effect of gender on cognitive dysfunction at baseline or month 24, we wanted to examine whether neuropsychiatric symptoms might drive gender differences in cognitive change between baseline and month 24. To analyze this, we entered the NPI severity

Table 26. Baseline neuropsychiatric symptoms do not mediate the effect of gender on global cognitive dysfunction.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Global Cognitive θ								
1	Age				.01 (.01)	.15	2.44	.02
	Education	.06	7.21 (2, 246)	<.01	-.04 (.01)	-.19	-3.07	<.01
2	Gender	.00	.63 (1, 245)	.43	.06 (.08)	.05	.79	.43
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Global Cognitive θ								
1	Age				.01 (.01)	.15	2.44	.02
	Education	.06	7.21 (2, 246)	<.01	-.04 (.01)	-.19	-3.07	<.01
2	NPI severity score				.01 (.01)	.05	.76	.45
	Gender	.01	.60 (2, 244)	.55	.07 (.08)	.06	.88	.38
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Global Cognitive θ								
1	Age				.02 (.00)	.27	8.09	<.001
	Education	.12	56.00 (2, 793)	<.001	-.05 (.01)	-.20	-6.01	<.001
2	Gender	.03	29.69 (1, 792)	<.001	-.23 (.04)	-.18	-5.45	<.001
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Global Cognitive θ								
1	Age				.02 (.00)	.27	8.09	<.001
	Education	.12	56.00 (2, 793)	<.001	-.05 (.01)	-.20	-6.01	<.001
2	NPI severity score				.04 (.01)	.13	4.06	<.001
	Gender	.05	23.36 (2, 791)	<.001	-.21 (.04)	-.17	-4.95	<.001

Note: Baseline NPI severity composite score and baseline global cognitive theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 27. Baseline neuropsychiatric symptoms do not mediate the effect of gender on memory dysfunction.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Memory θ								
1	Age				.01 (.01)	.10	1.63	.10
	Education	.02	2.03 (2, 246)	.13	-.02 (.01)	-.08	-1.29	.20
2	Gender	.01	2.35 (1, 245)	.13	.11 (.07)	.10	1.53	.13
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Memory θ								
1	Age				.01 (.01)	.10	1.63	.10
	Education	.02	2.03 (2, 246)	.13	-.02 (.01)	-.08	-1.29	.20
2	NPI severity score				.02 (.01)	.12	1.88	.06
	Gender	.02	2.95 (2, 244)	.05	.13 (.07)	.11	1.75	.08
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Memory θ								
1	Age				.02 (.00)	.16	4.64	<.001
	Education	.04	16.13 (2, 793)	<.001	-.03 (.01)	-.10	-2.81	<.01
2	Gender	.05	47.04 (1, 972)	<.001	-.34 (.05)	-.24	-6.86	<.001
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Memory θ								
1	Age				.02 (.00)	.16	4.64	<.001
	Education	.04	16.13 (2, 793)	<.001	-.03 (.01)	-.10	-2.81	<.01
2	NPI severity score				.05 (.01)	.14	4.06	<.001
	Gender	.07	32.24 (2, 791)	<.001	-.32 (.05)	-.22	-6.36	<.001

Note: Baseline NPI severity composite score and baseline memory theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 28. Baseline neuropsychiatric symptoms do not mediate the effect of gender on language dysfunction.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Language θ								
1	Age				.02 (.01)	.18	2.92	<.01
	Education	.08	9.93 (2, 246)	<.001	-.06 (.02)	-.22	-3.56	<.001
2	Gender	.00	.19 (1, 245)	.67	.04 (.09)	.03	.43	.67
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Language θ								
1	Age				.02 (.01)	.18	2.92	<.01
	Education	.08	9.93 (2, 246)	<.001	-.06 (.02)	-.22	-3.56	<.001
2	NPI severity score				.01 (.01)	.03	.54	.59
	Gender	.00	.24 (2, 244)	.79	.05 (.10)	.03	.49	.63
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Language θ								
1	Age				.02 (.00)	.18	5.33	<.001
	Education	.09	38.12 (2, 793)	<.001	-.06 (.01)	-.22	-6.37	<.001
2	Gender	.00	.07 (1, 792)	.79	-.01 (.05)	-.01	-.26	.79
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Language θ								
1	Age				.02 (.00)	.18	5.33	<.001
	Education	.09	38.12 (2, 793)	<.001	-.06 (.01)	-.22	-6.37	<.001
2	NPI severity score				.02 (.01)	.06	1.63	.10
	Gender	.00	1.37 (2, 791)	.26	-.00 (.05)	-.00	-.06	.96

Note: Baseline NPI severity composite score and baseline language theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 29. Baseline neuropsychiatric symptoms do not mediate the effect of gender on visuospatial dysfunction.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Visuospatial θ								
1	Age				.01 (.01)	.08	1.33	.19
	Education	.02	2.07 (2, 246)	.13	-.03 (.02)	-.10	-1.63	.11
2	Gender	.00	.70 (1, 245)	.40	-.08 (.10)	-.06	-.84	.40
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Visuospatial θ								
1	Age				.01 (.01)	.08	1.33	.19
	Education	.02	2.07 (2, 246)	.13	-.03 (.02)	-.10	-1.63	.11
2	NPI severity score				-.01 (.01)	-.05	-.83	.41
	Gender	.01	.70 (2, 244)	.50	-.09 (.10)	-.06	-.93	.35
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Visuospatial θ								
1	Age				.01 (.00)	.13	3.67	<.001
	Education	.06	23.61 (2, 793)	<.001	-.04 (.01)	-.19	-5.43	<.001
2	Gender	.01	5.55 (1, 792)	.02	-.10 (.04)	-.08	-2.36	.02
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Visuospatial θ								
1	Age				.01 (.00)	.13	3.67	<.001
	Education	.06	23.61 (2, 793)	<.001	-.04 (.01)	-.19	-5.43	<.001
2	NPI severity score				.02 (.01)	.08	2.32	.02
	Gender	.01	5.49 (2, 791)	<.01	-.09 (.04)	-.07	-2.05	.04

Note: Baseline NPI severity composite score and baseline visuospatial theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 30. Baseline neuropsychiatric symptoms mediate the effect of gender on executive/processing speed dysfunction for non-demented older adults.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Exec/Proc Speed θ								
1	Age				.02 (.01)	.16	2.63	.01
	Education	.07	9.26 (2, 246)	<.001	-.06 (.02)	-.22	-3.58	<.001
2	Gender	.01	1.42 (1, 245)	.24	.11 (.09)	.08	1.19	.24
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Exec/Proc Speed θ								
1	Age				.02 (.01)	.16	2.63	.01
	Education	.07	9.26 (2, 246)	<.001	-.06 (.02)	-.22	-3.58	<.001
2	NPI severity score				.01 (.01)	.03	.40	.69
	Gender	.01	.78 (2, 244)	.46	.11 (.09)	.08	1.23	.22
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Exec/Proc Speed θ								
1	Age				.03 (.00)	.29	8.61	<.001
	Education	.12	54.56 (2, 793)	<.001	-.04 (.01)	-.17	-5.05	<.001
2	Gender	.01	4.23 (1, 792)	.04	-.10 (.05)	-.07	-2.06	.04
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Exec/Proc Speed θ								
1	Age				.03 (.00)	.29	8.61	<.001
	Education	.12	54.56 (2, 793)	<.001	-.04 (.01)	-.17	-5.05	<.001
2	NPI severity score				.04 (.01)	.12	3.61	<.001
	Gender	.02	8.67 (2, 791)	<.001	-.08 (.05)	-.06	-1.60	.11

Note: Baseline NPI severity composite score and baseline executive/processing speed theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Exec/Proc Speed = Executive/Processing Speed.

Table 31. Baseline neuropsychiatric symptoms do not mediate the effect of gender on global cognitive dysfunction at month 24.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Global Cognitive θ								
1	Age				.01 (.01)	.06	.90	.37
	Education	.02	1.95 (2, 246)	.14	-.03 (.02)	-.12	-.181	.07
2	Gender	.00	.58 (1, 245)	.45	.08 (.10)	.05	.76	.45
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Global Cognitive θ								
1	Age				.01 (.01)	.06	.90	.37
	Education	.02	1.95 (2, 246)	.14	-.03 (.02)	-.12	-1.81	.07
2	NPI severity score				.03 (.02)	.13	2.04	.04
	Gender	.02	2.37 (2, 244)	.10	.10 (.10)	.07	1.00	.32
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Global Cognitive θ								
1	Age				.02 (.00)	.24	7.05	<.001
	Education	.11	46.33 (2, 793)	<.001	-.05 (.01)	-.20	-5.84	<.001
2	Gender	.02	15.03 (1, 792)	<.001	-.18 (.05)	-.13	-3.88	<.001
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Global Cognitive θ								
1	Age				.02 (.00)	.24	7.05	<.001
	Education	.11	46.33 (2, 793)	<.001	-.05 (.01)	-.20	-5.84	<.001
2	NPI severity score				.04 (.01)	.12	3.45	<.01
	Gender	.03	13.58 (2, 791)	<.001	-.16 (.05)	-.12	-3.44	<.01

Note: Baseline NPI severity composite score and month 24 global cognitive theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 32. Baseline neuropsychiatric symptoms do not mediate the effect of gender on memory dysfunction at month 24.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Memory θ								
1	Age				-.00 (.01)	-.02	-.33	.75
	Education	.01	.64 (2, 246)	.53	-.01 (.01)	-.07	-1.06	.29
2	Gender	.01	3.27 (1, 245)	.07	.13 (.07)	.12	1.81	.07
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Memory θ								
1	Age				-.00 (.01)	-.02	-.33	.75
	Education	.01	.64 (2, 246)	.53	-.01 (.01)	-.07	-1.06	.29
2	NPI severity score				.01 (.01)	.03	.45	.65
	Gender	.01	1.73 (2, 244)	.18	.14 (.07)	.12	1.85	.07
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Memory θ								
1	Age				.02 (.00)	.17	4.86	<.001
	Education	.05	19.96 (2, 793)	<.001	-.04 (.01)	-.12	-3.55	<.001
2	Gender	.03	29.72 (1, 792)	<.001	-.31 (.06)	-.19	-5.45	<.001
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Memory θ								
1	Age				.02 (.00)	.17	4.86	<.001
	Education	.05	19.96 (2, 793)	<.001	-.04 (.01)	-.12	-3.55	<.001
2	NPI severity score				.05 (.01)	.11	3.25	<.01
	Gender	.05	20.31 (2, 791)	<.001	-.29 (.06)	-.18	-5.03	<.001

Note: Baseline NPI severity composite score and month 24 memory theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 33. Baseline neuropsychiatric symptoms do not mediate the effect of gender on language dysfunction at month 24.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Language θ								
1	Age				.01 (.01)	.10	1.54	.13
	Education	.05	6.10 (2, 246)	<.01	-.06 (.02)	-.20	-3.23	<.01
2	Gender	.00	.14 (1, 245)	.71	.04 (.12)	.02	.37	.71
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Language θ								
1	Age				.01 (.01)	.10	1.54	.13
	Education	.05	6.10 (2, 246)	<.01	-.06 (.02)	-.20	-3.23	<.01
2	NPI severity score				.04 (.02)	.13	2.11	.04
	Gender	.02	2.29 (2, 244)	.10	.07 (.12)	.04	.62	.53
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Language θ								
1	Age				.02 (.00)	1.8	5.19	<.001
	Education	.08	36.33 (2, 793)	<.001	-.06 (.01)	-.21	-6.23	<.001
2	Gender	.00	.16 (1, 792)	.69	-.02 (.06)	-.01	-.40	.69
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Language θ								
1	Age				.02 (.00)	.19	5.36	<.001
	Education	.08	36.33 (2, 793)	<.001	-.06 (.01)	-.21	-5.92	<.001
2	NPI severity score				.03 (.01)	.08	2.19	.03
	Gender	.01	2.49 (2, 791)	.08	-.01 (.06)	-.00	-.12	.91

Note: Baseline NPI severity composite score and month 24 language theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 34. Baseline neuropsychiatric symptoms do not mediate the effect of gender on visuospatial dysfunction at month 24.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Visuospatial θ								
1	Age				-.00 (.01)	-.02	-.29	.77
	Education	.01	1.19 (2, 246)	.31	-.03 (.02)	-.10	-1.49	.14
2	Gender	.00	.10 (1, 245)	.75	-.04 (.12)	-.02	-.32	.75
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Visuospatial θ								
1	Age				-.00 (.01)	-.02	-.29	.77
	Education	.01	1.19 (2, 246)	.31	-.03 (.02)	-.10	-1.49	.14
2	NPI severity score				.02 (.02)	.07	1.13	.26
	Gender	.01	.69 (2, 244)	.50	-.02 (.12)	-.01	-.19	.85
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Visuospatial θ								
1	Age				.01 (.00)	.14	3.88	<.001
	Education	.05	21.83 (2, 793)	<.001	-.04 (.01)	-.17	-4.95	<.001
2	Gender	.00	2.90 (1, 792)	.09	-.07 (.04)	-.06	-1.70	.09
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Visuospatial θ								
1	Age				.01 (.00)	.14	3.88	<.001
	Education	.05	21.83 (2, 793)	<.001	-.04 (.01)	-.17	-4.95	<.001
2	NPI severity score				.02 (.01)	.07	1.88	.06
	Gender	.01	3.21 (2, 791)	.04	-.06 (.04)	-.05	-1.46	.15

Note: Baseline NPI severity composite score and month 24 visuospatial theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire.

Table 35. Baseline neuropsychiatric symptoms do not mediate the effect of gender on executive/processing speed dysfunction at month 24.

AD								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Exec/Proc Speed θ								
1	Age				.01 (.01)	.08	1.19	.24
	Education	.02	2.33 (2, 246)	.10	-.04 (.02)	-.12	-1.88	.06
2	Gender	.00	.79 (1, 245)	.38	.10 (.12)	.06	.89	.38
Step 2: DV = NPI severity score								
1	Age				-.01 (.03)	-.02	-.23	.82
	Education	.00	.44 (2, 246)	.64	-.07 (.08)	-.06	-.89	.37
2	Gender	.01	3.48 (1, 245)	.06	-.83 (.44)	-.12	-1.87	.06
Steps 3 & 4: DV = Exec/Proc Speed θ								
1	Age				.01 (.01)	.08	1.19	.24
	Education	.02	2.33 (2, 246)	.10	-.04 (.02)	-.12	-1.88	.06
2	NPI severity score				.02 (.02)	.08	1.30	.19
	Gender	.01	1.24 (2, 244)	.29	.12 (.12)	.07	1.04	.30
Non-Demented								
Order		**Model**			**Coefficients**			
of Entry	**Predictors in Set**	**ΔR^2**	**ΔF (df)**	***p***	***b* (s.e.)**	**β**	***t***	***p***
Step 1: DV = Exec/Proc Speed θ								
1	Age				.03 (.00)	.31	9.34	<.001
	Education	.13	60.64 (2, 793)	<.001	-.05 (.01)	-.16	-4.91	<.001
2	Gender	.00	3.49 (1, 792)	.06	-.10 (.05)	-.06	-1.87	.06
Step 2: DV = NPI severity score								
1	Age				-.03 (.01)	-.10	-2.89	<.01
	Education	.01	5.70 (2, 793)	<.01	-.05 (.03)	-.07	-2.02	<.05
2	Gender	.02	12.63 (1, 792)	<.001	-.52 (.15)	-.13	-3.55	<.001
Steps 3 & 4: DV = Exec/Proc Speed θ								
1	Age				.03 (.00)	.31	9.34	<.001
	Education	.13	60.64 (2, 793)	<.001	-.05 (.01)	-.16	-4.91	<.001
2	NPI severity score				.03 (.01)	.09	2.69	<.01
	Gender	.01	5.38 (2, 791)	<.01	-.08 (.05)	-.05	-1.52	.13

Note: Baseline NPI severity composite score and month 24 executive/processing speed theta score were entered in the above models. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Exec/Proc Speed = Executive/Processing Speed.

composite score as a covariate into the repeated-measures ANOVA models. As previously described, without controlling for neuropsychiatric symptoms, we found a significant within-subjects interaction between time, gender, and diagnostic status for memory. We also found a significant between-subjects interaction between gender and diagnostic status for average global cognitive dysfunction, as well as marginally significant effects of gender on average memory and average visuospatial dysfunction. After entering neuropsychiatric symptoms as a covariate in these repeated-measures ANOVA models (see Tables 36-40), there was still a significant within-subjects interaction between time, gender, and diagnostic status for a quadratic trend for memory, $F(1, 1038) = 5.71$, $p = .02$. Controlling for neuropsychiatric symptoms did not change the statistical significance of this interaction. The between-subjects interaction between gender and diagnostic status for average global cognitive dysfunction was also still significant after controlling for neuropsychiatric symptoms, $F(1, 1038) = 12.04$, $p < .01$. In contrast, after controlling for neuropsychiatric symptoms, the between-subjects effects of gender were no longer significant for average memory, $F(1, 1038) = 2.26$, $p = .13$, or average visuospatial dysfunction, $F(1, 1038) = 2.37$, $p = .12$. Interestingly, there was a significant within- subjects interaction between time and neuropsychiatric symptoms for a linear trend for language, $F(1, 1038) = 4.16$, $p < .05$. This suggests that the progression of change in language abilities was partially dependent on baseline neuropsychiatric symptoms.

Table 36. Global cognitive dysfunction: repeated-measures ANOVA within-subjects contrasts with neuropsychiatric symptoms as covariate.

Source	**Time**	***F*(1, 1038)**	***p***
time	Linear	3.08	.08
	Quadratic	1.03	.31
time*age	Linear	.57	.45
	Quadratic	1.42	.23
time*education	Linear	.08	.78
	Quadratic	.71	.40
time*NPI	Linear	1.86	.17
	Quadratic	1.09	.30
time*gender	Linear	1.01	.31
	Quadratic	.72	.40
time*dx	Linear	175.37	**<.001**
	Quadratic	.00	.97
time*gender*dx	Linear	.21	.65
	Quadratic	.72	.40

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. NPI represents the NPI severity composite score. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Results significant at p < .05 are bolded.

Table 37. Memory dysfunction: repeated-measures ANOVA within-subjects contrasts with neuropsychiatric symptoms as covariate.

Source	**Time**	***F*(1, 1038)**	***p***
time	Linear	3.18	.08
	Quadratic	.15	.70
time*age	Linear	.00	.99
	Quadratic	.00	.99
time*education	Linear	2.17	.14
	Quadratic	.49	.49
time*NPI	Linear	2.38	.12
	Quadratic	1.32	.25
time*gender	Linear	.34	.56
	Quadratic	3.01	.08
time*dx	Linear	118.23	**<.001**
	Quadratic	.65	.42
time*gender*dx	Linear	.02	.88
	Quadratic	5.71	**.02**

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. NPI represents the NPI severity composite score. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Results significant at p < .05 are bolded.

Table 38. Language dysfunction: repeated-measures ANOVA within-subjects contrasts with neuropsychiatric symptoms as covariate.

Source	**Time**	***F*(1, 1038)**	***p***
time	Linear	1.19	.28
	Quadratic	1.14	.29
time*age	Linear	.08	.77
	Quadratic	.82	.37
time*education	Linear	.10	.75
	Quadratic	.07	.79
time*NPI	Linear	4.16	**.04**
	Quadratic	.12	.73
time*gender	Linear	.08	.78
	Quadratic	.03	.87
time*dx	Linear	68.00	**<.001**
	Quadratic	.15	.70
time*gender*dx	Linear	.13	.72
	Quadratic	.00	.95

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. NPI represents the NPI severity composite score. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Results significant at p < .05 are bolded.

Table 39. Visuospatial dysfunction: repeated-measures ANOVA within-subjects contrasts with neuropsychiatric symptoms as covariate.

Source	**Time**	***F*(1, 1038)**	***p***
time	Linear	.56	.46
	Quadratic	.00	.97
time*age	Linear	.43	.51
	Quadratic	.10	.76
time*education	Linear	.24	.62
	Quadratic	.11	.74
time*NPI	Linear	1.55	.21
	Quadratic	1.32	.25
time*gender	Linear	.91	.34
	Quadratic	.23	.63
time*dx	Linear	24.81	**<.001**
	Quadratic	.35	.56
time*gender*dx	Linear	.19	.66
	Quadratic	.02	.90

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. NPI represents the NPI severity composite score. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Results significant at p < .05 are bolded.

Table 40. Executive/processing speed dysfunction: repeated-measures ANOVA within-subjects contrasts with neuropsychiatric symptoms as covariate.

Source	**Time**	***F*(1, 1038)**	***p***
time	Linear	.06	.81
	Quadratic	1.17	.28
time*age	Linear	.84	.36
	Quadratic	1.63	.20
time*education	Linear	.07	.80
	Quadratic	.31	.58
time*NPI	Linear	.15	.70
	Quadratic	.35	.56
time*gender	Linear	.00	.95
	Quadratic	.01	.94
time*dx	Linear	58.58	**<.001**
	Quadratic	.52	.47
time*gender*dx	Linear	.02	.88
	Quadratic	1.07	.30

Note: dx is a binary variable representing diagnosis at month 24: AD or non-demented. NPI represents the NPI severity composite score. The NPI severity score is a composite of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Results significant at p < .05 are bolded.

Aim 4: Analyze whether gender or neuropsychiatric symptoms predict odds of conversion to AD.

A binary logistic regression was conducted to analyze whether the odds of conversion to AD was related to either gender or neuropsychiatric symptoms. In the model, a binary variable representing conversion from CN or MCI to AD (0 = no, 1 = yes) was entered as the dependent variable. Gender and the baseline NPI severity composite score were entered as covariates in the model. The overall model was significant, $\chi^2 = 31.97$, $p < .001$. The model accurately predicted status on the conversion to AD variable approximately 84% of the time. The coefficient for gender was not statistically significant, $b = .08$, Wald $\chi^2 = .18$, $p = .68$. In contrast, the coefficient for the baseline NPI severity composite score was statistically significant, $b = .18$, Wald $\chi^2 = 29.66$, $p < .001$. A one-unit increase in NPI severity composite score multiplied the predicted odds of converting to AD by 1.20.

Consistent with these results, participants who converted to AD by month 24 had significantly higher scores on the NPI severity composite at baseline, $t(207.56) = 2.62$, $p < .05$, month 12, $t(231.13) = 4.14$, $p < .001$, and month 24, $t(201.27) = 6.05$, $p < .001$, compared to participants who did not convert from non-demented aging to AD (see Table 41). The effect sizes for these differences were small to medium (Cohen's *d*s = .27-.62). Converters also had notably higher rates of each specific neuropsychiatric symptom compared to non-converters (see Table 42 and Figure 19). Between 67-82% of converters reported any neuropsychiatric symptom, in contrast to 56-62% of non-converters.

Table 41. Neuropsychiatric symptoms differ for MCI participants based on conversion status.

	Converters to AD		Non-Converters		*t*-test		
Neuropsychiatric Indicator	***N***	***M(SD)***	***N***	***M(SD)***	***t(df)***	***p***	**Cohen's *d***
Baseline							
NPI Severity Composite	153	2.42 (3.41)	424	1.64 (2.37)	2.62 (207.56)	.01	.27
NPI Total	50	4.76 (6.53)	176	3.69 (6.15)	1.07 (224)	.28	.17
NPI-Q Total	103	2.47 (3.81)	248	1.63 (2.35)	2.08 (135.31)	.04	.27
Month 12							
NPI Severity Composite	153	3.14 (3.17)	422	1.96 (2.61)	4.14 (231.13)	<.001	.41
NPI Total	55	8.22 (8.14)	256	4.14 (6.79)	3.47 (71.06)	<.01	.54
NPI-Q Total	98	2.98 (3.34)	167	2.19 (2.71)	2.11 (263)	.04	.26
Month 24							
NPI Severity Composite	153	4.19 (4.09)	422	2.04 (2.68)	6.05 (201.27)	<.001	.62
NPI Total	55	11.91 (12.51)	262	4.62 (7.20)	4.18 (61.71)	<.001	.71
NPI-Q Total	98	3.99 (3.99)	160	2.21 (2.87)	3.84 (158.44)	<.001	.51

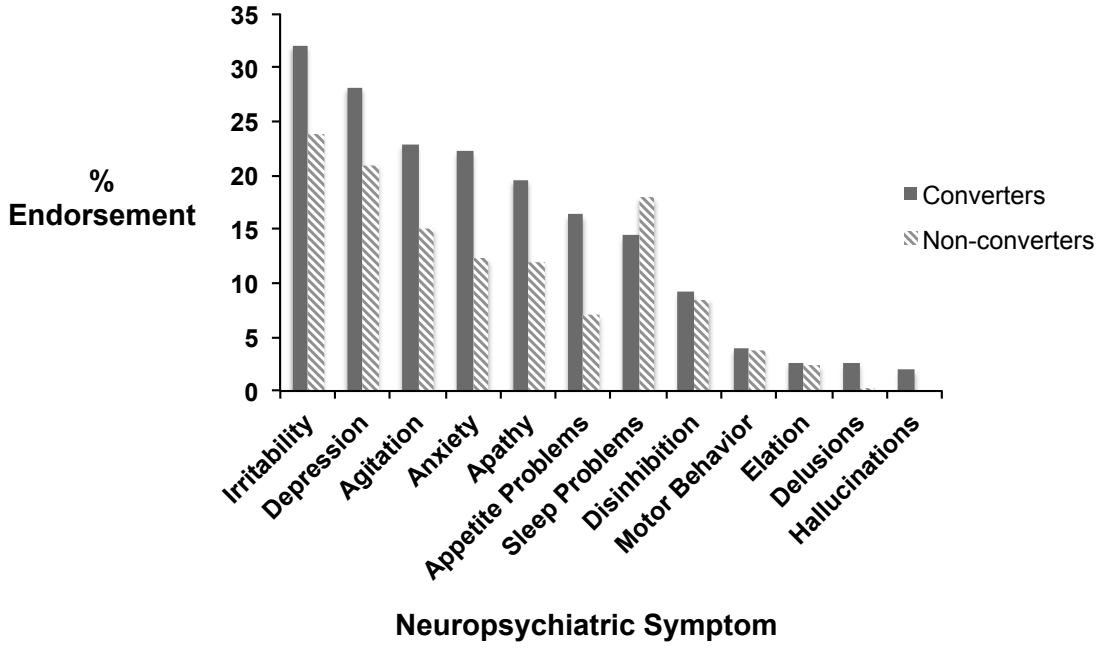
Note. MCI = mild cognitive impairment. AD = Alzheimer's disease. The NPI Severity Composite score is an average of severity ratings on the Neuropsychiatric Inventory and Neuropsychiatric Inventory-Questionnaire. Converters = participants who convert from MCI to AD between baseline and month 24. Non-Converters = participants whose diagnosis remains stable as MCI between baseline and month 24 (i.e., they do not convert to AD).

Table 42. Neuropsychiatric symptom endorsement differs for MCI participants based on conversion status.

CONVERTERS TO AD			
Symptom Endorsement: Y (%)	**Baseline**	**Month 12**	**Month 24**
Delusions	4 (3%)	7 (5%)	12 (8%)
Hallucinations	3 (2%)	5 (3%)	9 (6%)
Agitation/Aggression	35 (23%)	38 (25%)	49 (32%)
Depression/Dysphoria	43 (28%)	49 (32%)	61 (40%)
Anxiety	34 (22%)	47 (31%)	47 (31%)
Elation/Euphoria	4 (3%)	3 (2%)	6 (4%)
Apathy/Indifference	30 (20%)	51 (33%)	58 (38%)
Disinhibition	14 (9%)	21 (14%)	30 (20%)
Irritability/Lability	49 (32%)	55 (36%)	60 (39%)
Aberrant Motor Behavior	6 (4%)	11 (7%)	27 (18%)
Sleep	22 (14%)	36 (24%)	44 (29%)
Appetite and Eating Disorders	25 (16%)	32 (21%)	42 (27%)
Any Symptom	103 (67%)	121 (79%)	125 (82%)
NON-CONVERTERS			
Symptom Endorsement: Y (%)	**Baseline**	**Month 12**	**Month 24**
Delusions	1 (0%)	3 (1%)	6 (1%)
Hallucinations	0 (0%)	2 (0%)	4 (1%)
Agitation/Aggression	64 (15%)	73 (17%)	83 (20%)
Depression/Dysphoria	89 (21%)	106 (25%)	107 (25%)
Anxiety	52 (12%)	68 (16%)	71 (17%)
Elation/Euphoria	10 (2%)	12 (3%)	12 (3%)
Apathy/Indifference	51 (12%)	55 (13%)	61 (14%)
Disinhibition	36 (8%)	36 (9%)	37 (9%)
Irritability/Lability	101 (24%)	118 (28%)	110 (26%)
Aberrant Motor Behavior	16 (4%)	18 (4%)	18 (4%)
Sleep	76 (18%)	91 (22%)	85 (20%)
Appetite and Eating Disorders	30 (7%)	36 (9%)	49 (12%)
Any Symptom	238 (56%)	261 (62%)	260 (62%)

Note. MCI = mild cognitive impairment. AD = Alzheimer's disease. Converters to AD: n = 153; non-converters: n = 424 at baseline, n = 422 at month 12 and month 24. Converters = participants who convert from MCI to AD between baseline and month 24. Non-Converters = participants whose diagnosis remains stable as MCI between baseline and month 24 (i.e., they do not convert to AD). These ratings represent frequency of endorsement of each symptom across the Neuropsychiatric Index and Neuropsychiatric Index Questionnaire.

Figure 19. Baseline endorsement of neuropsychiatric symptoms differs for MCI participants based on conversion status.



Note. MCI = mild cognitive impairment. Converters to Alzheimer's disease: n = 153; non-converters: n = 424 at baseline, n = 422 at month 12 and month 24. Converters = participants who convert from MCI to Alzheimer's disease between baseline and month 24. Non-Converters = participants whose diagnosis remains stable as MCI between baseline and month 24 (i.e., they do not convert to Alzheimer's disease). These ratings represent frequency of endorsement of each symptom across the Neuropsychiatric Index and Neuropsychiatric Index Questionnaire.

SUMMARY AND DISCUSSION

In light of important, unanswered questions about the relationships among gender, neuropsychiatric symptoms, and cognitive dysfunction in AD, the current study had four main aims: 1) to develop cross-sectional and longitudinal statistical models of AD-associated cognitive dysfunction, 2) to analyze gender differences in AD-associated cognitive dysfunction, 3) to examine whether neuropsychiatric symptoms mediated any gender effect on AD-associated cognitive dysfunction, and 4) to analyze whether gender or neuropsychiatric symptoms increased odds of conversion to AD. Results, limitations, and implications of the findings are discussed below for each aim.

Aim 1: Model cognitive dysfunction in AD

The present study generated cross-sectional and longitudinal statistical models of the ADNI neuropsychological battery in a mixed sample of older adults who were either diagnosed with AD or were non-demented. A cross-sectional, higher-order CFA provided good fit to the data, suggesting that the 15 neuropsychological tests of interest mapped onto four cognitive domains: memory, language, visuospatial, and executive/processing speed. In turn, these four cognitive domains reflected one higher-order factor of general cognitive dysfunction. This structural model is generally consistent with a previous CFA of a slightly different subset of the ADNI neuropsychological battery (Park et al., 2012). In Park and colleague's study, they fit a model of five neuropsychological domains (memory, language, visuospatial, attention, and executive/processing speed) based on data from ADNI1. In contrast, we analyzed neuropsychological data from across all three phases of ADNI (i.e., ADNI1, ADNI-GO,

and ADNI2), noting that the neuropsychological battery has changed slightly across these phases. For example, Category Fluency-Vegetables and WAIS-R Digit Span and Digit Symbol subtests were dropped after ADNI1. Each of these three subtests was part of Park and colleague's CFA, and in fact the two Digit Span subtests (Forward and Backward conditions) were the only measures that loaded onto their Attention factor. Because our goal was to examine longitudinal cognitive data across all three ADNI phases, we adapted this structural model to include key neuropsychological indicators from the core ADNI neuropsychological battery. We also added the higher-order factor of global cognitive dysfunction, which fit the data well. Our structural model enabled us to maximize the cognitive data we analyzed from across all three phases of ADNI, thereby analyzing the majority of ADNI participants instead of just those participating in ADNI1. Our structural model also enabled us to examine global AD-associated cognitive dysfunction, in addition to four discrete cognitive domains.

The current study also provided an IRT model of how the four cognitive domains function across the spectrum of AD-associated cognitive dysfunction. The memory and language domains were the most sensitive to mild degrees of cognitive impairment in this sample, whereas the executive/processing speed domain was most sensitive to moderate degrees of cognitive dysfunction. The visuospatial domain had poorer discriminative power than the other three cognitive domains and was only sensitive to cognitive impairment at moderate-to-severe levels. These findings generally correspond to the pattern of cognitive deterioration in AD and related amnestic conditions (e.g., MCI), which is typically marked by early declines in episodic memory and semantic

language abilities (e.g., Albert et al., 2011; Caselli et al., 2014; Salmon & Bondi, 2009). Visuospatial abilities are impacted as the disease becomes more severe (Salmon & Bondi, 2009). Although complex executive functions are known to decline early in the course of AD (Albert et al., 2011; Sacuiu et al., 2005; Salmon & Bondi, 2009), the executive/processing speed factor in this study functioned best in moderate degrees of cognitive dysfunction. This factor was comprised of two processing speed measures but only one complex executive measure. Although these measures all assess frontal lobe functions, executive abilities and processing speed are not perfectly correlated and in fact are often considered as separate (but related) neuropsychological functions. This combination of one executive measure and two processing speed measures may explain why the executive/processing speed factor was optimally sensitive in moderate degrees of AD-associated cognitive dysfunction, rather than in mild degrees.

We also modeled how each of the 15 neuropsychological tests function across the spectrum of AD-associated cognitive dysfunction. Within the memory domain, measures of verbal learning and recall (i.e., RAVLT Learning, Short-Delay Recall, Delayed Recall; ADAS-Cog Delayed Recall) were more sensitive to mild degrees of cognitive dysfunction than measures of recognition memory (i.e., RAVLT Recognition, ADAS-Cog Recognition). The RAVLT Learning measure, an index of the number of words the participant was able to learn between trial 1 and trial 5, was most sensitive to very mild degrees of cognitive dysfunction. This suggests that even older adults who are cognitively intact experience mild difficulty with their ability to learn verbal information that is presented to them in an auditory manner. Older adults with overt cognitive

dysfunction (e.g., those with MCI or AD) have noticeably greater difficulty with this task. In fact, at baseline, cognitively intact older adults learned almost six words on average (M = 5.87, SD = 2.32), whereas older adults with MCI only learned about four words (M = 4.22, SD = 2.57) and older adults with AD only learned two words (M = 2.16, SD = 1.76) across the five trials. This indicator of verbal learning across a series of trials may serve as a sensitive indicator to early cognitive dysfunction.

The format in which information is presented to participants for learning may influence later retrieval and recall. During the RAVLT, a list of words is read aloud to the participant for learning, whereas during the ADAS-Cog, the participants hears and sees the sequence of words to be learned. The RAVLT appears to be harder, based on the fact that the two RAVLT indicators of recall (Short-Delay Recall and Delayed Recall) are more optimally sensitive in milder degrees of cognitive dysfunction than the ADAS-Cog Delayed Recall subtest. This is likely due to the fact that learning is reinforced using two presentations—auditory and visual—on the ADAS-Cog, but just using one presentation—auditory—on the RAVLT. Clinical researchers deciding between these tests should consider how impaired their sample is; if they are studying preclinical, non-demented samples, then the RAVLT may be best at discriminating between degrees of cognitive difficulty. On the other hand, if the sample is made up of older adults with AD, then the ADAS-Cog may be sufficient for measuring difficulties with verbal recall.

Finally, we found that recognition memory was a less sensitive measure of AD-associated cognitive dysfunction than learning or free recall. Both the RAVLT and

ADAS-Cog recognition subtests functioned equivalently and were most sensitive to moderate-to-severe degrees of cognitive impairment, corresponding to participants with late MCI to mild AD. For individuals who are cognitively normal or even have preclinical AD, recognizing words that were previously presented to them is relatively easy (Backman et al., 2005). However, as AD neuropathology spreads throughout the brain and cognitive and functional deficits become measurable, memory deficits become more obvious. Individuals with AD struggle to encode and consolidate new information and thus they cannot recall it, even when presented with a cue such as on a recognition memory task (Helkala, Laulumaa, Soininen, & Riekkinen, 1988; Weintraub, Wicklund, & Salmon, 2012).

Among the language measures, Category Fluency-Animals, a measure of semantic verbal fluency, was by far the most sensitive measure to mild and moderate degrees of AD-associated cognitive dysfunction. The Boston Naming Test was a sensitive measure of moderate-to-severe degrees of cognitive dysfunction, but the ADAS-Cog Naming subtest was relatively uninformative until cognitive dysfunction was fairly severe in this sample. These findings suggest that including a measure of verbal fluency (such as Category Fluency-Animals) is likely to be useful as an assessment of language in a range of elderly samples, including non-demented and AD samples. However, it appears that, in the ADNI sample, only those participants with AD experience notable difficulty with confrontation naming on the Boston Naming Test or ADAS-Cog Naming subtest. However, even the ADAS-Cog Naming subtest was relatively easy for the participants with AD (M = .47, SD = .75) at baseline. It should be

noted that these participants had mild AD, so these measures of confrontation naming may be more useful among more advanced forms of AD.

Among the visuospatial measures, both Clock Drawing Test conditions functioned best in moderate-to-severe degrees of cognitive impairment, but the ADAS-Cog Construction subtest was relatively insensitive to capturing any information about the range of AD-associated cognitive dysfunction analyzed in this sample. The ADAS-Cog Construction subtest involves copying mostly basic, two-dimensional geometric figures (e.g., circle, diamond), and researchers have found that it is a relatively coarse, insensitive measure to mild AD and non-demented cognitive dysfunction (Benge, Balsis, Geraci, Massman, & Doody, 2009; Wouters et al., 2012). The result that the Clock Drawing Test was optimally sensitive to moderate-to-severe degrees of cognitive dysfunction was consistent with other work demonstrating that this measure is not suitable to screen for mild forms of cognitive dysfunction such as MCI or very mild AD (Ehreke, Luppa, Konig, & Riedel-Heller, 2010; Nishiwaki et al., 2004; Powlishta et al., 2002). Indeed, in the ADNI sample, both cognitively intact participants and participants with MCI performed well on the command (M = 4.68, SD = .63; M = 4.39, SD = .89, respectively) and copy (M = 4.88, SD = .37; M = 4.71, SD = .62, respectively) conditions at baseline.

All three executive/processing speed measures were most sensitive in moderate degrees of AD-associated cognitive dysfunction. Not surprisingly, Trail Making B, the only measure of complex executive functions, was sensitive in milder degrees of impairment than Trail Making A or ADAS-Cog Number Cancellation, both of which

involve visual processing speed. This is consistent with research showing that executive functions decline earlier in the disease process than processing speed (Salmon & Bondi, 2009; Weintraub, Wicklund, & Salmon, 2012).

Over the two-year study period of interest, results of repeated-measures ANOVAs indicated that an AD sample (i.e., participants who were diagnosed with AD within the first two years of their ADNI enrollment) experienced significant linear decline in all cognitive domains: memory, language, visuospatial, executive/processing speed, and global cognitive functions. We tested for quadratic rates of change, but the results were not significant for any domain; rather, a linear slope fit the data best. Other studies (e.g., Wilson et al., 2012) have found non-linear rates of global cognitive decline due to AD, but these studies have typically examined a much longer study period than two years. For example, Wilson and colleagues studied cognitive decline over a period of 20 years. It is possible that the linear cognitive decline in the current study was the best fit for the shorter time frame of two years, but that AD-related cognitive decline may accelerate or decelerate beyond month 24 of ADNI enrollment. As the ADNI clinical trials continue, there will be a larger sample size of participants who have completed cognitive testing beyond month 24. Additional research should continue to analyze patterns of AD-associated cognitive decline in the ADNI database and other AD clinical databases.

Participants who remained non-demented within the two-year period experienced relatively little change in their memory, language, visuospatial, executive/processing speed, or global cognitive functions. This seems inconsistent with the body of literature

showing steady linear declines in numerous cognitive abilities (e.g., processing speed, language skills, visuospatial functions) in non-diseased aging (e.g., Bopp & Verhaeghen, 2005; Caselli et al., 2014; Salthouse, 2004, 2009a). The lack of cognitive decline in our non-demented sample may be related to the somewhat short two-year time period that was analyzed; possibly a longer timeframe could have better captured these age-related declines. Alternatively, perhaps this sample of non-demented older adults remained stable for these specific neuropsychological measures, but might have shown decline on different cognitive measures. For example, there may have been a ceiling effect on the ADAS-Cog, such that some of the subtests (e.g., copying basic geometric figures, naming common household items) were easy enough for these non-demented adults to complete successfully; therefore these ADAS-Cog subtests may be unable to capture subtle cognitive difficulties. A neuropsychological battery that is composed of more complex, difficult assessments may yield a different pattern of change for this non-demented sample.

The discrepancy between the age-related declines reported in the literature and the cognitive stability in this sample of non-demented older adults may also be related to unique characteristics of this sample. It may be that non-demented older adults who voluntarily participate in a clinical trial like ADNI are cognitively healthier than their peers. This could be related to the fact that participants were excluded from ADNI enrollment if they had a history of certain neurological or medical conditions (e.g., seizure disorder, infarctions or lesions on brain scans, history of head trauma, alcohol abuse within the previous two years) or were currently using certain medications (e.g.,

sedative hypnotics, neuroleptics, certain antidepressants). Exclusion criteria such as these yielded an elderly sample that was much more physically healthy than the general older adult population in America, which may have also translated into greater cognitive health and stability over the two-year period.

In addition, non-demented adults are likely to show a practice effect on the cognitive measures, especially considering that many of them completed neuropsychological testing just six to twelve months apart (i.e., at baseline, month 6, month 12, month 24). Supporting this interpretation, the ADNI sample was not demographically representative of the general United States population; the sample was highly educated, with nearly a college education on average. Highly educated older adults have been shown to demonstrate an even larger practice effect than less educated older adults (Karlamangla et al., 2009). It is likely, then, that the high education level of the ADNI sample contributed to the cognitive stability seen in non-demented participants.

The high mean education level may also be indicative of a sample that comes from a higher socioeconomic status (SES) background, as is true of many clinical trial samples (Gul & Ali, 2010), although other indicators of SES (e.g., income) were not measured in the ADNI sample. Individuals from a higher SES background tend to have greater access to certain protective factors for cognitive health, such as better medical care and lifelong educational experiences, such that they can build up a larger cognitive reserve relative to individuals from a lower SES background. In fact, Karlamangla and colleagues (2009) found that high SES older adults performed better than low SES older

adults cross-sectionally, but SES was not associated with rate of cognitive decline. SES may be partially related to the cognitive stability of the non-demented ADNI sample, but it is likely that other factors such as practice effects and the selection of the ADNI neuropsychological battery were more greatly involved.

Aim 2: Analyze gender differences in AD-associated cognitive dysfunction

The present study analyzed gender differences at baseline, as well as whether there were significant gender differences in trajectories of cognitive change for both the AD group and the non-demented group. At baseline, the results for the overall sample revealed significant gender differences in latent global and memory scores and a marginally significant gender difference in latent visuospatial scores. Men had worse cognitive performance in each of these areas than women. However, it appears that this pattern was driven primarily by gender differences in the non-demented group. Non-demented men had significantly poorer latent global and memory scores than non-demented women at baseline, month 12, and month 24. This women's advantage in the memory domain, comprised of verbal episodic memory measures, is consistent with previous studies (Barnes et al., 2003; Munro et al., 2012). Unlike the results of these previous studies, though, non-demented women did not perform worse than non-demented men for visuospatial or language abilities.

Diagnostic status moderated the effect of gender such that there was the reverse pattern of gender differences among participants with AD. In this group, women performed worse than men in latent global, memory, language, and executive domains; however, this gender difference was not statistically significant at baseline. At month 12

and month 24, the poorer memory performance by women with AD relative to men with AD was statistically significant. This deficit in verbal memory for women mirrors other recent findings in AD samples (e.g., Chapman et al., 2011; Pusswald et al., 2015). In addition, there was a marginally significant trend for women to have worse latent global cognitive scores than men at month 12. A recent meta-analysis by Irvine and colleagues (2012) found that women showed small but consistent deficits in all areas of cognitive functioning relative to men in AD samples, but in the present study, gender differences in AD-associated cognitive dysfunction were restricted to memory and global cognitive functions.

In addition to considering mean differences in cognitive performance, we analyzed whether there were gender differences in the statistical models of AD-associated cognitive dysfunction. At baseline, we were interested in whether the cognitive domains and individual items (subtests) functioned differently for men versus women. Using IRT DIF analyses, we found that all of the cognitive subtests functioned relatively equivalently for men and women with the exception of the Clock Drawing Test-command condition. This subtest was more strongly related to the latent continuum of AD-associated cognitive dysfunction and discriminated in relatively milder degrees of cognitive dysfunction for men than women. For both men and women, this subtest provided the most amount of information about moderate-to-severe degrees of AD-associated cognitive dysfunction. This segment of the latent continuum in the current sample corresponds to MCI and mild AD. These results suggest that Clock Drawing Test-command condition is a more sensitive assessment of visuospatial abilities in men,

and that it can capture somewhat milder cognitive problems in men than women. According to our IRT model, in moderate-to-severe degrees of latent cognitive dysfunction, men and women with the same degree of latent AD-associated cognitive dysfunction performed differently on the Clock Drawing Test-command condition (as represented by the gap between the two item curves in Figure 12). It may be that in the mildest stages of AD, men develop subtle visuospatial difficulties slightly earlier than women. Alternatively, perhaps the Clock Drawing Test is a more precise, sensitive assessment of AD-associated visuospatial dysfunction in men than women.

Longitudinally over the two-year period, women with AD had a different rate of decline in their memory compared to men with AD. Both men and women with AD demonstrated quadratic rates of memory decline, but the parabolas representing each gender's memory decline over the two-year period was a different shape. Women with AD had an "upside down" U-shaped parabola, indicating that they had fast decline in their memory between baseline and month 12; the rate of their memory decline decelerated from month 12 to month 24. In contrast, men with AD had slightly slower memory decline from baseline to month 12, but the rate of memory decline accelerated from month 12 to month 24, as depicted by the U-shaped parabola. It is uncertain whether there would be gender differences in rate of memory decline after month 24 of ADNI enrollment. It is possible that men and women had slightly different rates of memory decline within this two-year period, but that both sexes experienced equivalent rates of decline during subsequent years that were not examined for these analyses. Alternatively, it is possible that this gender difference in rate of memory decline

persisted after month 24. Further research should examine gender differences in AD-associated memory dysfunction within a longer study period to clarify this uncertainty.

Given the general dearth of research on sex differences in specific domains of cognitive change in AD, it is impossible to know whether this gender difference in the trajectory of memory decline is specific to the ADNI sample or reflective of a true gender difference in AD. The current results did not indicate any gender differences in rate of change for latent global, language, visuospatial, or executive/processing speed in the AD group. Two other studies have examined gender differences in global cognitive decline and yielded mixed results. Holland and colleagues (2013) found faster global decline in women than men with MCI, but equivalent global decline in men and women with AD. On the other hand, Tschanz and colleagues (2011) showed that females with AD had faster global decline than men with AD. These studies analyzed change on the CDR-SB, ADAS-Cog, and MMSE, which are all widely used measurements used to stage dementia severity. In contrast, the present study derived its global cognitive dysfunction score from a battery of neuropsychological tests. Additional research is needed to further tease apart the potential gender difference in global AD-associated cognitive dysfunction, as well as specific domains of cognitive functioning. It is critical to better understand whether men and women experience a slightly different cognitive profile and/or cognitive trajectories of AD, as the current results suggest regarding differing rates of memory decline.

Although there was not a gender difference in the rate of global cognitive decline, there was an interaction between gender and diagnostic status for global

cognitive dysfunction averaged across the three time points. This finding revealed that women had worse global cognitive dysfunction than men across these time points in the AD group, but the opposite was true in the non-demented group: non-demented men had worse global cognitive dysfunction than non-demented women averaged across the two-year period. Among the non-demented sample, there were no gender differences in rate of cognitive change over the three time points; both non-demented men and women experienced relatively flat rates of cognitive change, reflecting stable cognitive performance.

Aim 3: Examine whether neuropsychiatric symptoms mediate potential effects of gender on AD-associated cognitive dysfunction

Neuropsychiatric symptoms were much more common in the AD sample than the non-demented sample, consistent with other research (e.g., Canevelli et al., 2013; Geda et al., 2008; Peters et al., 2015). Despite this, the results of mediation analyses did not support the hypothesis that neuropsychiatric symptoms would mediate a gender difference in cognitive dysfunction among those with AD. As described above, the primary gender difference in the AD sample was in memory: women had poorer memory performance at month 12 and month 24. After controlling for age and education, gender remained a significant predictor of memory performance at month 12 and was a marginally significant predictor of memory dysfunction at month 24. However, neuropsychiatric symptoms did not mediate these effects. At baseline, gender did not significantly predict memory dysfunction or any of the other cognitive domains for the AD group. Cross-sectional mediation by neuropsychiatric symptoms therefore

could not be demonstrated in this AD group. Longitudinally, men and women had differing patterns of memory decline over the two-year period, but this gender difference remained statistically significant even after controlling for neuropsychiatric symptoms. Neuropsychiatric symptoms did not account for gender differences in rates of AD-associated memory decline.

For the entire sample at baseline, neuropsychiatric symptoms did mediate the effect of gender on executive/processing speed dysfunction. When diagnostic status was entered as a moderating variable, results indicated that this mediation held up only for the non-demented sample. This indicates that any gender difference in executive/processing speed difficulties in this non-demented sample is likely driven by neuropsychiatric distress. In the present non-demented sample, men performed worse than women on executive/processing speed measures, but they also had higher neuropsychiatric severity scores. This mediation finding suggests that controlling for neuropsychiatric symptoms adjusted the men's executive/processing speed scores to be closer to the women's scores among the non-demented sample.

Brodaty and colleagues (2012) found that neuropsychiatric symptoms were related to worse executive functioning among non-demented older adults. Depression, anxiety, and apathy have also been linked to poorer performance on executive functions and processing speed (Brodaty et al., 2012; Drijgers et al., 2011). Between 13-18% of men had partner-endorsed symptoms of depression, anxiety, and apathy at baseline in the current study, which may have contributed to their executive/processing speed difficulties. Men experienced depression and anxiety at relatively similar rates as

women, though, and there was only a slight gender difference in rates of apathy. Approximately 13% of men had apathy at baseline, relative to 9% of women. Therefore, it seems unlikely that these specific symptoms had a unique impact on executive functioning. Rather, it may be that overall neuropsychiatric symptom severity accounted for a portion of executive dysfunction, particularly in men.

Longitudinally, the overall effect of gender on average memory dysfunction across the three time points was no longer significant after controlling for neuropsychiatric symptoms. This result was not moderated by diagnostic status. Because the majority of the overall sample was non-demented, this effect was likely heavily influenced by the pattern of gender differences among the non-demented individuals for memory. Non-demented men had significantly worse memory at each of the three time points than non-demented women, and they also had significantly higher neuropsychiatric scores. Again, it appears that partialing out the influence of neuropsychiatric distress reduced the gap between men and women's performance on memory, but primarily among older adults who were non-demented. No known previous studies have examined the interplay between neuropsychiatric symptoms and gender on AD-associated cognitive decline, so these findings are a preliminary contribution to the literature. More research needs to be done to further analyze these questions.

Although neuropsychiatric symptoms generally did not appear to mediate a gender difference in cognitive dysfunction, there was preliminary evidence of an independent contribution of neuropsychiatric symptoms to the progression of AD-associated cognitive dysfunction. Neuropsychiatric symptoms significantly interacted

with time for language dysfunction across the entire sample of 1045 participants, suggesting that language decline depended on neuropsychiatric status. A handful of previous studies have also found that certain neuropsychiatric symptoms, such as apathy, anxiety, agitation, euphoria, or sleep problems, have been linked with faster cognitive decline in clinical samples (Brodaty et al., 2012; Canevelli et al., 2013; Pocnet et al., 2015). The results of this study suggest that overall severity of neuropsychiatric symptoms may influence the rate of decline in language. This is a preliminary finding, so additional research should seek to characterize the effects of neuropsychiatric symptoms on AD-associated cognitive trajectories.

Men had more problems with neuropsychiatric symptoms than women in both the AD and non-demented samples. This is inconsistent with the general elderly population, where women tend to have more neuropsychiatric symptoms. Even at the symptom level, findings were inconsistent. Women did not have higher rates of depression or anxiety, as numerous studies have found in late life (Apostolova & Cummings, 2008; Brodaty et al., 2015; Van der Mussele et al., 2014) and throughout the lifespan (Leach et al., 2008; McLean & Anderson, 2009; Seeman, 1997). It is possible that the higher rates of neuropsychiatric symptoms in men than women in this sample is related to the particular neuropsychiatric assessments analyzed for this study. Both the NPI and NPI-Q depend on caregiver report rather than self-report by the study participant. It is possible that relying on an informant may affect the pattern of gender differences in neuropsychiatric symptoms, particularly if the informant is also the patient's caregiver. The only other known study examining gender differences on

caregiver-report instruments (specifically the NPI or NPI-Q) was conducted by Brodaty and colleagues (2015), using an Australian sample of older adults with AD and other types of dementia. This study found higher rates of overall neuropsychiatric symptoms for men, similar to the present results. Brodaty also showed that men were more likely to demonstrate apathy, agitation, disinhibition, irritability, and delusions. The present study did find slightly higher rates of each of these symptoms among men relative to women except delusions. However, the current study did not find higher rates of depression, as Brodaty's team did. The handful of other studies that have considered gender differences in neuropsychiatric symptoms among older adults (e.g., Apostolova & Cummings, 2008; Van der Mussele et al., 2014) utilized a mixture of self-report and other-report measures. Caregivers are likely to be more distressed about the patient's neuropsychiatric symptoms than clinicians or perhaps even the patients themselves if the patients are demonstrating limited insight into their symptoms. In fact, there may even be gender differences in the amount of distress experienced by caregivers, with some studies finding that female caregivers reported higher levels of personal distress and depressive symptoms, as well as more patient behavioral problems (Pinquart & Sorensen, 2006; Schulz & Williamson, 1991). Data are not available on the gender of each ADNI participant's caregiver/informant, but it is likely that female caregivers accompanied most of the male participants, particularly for the 88% of male subjects who were married. Therefore, there may be an interaction between the sex of the caregiver and the sex of the patient that influences severity of reported neuropsychiatric symptoms. This

could explain why men in the current sample had higher levels of neuropsychiatric symptoms.

Aim 4: Analyze rates of conversion to AD by gender and neuropsychiatric symptoms.

Results of a binary logistic regression model revealed that men and women did not have different odds of converting to AD. The women in this ADNI sample had an incidence rate of conversion to AD that was slightly less than the incidence rate for men: approximately 13% of women and 16% of men converted to AD between baseline and month 24. Many studies have found that men and women have similar incidence rates of AD (e.g., Bachman et al., 1993; Ganguli et al., 2000; Hebert et al., 2001), whereas other studies have shown significantly higher incidence rates in women (e.g., Aronson et al., 1990; Fratiglioni et al., 1997, 2000; Gao et al., 1998). These latter studies primarily were conducted with European, Asian, or regional American samples. In the Cache County Study, a population-based study in Utah, Zandi and colleagues (2002) found similar incidence rates for American men and women between ages 65 to 80; it was only after the age of 80 that women had higher incidence rates of AD than men. The majority of the ADNI sample (79% of participants) was between 55 to 79 years old, so this may indicate why incidence rates were similar for men and women. Perhaps if the ADNI sample had more participants in their 80s and 90s, a gender difference may have emerged in incidence rates of AD.

Furthermore, the ADNI sample is not representative of the United States demographics, as evidenced by the high mean level of education and racial/ethnic

homogeneity (94% identified as white/Caucasian and 97% identified as non-Hispanic/non-Latino). Although studies in the United States have shown mixed results regarding a gender difference in incidence rates of AD, many have utilized samples that were representative of their regional population (e.g., Bronx, Cache County in Utah) and had greater ethnic diversity. Because the ADNI sample is a homogeneous clinical sample, it is difficult to determine whether there are gender differences in incidence rates of AD among the larger, more diverse population of Americans with AD. Population-based studies should continue to examine whether women are more vulnerable to developing AD than men. In the ADNI sample, there was no significant gender difference in incidence rates.

The binary logistic regression model revealed that baseline neuropsychiatric symptoms did increase odds to converting to AD by 1.20 for every one-unit increase in the total NPI severity composite score. Rosenberg and colleagues (2013) also found that neuropsychiatric symptoms increased the risk of developing AD dementia. Other studies have shown a unique predictive role of specific neuropsychiatric symptoms, including depression, anxiety, agitation, and apathy (e.g., Banks et al., 2014; Brodaty et al., 2012; Copeland et al., 2003; Palmer et al., 2011; Van der Mussele et al., 2014). In the present study, participants who converted to AD between baseline and month 24 had significantly higher NPI severity composite scores at each time point. Participants who converted from MCI to AD were more likely (67-82%) to endorse any neuropsychiatric symptom than participants who did not convert from MCI to AD (56-62%). Individuals who converted from MCI to AD were also more likely to endorse most of the individual

neuropsychiatric symptoms than individuals who did not convert from MCI to AD during the study period. These results underscore the notion that neuropsychiatric symptoms may influence the progression and cognitive expression of AD-associated cognitive dysfunction independent of gender.

Limitations and Conclusions

In sum, this study achieved four main aims: 1) to model AD-associated cognitive dysfunction cross-sectionally and longitudinally, 2) to analyze gender differences in AD-associated cognitive dysfunction, 3) to examine whether neuropsychiatric symptoms mediate any gender effect on AD-associated cognitive dysfunction, and 4) to analyze whether gender or neuropsychiatric symptoms increased odds of conversion to AD. This study provided cross-sectional and longitudinal models of AD-associated cognitive dysfunction in IRT and SEM frameworks. In the ADNI sample, memory and language measures were the most sensitive to mild degrees of AD-associated cognitive impairment. In particular, the RAVLT measures of learning and free recall and the Category Fluency-Animals test provided the most information about cognitive dysfunction. Other cognitive measures functioned best at more moderate degrees of AD-associated cognitive dysfunction, corresponding to MCI and mild AD. The results also confirmed the expected pattern of individuals with AD performing worse than non-demented participants cross-sectionally. The participants with AD demonstrated linear rates of decline in all cognitive domains, whereas the non-demented participants showed flat, stable rates of change in their cognitive functions.

There were select gender differences in AD-associated cognitive dysfunction. Among those with AD, women had significantly worse memory dysfunction than men. Women with AD had marginally worse global cognitive dysfunction than men with AD at month 12. Women and men with AD had different rates of memory decline as well. The reverse pattern was true in the non-demented sample: men had worse global cognitive and memory performance than women. This moderation of gender differences in cognitive dysfunction by diagnostic status is interesting and raises additional questions. Does the AD neuropathological process somehow affect women differently, so that they have stronger memory performance when they are non-demented but then experience a sharper decline in memory than men also affected by AD? If AD does have a different neurobiological impact on women, then what causal factors are involved?

The hypothesis that neuropsychiatric symptoms would mediate a gender effect on cognitive dysfunction was generally not supported. Women had significantly worse memory dysfunction and a different rate of memory decline than men in the AD group, but this gender effect was not attenuated after controlling for neuropsychiatric symptoms. We need additional research to uncover what mechanisms might account for this important gender difference in AD-associated cognitive dysfunction.

Neuropsychiatric symptoms did mediate the effect of gender on executive/processing speed dysfunction, but only in the non-demented sample; non-demented men had worse executive/processing speed performance and higher levels of neuropsychiatric symptom severity. Controlling for neuropsychiatric symptoms reduced the gender difference for performance on executive/processing speed measures. It may

be that neuropsychiatric symptoms are more closely related to executive/processing speed problems in non-demented men than in non-demented women.

There are some limitations of the current study that should be noted. First, the ADNI neuropsychological battery has key weaknesses. This battery has several measures of verbal memory, but there are no measures of visual memory. In terms of language, there are only measures of semantic language and speech production, involving components of confrontation naming (Boston Naming Test) and verbal fluency (Category Fluency-Animals). Only ADNI1 contained any assessments of attention, but it was restricted to the WAIS-R Digit Span test. Neither the ADNI-GO nor ADNI2 neuropsychological batteries include measures of pure attention, although of course attentional abilities are implicit in other measures such as Trails A (visual processing). There are relatively few measures of executive abilities, especially complex executive functions that are known to decline early in AD. The only executive measure in the core ADNI neuropsychological battery was Trails B, which involves working memory, visual set shifting, and graphomotor speed. Finally, assessment of visuospatial abilities is restricted primarily to the Clock Drawing Test, which also is sensitive to executive functions (Royall, Mulroy, Chiodo, & Polk, 1999). The neuropsychological battery would have been strengthened by the inclusion of more complex measures that are sensitive to milder degrees of cognitive dysfunction, as well as additional measures to better assess a broader range of cognitive abilities, including basic attention, visual memory, executive functions, and visuospatial abilities.

Certain limitations of the ADNI sample relevant to gender should also be noted. Men are overrepresented in the ADNI sample, both among those with AD and those who were non-demented. Almost two-thirds of individuals in the United States with AD are women (Alzheimer's Association, 2015; Carter et al., 2012), but in this sample only 41% of the participants with a diagnosis of AD at month 24 were women. The Aging, Demographics, and Memory Study (Plassman et al., 2007) found that among Americans over the age of 71 years, 11.48% of women and 7.05% of men had AD; in this ADNI sample, 22.4% of women and 24.9% of men had AD by month 24. The rates of AD were higher in this sample because of ADNI's priority to recruit a clinical sample of participants with AD and MCI. Even so, more men had AD than women in the ADNI sample, which is contrary to the pattern in the general population. Even among the non-demented sample, only 44% were female. This sample characteristic is discrepant from the general population in the United States over the age of 65 years, of which approximately 56% are women (Administration on Aging et al., 2015).

There were also differences in marital status that may be pertinent to the results. In the general United States population of adults 65 years and older, 70% of men and only 45% of women are married; 12% of men and 34% of women are widowed (Administration on Aging et al., 2015). In the ADNI sample, approximately 88% of the male participants were married and 62% of the female participants were married. Women were much more likely to be widowed (19%) or divorced (14%) compared to the men in the sample (5% widowed and 5% divorced). The likelihood of being married was much greater in the ADNI sample than in the general United States population, but

the gender difference in marital status remained, with men being more likely to be married than women. Among the AD sample, 66% of women and 93% of men were married. Some studies have found that widowed and never-married older adults have faster rates of cognitive decline than married older adults (Karlamangla et al., 2009). This risk of faster cognitive decline may be due to social factors, since married older adults have a built-in social support in their spouse, whereas widowed and never-married older adults may have fewer social opportunities. Because a greater proportion of women in the ADNI sample were married than in the general population (62% vs. 45%, respectively), this might partially explain the fact that women in ADNI had lower levels of depression and anxiety than would be expected. The gender differences in marital status may also contribute to the varying rates of memory decline in women compared to men with AD, but it likely had a small effect since there were not any other significant gender differences in AD-associated cognitive trajectories.

Unfortunately, the ADNI database does not include information about cardiovascular disease, estrogen changes (e.g., age at menopause, use of hormone replacement therapy), or many other variables that may contribute to the gender gap in AD. In the current ADNI sample, men (M = 16.63, SD = 2.64) were significantly more educated than women (M = 15.44, SD = 2.78), although the mean difference was only one year. Despite this possible indicator of slightly higher cognitive reserve in the male participants, men actually performed more poorly than women in the non-demented sample. Instead, other factors (e.g., recruitment strategies) may have contributed to the pattern of gender differences in the ADNI sample. These non-representative

characteristics of men and women in ADNI unfortunately limit the generalizability of the present results to other populations.

Participants in ADNI had relatively mild degrees of neuropsychiatric problems, which also limits the generalizability of these results. Participants were excluded from ADNI if they had a history of major depression within the year prior to enrollment or if they exhibited notable agitation or behavioral problems that might interfere with their research study compliance. This may have created a restricted sample that is not representative of the general older adult population or the AD population. Some of the previous studies that have examined gender differences in neuropsychiatric symptoms have utilized nursing home samples (e.g., Buchanan et al., 2004; Zuidema et al., 2009), which are likely to be more cognitively and neuropsychiatrically impaired than the ADNI sample, which includes community-dwelling older adults. Thus, based on the characteristics of the ADNI sample, the results may not fully capture the role that neuropsychiatric symptoms play in AD-associated cognitive dysfunction.

Despite these limitations, the current study provided some key findings that have important implications. First, among the AD sample, women had worse memory performance than men and exhibited different rates of memory decline. Additional research should further explore this topic and seek to discover why this gender difference may exist. We need research that examines whether the AD neuropathological process differentially impacts women relative to men at a basic neurobiological level or whether other factors may be involved. Neuropsychiatric symptoms did not mediate this gender effect, but other sociocultural, psychological, or environmental factors may be

involved. There is likely a complex web of factors, including variables such as estrogen, cardiovascular disease, life expectancy, sociocultural roles and support, and psychological health that contribute to women's increased risk of developing AD. Although the current study was unable to determine the cause of the gender difference in AD, results add to the literature by clearly demonstrating the presence of a gender difference in memory and they rule out a contribution of neuropsychiatric symptoms in the ADNI sample. It is important to remember that these findings are not generalizable to the general older adult population, though, given the key limitations of the ADNI sample as described above. It is possible that neuropsychiatric symptoms might mediate gender differences in cognitive dysfunction in other AD samples.

Although neuropsychiatric symptoms did not mediate this gender effect on memory in the AD group, there was evidence that overall neuropsychiatric symptom severity increased odds of converting to AD. Results also showed that neuropsychiatric symptom severity interacted with time for decline in language functions. These initial findings are consistent with prior studies and suggest that neuropsychiatric symptoms may be a risk factor not only for converting to AD but also for faster cognitive decline. It is critical for clinicians to assess neuropsychiatric symptoms in older adults as a potential proxy for risk of converting to AD. Furthermore, clinicians should emphasize early treatment of these psychological symptoms to potentially decrease the rate of cognitive decline due to AD and improve psychological health. Finally, additional research should examine the role of neuropsychiatric symptoms in a more representative population of older adults, especially older adults with AD. Considering that women are more likely to

suffer from depression and anxiety throughout their lifetime and in late life, it may still be true that these negative affect symptoms influence cognitive dysfunction, despite the inability to clearly demonstrate that in the current study.

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