LONGITUDINAL IMPACTS OF CAREGIVER DISTRESS ON COGNITIVE AND NEUROANATOMICAL INDICATORS OF ALZHEIMER'S DISEASE SEVERITY

A Thesis

by

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes cognitive impairment, reduced functional status, and behavioral disturbances. As patients become increasingly impaired across these domains of functioning, they require greater assistance completing basic and instrumental activities of daily life. This assistance is overwhelmingly provided by informal caregivers. The adverse effects of increased AD severity on caregiver distress levels have been well documented in the literature. However, the reverse effects of baseline caregiver distress on future AD severity remain unknown. The present study used hierarchical linear regression to explore longitudinal downstream effects of baseline caregiver distress on cognitive and neuroanatomical indicators of AD severity. Analyses were completed using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (N = 184). Results indicated that baseline caregiver distress predicted cognitive status at both 12 and 24 months follow-up. Future research is needed to corroborate this finding, which may have significant clinical implications in regards to improving patient outcomes by alleviating caregiver distress.

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CHAPTER I

INTRODUCTION AND LITERATURE REVIEW

Alzheimer's disease Epidemiology and Pathology

Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes cognitive impairment, reduced functional status, and behavioral disturbances. With the rapid growth of the older adult (65 years and older) population over the last fifty years, AD has become one of the most pressing health concerns in the United States. AD affects more than 5 million American adults, almost two thirds of whom are women (Alzheimer's Association, 2016). A new case of AD is diagnosed approximately every 66 seconds (Alzheimer's Association, 2016), and it is currently the sixth leading cause of death in the United States (Alzheimer's Association, 2016; Centers for Disease Control, 2016).

While the exact etiology of AD remains unknown, evidence suggests that AD pathology is linked to abnormal deposits of proteins in the brain. These protein deposits form amyloid plaques and neurofibrillary tau tangles in and around neurons (National Institutes on Aging, 2016). As previously healthy neurons become diseased, they cease functioning, lose synaptic connections with surrounding neurons, and die (National Institutes on Aging, 2016). Progressive neuronal death results in atrophy, or shrinkage, of vital brain structures, leading to impairments in processes regulated by those structures, including cognitive, behavior, emotional, and adaptive function.

Caregiver Distress

As patients become increasingly impaired across these domains of functioning, they require greater assistance completing basic and instrumental activities of daily life. This assistance is overwhelmingly provided by informal caregivers, with more than 80% of long-term care for AD patients provided by informal caregivers (Alzheimer's Association, 2016). Informal caregivers are family members and friends who provide daily help and support to individuals who are either temporarily or permanently unable to function independently (Los Angeles County Department of Public Health, 2010). There are currently more than 15 million caregivers for Americans with AD and other dementias (Alzheimer's Association, 2016). 30% of dementia patients rely on three or more unpaid caregivers (Alzheimer's Association, 2016), partially explaining the 3 to 1 ratio of caregivers to patients. On a national scale, the time and financial costs of caregiving are astounding. In 2015, almost 16 million unpaid caregivers provided roughly 18 billion hours of care to patients with AD or other dementias, a contribution valued at more than $221 billion (Alzheimer's Association, 2016).

Looking more closely at the consequences of caregiver burden at an individual level, caregivers report significant financial burden related to their caregiving duties. Eighty-six percent of dementia caregivers have provided care and assistance for at least the past year, and caregivers of AD patients provide care for a longer time than do caregivers of older adults with other conditions (Alzheimer's Association, 2016). Approximately 1 out of 4 caregivers spends at least 36 hours weekly caring for an AD patient (American Psychological Association, 2006), which equates to roughly 32% of

their total waking hours in a given week. Often, caregiving obligations take time away from work (Alzheimer's Association, 2016), leading to lost wages and a decrease in income. Additionally, expenses directly related to care provision exceed an average of $5,000 annually per family (Alzheimer's Association, 2016). This is a considerably concerning figure given that 41% of caregivers have a household income of $50,000 or less (Alzheimer's Association, 2016).

Caregivers are also affected by adverse physical and psychological health issues. Caregivers are at increased risk of developing symptoms of anxiety or depression (Mahoney, Regan, Katona, & Livingston, 2006) and report increased physical ailments (Roth, Haley, Owen, Clay, & Goode, 2001; Vitaliano, Zhang, & Scanlan, 2003), poorer immune status (Fredman et al., 2008), and reduced health-related quality of life (Serrano-Aguilar, Lopez-Bastida, & Yanes-Lopez, 2006), relative to non-caregivers. Caregivers may also be at an elevated risk for all-cause mortality (Perkins et al., 2012; Talley & Crews, 2007). Thirty-four percent of caregivers are over the age of 65 (Alzheimer's Association, 2016) and are at an increased risk for the aforementioned health related issues due to their advanced age.

Effects of Neuropsychiatric Symptoms on Caregiver Distress

While caregivers of AD patients often report elevated levels of general distress (Alzheimer's Association, 2016), they are often particularly distressed by neuropsychiatric symptoms (Kaufer et al., 1998), perhaps even more than they are by cognitive impairments (Fauth & Gibbons, 2014; Fuh, Liu, Mega, Wang, & Cummings, 2001). Neuropsychiatric symptoms commonly observed among AD patients can be

generally grouped into three categories: behavioral disturbances, psychosis symptoms, and affective symptoms. Behavioral disturbances include aberrant motor behavior, changes in appetite, and sleep disturbances/nighttime behaviors. Psychosis primarily consists of hallucinations and delusions. Affective symptoms include feelings of depression, anxiety, and apathy.

Patients may present with different constellations of symptoms, based on comorbid conditions and their stage in the disease process. For example, symptoms of depression and anxiety have been reported to be predictive of conversion from mild cognitive impairment to AD (Gallagher et al., 2011; Palmer et al., 2007), while hallucinations and delusions are more likely to be observed at a higher level of AD severity (Fuller, Choudhury, Lowe, & Balsis, 2016). Estimated prevalence rates of individual neuropsychiatric symptoms within the AD population vary, but evidence suggests that symptoms of apathy or indifference are some of the most frequently reported (Fauth & Gibbons, 2014; Kaufman et al., 1998; Mega, Cummings, Fiorello, & Gornbein, 1996). Agitation, anxiety, and irritability (Fauth & Gibbons, 2014; Mega, Cummings, Fiorello, & Gornbein, 1996) are also commonly observed neuropsychiatric symptoms among AD patients.

There are many factors that influence which neuropsychiatric symptoms are most distressing and why. While symptoms of apathy and agitation are often cited as two of the most frequently observed symptoms in AD patients, these symptoms are not necessarily described as the most distressing. As such, the relationship between frequency of symptom presentation and resulting distress remains unclear (Fauth &

Gibbons, 2014; Mioshi, Bristow, Cook, & Hodges, 2009). Research suggests that while frequently observed neuropsychiatric symptoms, such as symptoms of apathy and anxiety, are often very distressing to caregivers (Fuh, Liu, Mega, Wang, & Cummings, 2001; de Vugt et al., 2006), some of the most distressing neuropsychiatric symptoms are less frequently observed, such as delusions (Fauth & Gibbons, 2014; Fuh, Liu, Mega, Wang, & Cummings, 2001). Frustration or distress related to neuropsychiatric symptoms may also vary as the disease progresses, with higher levels of distress often observed at onset and lower levels observed as the disease continues (Motenko, 1989), despite the likelihood of neuropsychiatric symptoms increasing as the disease progresses and cognition declines (Ricci et al., 2009). In sum, caregiver distress may arise differentially across symptoms and stages of AD severity.

Research on patients' neuropsychiatric symptoms and resulting caregiver distress has often included use of the Neuropsychiatric Inventory (NPI; Cummings, 1997), one of the most commonly used measures of neuropsychiatric symptoms in both clinical and research settings with documented reliability and validity (Cummings et al., 1994; Cummings, 1997). The NPI is a clinician-administered structured interview protocol that assesses the presence, frequency, and severity of 12 neuropsychiatric symptoms: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behaviors, and appetite/eating. In addition to evaluating the symptoms themselves, caregivers are asked to rate their subjective levels of distress in response to those symptoms, from "not at all" to "very severely or extremely"

distressing. It is important to note that the NPI prompts respondents to consider their distress in response to the designated neuropsychiatric symptoms specifically, rather than their global distress in response to the disease overall.

The relationship between patients' neuropsychiatric symptoms and caregiver distress has been studied frequently using the NPI and is well documented in the literature (Clyburn, Stones, Hadjistavropoulos, & Tuokko, 2000; Craig, Mirakhur, Hart, McIlroy, & Passmore, 2005; Kaufer et al., 1998). As neuropsychiatric symptoms worsen in concordance with increasing AD severity, caregiver distress also increases. These findings have highlighted the importance of pharmacological treatment of neuropsychiatric symptoms as well as psychoeducational interventions to prepare caregivers, with the primary goal of alleviating distress. Interestingly, there is currently little to no examination of the impact of caregiver distress on AD severity. Specifically, neuropsychiatric symptoms are shown to have an effect on caregiver distress, which may in turn have downstream effects on other of AD severity, such as cognitive impairment and neurodegeneration.

Effects of Caregiver Distress on Alzheimer's disease Severity

If indeed increased caregiver distress contributes to increased AD severity, as reflected by changes in cognitive or neuroanatomical indicators, this phenomenon may be partially attributable to the close nature of the caregiver/patient relationship, the importance of which is undisputed. Caregivers often play a prominent role, if not the only role, in an AD patient's life. As such, the relationship between patient and caregiver is especially intimate and important. After prolonged contact and interaction, patients'

neuropsychiatric symptoms become troublesome for caregivers. Conversely, emotional distress in caregivers may have a more salient adverse effect on patient functioning (presumably due to increased AD severity). Increased AD severity may then lead to increased neuropsychiatric symptoms which then lead to increased caregiver distress, creating a cycle of increasingly troublesome caregiver distress and patient AD severity. If this cyclical relationship exists, then the motivation for treating neuropsychiatric symptoms and educating caregivers goes beyond simply alleviating caregiver distress. Treating neuropsychiatric symptoms, which may in turn result in reduced caregiver distress, may contribute to slower, even if minimally, disease progression. Before this cyclical relationship can be established, however, we must first establish that caregiver distress indeed has downstream effects on cognitive or neuroanatomical aspects of AD severity in the early stage of the disease.

Various animal and human subjects studies have shown that long-term or chronic stress can result in damage to areas of the brain such as the hippocampus (Bremner, 1999; Carrion, Weems, & Reiss, 2007; Frodl & O'Keane, 2013), one of the primary structures affected in early AD. In these studies, hippocampal volume reduction was documented with magnetic resonance imaging (MRI) data and inferred from deficient performance on neuropsychological measures reflective of hippocampal function (Bremner, 1999; Carrion et al., 2007; Frodl & O'Keane, 2013). Evidence suggests that hippocampal damage is mediated through neurotoxicity secondary to increased cortisol exposure and possible neuroinflammation, a theory known as the glucocorticoid cascade hypothesis (Frodl & O'Keane, 2013; Sapolsky, Krey, & McEwen, 1986). While the

hypothesized mechanism through which hippocampal damage is inflicted is complex, findings from studies in this area have been robust and consistent.

In addition to chronic stress, various anxiety-related and depressive disorders have been associated with adverse changes in both anatomy and physiology of the hippocampus as well as other areas, such as the amygdala and the prefrontal cortex (Lupien, McEwen, Gunnar, & Herim, 2009; McEwen, 2007). These disorders include posttraumatic stress disorder (Bremner, 2002) and major depressive disorder (Rajkowska, 2000; Sheline, Gado, & Price, 1998; Stockmeier et al., 2004).

Presently, this area of literature has focused on intrapersonal processes; specifically, the same individual who has experienced intense stress demonstrates hippocampal volumetric and functional deficits. Extending this methodology, one may consider interpersonal processes and examine the possible effects of intense stress experienced external to the individual. That is to say, can stress (or relatedly, anxious or depressed mood) experienced by someone in an individual's environment have similar effects on his or her brain? If so, then caregiver of AD patients, who are known to be at elevated risk of experiencing frequent and severe bouts of stress and poor mood, may be inadvertently negatively affecting their loved ones at a molecular level.

If caregiver distress can be considered as a potential aggravator of AD severity, then caregiver contentment can be considered as a potential protective factor against disease progression. Caregivers who are relatively less chronically distressed are presumably more able to maintain a strong, positive relationship with their patients. A healthy caregiver-patient relationship can be a significant asset for AD patients, who, as

stated previously, often have very few meaningful social connections left as the disease progresses. While a fractious caregiver-patient relationship may qualify as a psychosocial risk factor for adverse health outcomes (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), a strong caregiver-patient relationship can promote social support and reduce loneliness for the patient, both of which have been documented as protective factors across a wide variety of diagnoses (Heinrichs et al., 2003; McEwen, 2007). When considering AD specifically, a handful of studies have found that social connectedness is a protective factor against incidence of dementia (Fratiglioni, Hui-Xin, Ericsson, Maytan, & Winblad, 2000) and cognitive dysfunction secondary to AD pathology (Bennett, Schneider, Tang, Arnold, & Wilson, 2006). In sum, the nature of the caregiver-patient relationship, impacted substantially by caregiver distress, may result in subtle but meaningful changes in an AD patient's disease severity.

Indicators of Alzheimer's disease Severity

Because AD is a multifaceted disease that affects an individual at the anatomical, physiological, and functional levels, AD severity cannot simply be operationalized as change in one particular variable or be represented by one indicator alone. Furthermore, changes observed in certain indicators (namely, cognitive functioning and neuropsychiatric symptoms) may be attributable to etiological factors other than AD pathology or may simply be typical of normal aging. For example, cognitive change associated with normal aging has been well documented in the literature (Erickson & Barnes, 2003; Harada, Love, & Triebel, 2013) and is observed in individuals who never go on to develop AD. Cognitive decline is also associated with separate psychiatric and

medical conditions, including depression (Rodda, Walker, & Carter, 2011) and various vascular conditions (Gorelick et al., 2011). Neuropsychiatric symptoms such as changes in mood, appetite, and sleep may be caused by a psychiatric condition, such as depression (Fiske, Wetherell, & Gatz, 2009; Rodda, Walker, & Carter, 2011), or hormonal changes, such as those related to menopause (Lamberts, van den Beld, & van der Lely, 1997). Certain neuroanatomical changes, such as volume loss, are also associated with normal aging (Raz et al., 2011; Scahill et al., 2003). However, accelerated atrophy within the temporal lobe is associated with dementing conditions, such as AD, specifically (Chan et al., 2001; Jack et al., 1998).

To account for the multiple types of impairment that characterize AD and address possible confounding causes of those impairments, AD severity is often operationalized across multiple domains of AD-associated symptoms within one study. Specifically, global cognitive decline and neurodegeneration are two domains that are documented in the literature as being associated with or related to AD pathology (Balsis et al., 2016; Jack et al., 2010; 2013) and capture unique aspects of the disease process. Cognitive decline is apparent in AD patients but not exclusively associated with AD pathology. Including measures of neurodegeneration will allow for a stronger causal link to be established between present caregiver distress and future AD severity. Additionally, by examining the possible relationship between caregiver distress and each of different AD severity domains, we may be able to ascertain if caregiver distress affects each domain differentially. More specifically, current caregiver distress may be more strongly associated with future cognitive decline than with neurodegeneration.

Effects of Demographic Variables on Caregiver Distress

Caregiver distress may vary in response to variations in symptoms or AD severity, but it may also be affected by demographic variables, such as caregiver gender, as well as the nature of the relationship between the caregiver and the patient. Approximately two thirds of caregivers are women (Alzheimer's Association, 2014; Kasper, Freedman, & Spillman, 2014); more specifically, over one third of dementia caregivers are daughters (Langa et al., 2005). More than half of caregivers take care of one or both parents (Fisher et al., 2011), but this is not limited to adults. As many as 250,000 children and adolescents between 8 and 18-years-old provide help to an AD patient (National Alliance for Caregiving & United Hospital Fund, 2005). In regards to spousal care, it is more common for wives to provide informal care for a husband than vice versa (National Alliance for Caregiving & AARP, 2009). Collectively, whether the caregiver is a spouse or child, female caregivers (i.e. wives and daughters) are more likely to experience higher levels of burden and distress related to caregiving than their male counterparts (Alzheimer's Association, 2016; Lutzky & Knight, 1994). Despite the availability of epidemiological data to characterize the population of caregivers and identify possible factors in caregiver distress, the exact mechanism of distress onset or exacerbation remains unknown. Examining variance in caregiver distress across different types of caregivers (for example, spouse versus child) may reveal groups of caregivers who are more vulnerable to subjective distress and therefore require tailored preparation or intervention.

Present Study

Through this study, we sought to take the first steps towards understanding the possible adverse effects of caregiver distress on patient AD severity, which may have several important research and clinical implications. To do this, we first examined the effects of patient demographic variables on caregiver distress to determine which, if any, variables should be statistically controlled for subsequent analyses. Second, we determined if baseline caregiver distress had downstream effects on future cognitive or neuroanatomical indicators of AD severity, controlling for baseline cognitive status and neuroanatomical volumes. Given these aims, we hypothesized that the patient's gender, baseline diagnosis, and education level would have an effect on caregiver distress. We also hypothesized that baseline caregiver distress would account for unique variance in future AD severity, controlling for baseline cognitive status and neuroanatomical volumes.

CHAPTER II

METHODS

Data used in the preparation of this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, adni.loni.usc.edu. The ADNI was launched in 2003 as a public-private partnership. The initial goal of ADNI was to recruit 800 participants but ADNI has been followed by two other initiatives, ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research. The sample consists of older adults who are cognitively healthy, those with early or late mild cognitive impairment (MCI), and those with early AD. Demographic information and clinical data used for this study were downloaded from the ADNI data repository (adni.loni.usc.edu) on May 28, 2014. Data for the current analyses came from individuals who completed baseline and follow-up assessments and had complete data for key neuropsychiatric, cognitive, and MRI variables described below.

Participants

Sample Selection

The analyses for the present study used data from baseline, 12, and 24-months follow-up from participants enrolled across all three ADNI phases. The effects of caregiver distress on cognitive or neuroanatomical indicators of AD severity may not be immediately detectable by statistical analysis. As such, using data from 12 and 24 months follow-up us to examine changes in outcome data over time and detect subtle effects. Demographic data, including age, gender, education level, race, and marital

status were mined for each participant. Baseline diagnosis was also recorded. In this dataset, baseline diagnoses represented a range of cognitive impairment, from cognitively normal through mild cognitive impairment (MCI) to presumed mild AD. Cognitively normal participants were included to capture potential conversion from baseline to 12 months follow-up, thereby reflecting the continuum of normal aging to dementia. In the ADNI, cognitively normal participants serve as the controls and show no signs of MCI or dementia.

Participants were excluded from the analyses if they had a premorbid history of significant neurologic disease (including multi-infarct dementia and subdural hematoma), as well as various neuropsychiatric disorders such as major depressive disorder, schizophrenia, and bipolar disorder. Participants were also excluded based on absent or incomplete baseline or follow-up data. After an iterative procedure of eliminating cases with absent or incomplete data, the final sample size was N = 184.

Measures

AD severity was operationalized across two categories of AD-associated symptoms: global cognitive decline and neurodegeneration. To characterize global cognitive status, ADNI participants were given the Alzheimer's Disease Assessment Scale (ADAS-cog; Mohs & Cohen, 1988). Structural MRI scans were used to assess volume of the whole brain as well as cortical volumes of three temporal lobe regions: the entorhinal cortex, hippocampus, and middle temporal gyrus. Together, these measures were used to operationalize AD severity. The Neuropsychiatric Inventory (NPI; Cummings, 1997) was used to asses for frequency and severity of neuropsychiatric

symptoms, as well as caregiver distress in response to those symptoms. For this study, we used data from baseline (0 months), 12, and 24 months follow-up. The procedures used for each of these domains are briefly described below (full description online at adni.loni.usc.edu).

Global Cognitive Status

Neuropsychological measures of screening and staging are commonly used in clinical research to characterize global cognitive status. One of the clinician-administered measures used in the ADNI is the Alzheimer's Disease Assessment Scale (ADAS-cog; Mohs & Cohen, 1988). While additional cognitive screening and staging measures are given to ADNI participants, such as the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), we only used the ADAS-cog for this study. The ADAS-cog is more specific to AD-related cognitive impairment, while the MMSE is not disorder-specific. Additionally, the ADAS-cog is scored out of 70 points, as opposed to the 30-point scale used on the MMSE. This allowed for increased measurement precision that reflected wider variability in performance on the ADAS-cog and consequently more accurate characterization of participants' cognitive status. The ADAS-cog consists of 11 tasks measuring disturbances of memory, language, praxis, and attention. ADAS-cog scores are reported as errors made out of 70 points total (i.e. higher scores correspond to more compromised cognitive status).

MRI Volume.

Structural MRI scans enable volumetric measurements of the entire brain as well as specific neuroanatomical regions, which can indicate patterns of volumetric changes

and brain atrophy associated with AD. This study examined MRI volumes (cubic millimeters) of the whole brain and three temporal lobe brain sub-regions implicated in the neurodegenerative component of AD pathology: the entorhinal cortex, hippocampus, and the middle temporal gyrus. All MRI volumes were corrected for variance due to participant age and gender using linear regression. MRI volumes for the three sub-regions were also corrected for intracranial volume. The residual values that were derived from the regression analyses were used for all subsequent analyses.

Neuropsychiatric Symptoms

The NPI (Cummings, 1997) was administered to caregivers to assess the presence, frequency, and severity of 12 neuropsychiatric symptoms: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behaviors, and appetite/eating. Presence is scored on a binary scale ("yes" or "no"). Frequency is rated on a four-point scale as follows: 1 for "rarely", 2 for "sometimes", 3 for "often", and 4 for "very often". Severity is rated on a three-point scale as follows: 1 for "mild", 2 for "moderate", and 3 for "severe". Tables 1a and 1b illustrate the rating schemas, including operational definitions, for both frequency and severity. A total NPI score can be calculated by adding the frequency and severity ratings together for all endorsed symptoms (Cummings, 1997).

Caregiver Distress

The NPI (Cummings, 1997) was also administered to caregivers to assess subjective levels of distress in response to neuropsychiatric symptoms. Caregivers were

asked to rate their own distress levels on a six-point scale as follows: 0 for “not at all”, 1 for “minimally distressing”, 2 for “mildly distressing”, 3 for “moderately distressing”, 4 for “severely distressing”, and 5 for “very severely or extremely distressing”. Table 1c illustrates the rating schema, including operational definitions, for caregiver distress. For this study, we calculated a total caregiver distress score by summing distress ratings across all endorsed symptoms in order to capture variance in both intensity and breath of caregiver distress. While the total distress metric is described by Cummings as part of the repertoire of results that can be derived from the NPI (1997), these values were not listed in the ADNI database and therefore were calculated manually during the data analysis phase.

Data Analyses

SPSS Statistics 22.0 (IBM, 2013) was used to perform all analyses in this study. To characterize the sample of patients, we generated descriptive statistics (means and standard deviations) and frequencies for baseline data for the six demographic/clinical variables: age, gender, education level, race, marital status, and baseline diagnosis. Sample characteristics are described in greater detail in the Results section. Descriptive statistics for NPI results were also generated, including frequencies of endorsed symptoms and mean severity and caregiver distress ratings across symptoms. Repeated measures analysis of variance (ANOVA) was used to determine if sample characteristics for NPI results differed significantly across time points.

In the next part of the analyses, we used one-way ANOVA to examine the effects of categorical participant demographic variables on baseline caregiver distress (gender,

race, marital status, and baseline diagnosis), using $p < 0.05$ as the significance threshold. Pearson product-moment correlation coefficients (Pearson's r) were generated between the continuous participant demographic variables (age, education level, baseline residual neuroanatomical volumes, and baseline ADAS-cog score) and baseline caregiver distress. We again used $p < 0.05$ as the significance threshold. The results of these initial analyses were used to determine which, if any, demographic variables must be controlled for in subsequent analyses.

The third part of the analyses featured hierarchical linear regression to examine the effects of baseline caregiver distress on future AD severity. Categorical demographic variables (gender, marital status, race, and baseline diagnosis) were dummy coded using zeroes and ones prior to this phase of the analyses. Each regression model consisted of seven steps. In the first four steps of the regression, we entered only demographic variables (age, gender, education level, marital status, race, and baseline diagnosis) to control for their effects on future AD severity. Specifically, age, gender, and education level were entered in step one. Baseline diagnosis (dummy coded) was entered in step two. Race (dummy coded) was entered in step three, and marital status (dummy coded) was entered in step four. In the fifth and sixth steps of the model, we entered baseline ADAS-cog score and baseline residual neuroanatomical volumes as predictor variables, respectively. In the seventh and final step, we entered baseline caregiver distress in response to all endorsed neuropsychiatric symptoms as a predictor variable to determine if it accounted for unique variance above and beyond the previously entered predictors. Figure 1 graphically illustrates the structure of this section of the regression analyses.

Within this phase of the analyses, the outcome variable was changed to reflect the two operational definitions of AD severity used in this study: cognitive dysfunction (ADAS-cog score) and neurodegeneration (whole brain and temporal lobe volumes). Figure 2 illustrates the final step of each model with the outcome variable changed. As each hierarchical regression consisted of 7 steps, this phase of the analyses ultimately featured 35 regression equations in total (7 steps per hierarchical regression *x* 5 operational definitions of AD severity). Both models (cognitive dysfunction and neurodegeneration as outcome variables) were replicated using data from 24 months follow-up in addition to 12 months follow-up, as illustrated in Figure 3. Consequently, we derived 35 additional regression equations divided into 5 models. In total, we generated 70 regression equations divided into 10 models, as illustrated in Figure 4.

CHAPTER III

RESULTS

Sample Characteristics

The analyses for the present study used baseline data from 184 participants (87 female, 47%) enrolled across all three ADNI phases. At baseline, participants were an average of 71.63 years old (*SD* = 6.82), with ages ranging from 55 to 90. Participants were also highly educated (*M* = 16.49, *SD* = 2.58 years), with all participants having completed at least the 11th grade. The majority identified their race as white (*n* = 175, 95%); other races represented included black or African American (*n* = 6, 3%), Asian (*n* = 2, 1%), and Hawaiian/Pacific Islander (*n* = 1, 0.5%). In regards to marital status, the majority of participants were married at the time of the baseline assessment (n = 139, 76%). 17 (9%) were widowed, 24 (13%) were divorced, and 4 (2%) were never married.

Baseline diagnoses represented a range of cognitive impairment: 73 (40%) were cognitively normal and 103 (56%) had MCI. Eight participants (4%) had presumed Alzheimer's dementia at baseline. We included the cognitively normal (CN) participants in order to capture possible conversion in diagnostic status over the course of the analyses. Mean total NPI score was 3.32 (SD = 6.21), and mean caregiver distress rating across the 12 neuropsychiatric symptoms assessed was 0.17 (SD = 0.28). Mean ADAS-Cog score was 8.43 (SD = 4.60). Residual values for MRI volumes ranged from -242462.23 mm^3 to 206685.68 mm^3 for the whole brain. Residual values for MRI volumes of temporal lobe sub-regions ranged from -2089.36 mm^3 to 2122.12 mm^3 for

the hippocampus, -2197.50 mm^3 to 2072.57 mm^3 for the entorhinal cortex, and -7668.04 mm^3 to 6174.58 mm^3 for the middle temporal gyrus.

Neuropsychiatric Symptom Characteristics

Neuropsychiatric symptoms and associated caregiver distress were characterized for the sample at baseline, 12 months, and 24 months follow-up. At baseline, the mean total NPI score was 3.32 (SD = 6.21). At 12 months follow-up, the mean total NPI score was 3.86 (SD = 6.60), and at 24 months follow-up, the mean total NPI score was 5.44 (SD = 9.56). At baseline, the highest observed total NPI score was 43. At 12 months follow-up, the highest observed total NPI score was 47, and at 24 months follow-up, the highest observed total NPI score was 61, 18 points greater than the highest observed score at baseline. Repeated measures ANOVA was used to compare mean total NPI score across baseline, 12 months, and 24 months follow-up. Mean total NPI score at baseline was significantly different from mean total NPI score at 24 months follow-up ($p < 0.05$). Mean total NPI score at 12 months follow-up was also significantly different from mean total NPI score at 24 months follow-up ($p < 0.05$). Figure 5 illustrates the marginal means for mean total NPI score from baseline through 24 months follow-up for the entire sample.

In regards to symptom frequency, most frequently endorsed symptom at baseline was depression/dysphoria (N = 36, 20%), followed by irritability/lability (N = 34, 19%), and sleep disturbance (N = 32, 17%). All neuropsychiatric symptoms were endorsed by at least one caregiver at baseline. At 12 months follow-up, the most frequently endorsed symptom was irritability/lability (N = 37, 20%), followed by depression/dysphoria (N =

36, 20%) and sleep disturbance (N = 36, 20%). All neuropsychiatric symptoms were endorsed by at least one caregiver at 12 months follow-up. At 24 months follow-up, the most frequently endorsed symptom was irritability/lability (N = 42, 23%), followed by depression/dysphoria (N = 38, 21%), and apathy/indifference (N = 36, 20%). Again, all neuropsychiatric symptoms were endorsed by at least one caregiver at 24 months follow-up. Figures 6a and 6b illustrate the distribution of symptom endorsement from baseline through 12 and 24 months follow-up for the entire sample.

Average symptom severity rating varied from 0.13 (SD = 0.21) at baseline to 0.14 (SD = 0.20) at 12 months and 0.17 (SD = 0.27) at 24 months follow-up for the entire sample. At baseline, 3 symptoms were rated by at least one caregiver as markedly severe: delusions, sleep disturbance, and disordered appetite/eating. At 12 months follow-up, 5 symptoms were rated by at least one caregiver as markedly severe: anxiety, disinhibition, irritability/lability, sleep disturbance, and disordered appetite/eating. At 24 months follow-up, 8 symptoms were rated by at least one caregiver as markedly severe: delusions, agitation/aggression, depression/dysphoria, anxiety, disinhibition, irritability/lability, aberrant motor behavior, and sleep disturbance. Figures 7a and 7b illustrate the distribution of severity ratings per symptom from baseline through 12 and 24 months follow-up for only those caregivers who endorsed the presence of a symptom to begin with.

Caregiver Distress Characteristics

In regards to caregiver distress related to neuropsychiatric symptoms, average distress ratings varied from 0.17 (SD = 0.28) at baseline to 0.18 (SD = 0.30) at 12

months and 0.24 (SD = 0.42) at 24 months follow-up for the entire sample. At baseline, three symptoms were described by at least one caregiver as very severely or extremely distressing: anxiety, sleep disturbance, and disordered appetite/eating. At 12 months follow-up, none of the symptoms were described as very severely or extremely distressing. At 24 months follow-up, a different set of three symptoms were described by at least one caregiver as very severely or extremely distressing: agitation/aggression, depression/dysphoria, and irritability/lability. Figures 8a and 8b illustrates the distribution of caregiver distress ratings per symptom from baseline through 12 and 24 months follow-up for only those caregivers who endorsed the presence of a symptom to begin with.

In addition to mean distress ratings, total distress ratings across symptoms were calculated by summing individual distress ratings for each symptom per caregiver. Higher total distress ratings corresponded to greater numbers of symptoms rated as distressing. In other words, a mean distress rating of 3 could be derived from simply one response (i.e. "Symptom A elicits a distress rating of 3; no other symptoms are distressing.") or from three responses (i.e. "Symptom A elicits a distress rating of 2, Symptom B elicits a distress rating of 3, and Symptom C elicits a distress rating of 4."). While both caregivers would receive a mean rating score of 3, the second caregiver was clearly distressed by a larger number of symptoms than was the first. Hence, total distress rating values were calculated to capture additional variance in breadth of distress.

At baseline, the mean total distress rating score was 1.99 (SD = 3.37). At 12 months follow-up, the mean total distress rating score was 2.16 (SD = 3.57), and at 24 months follow-up, the mean total distress rating score was 2.86 (SD = 5.00). At baseline, the highest observed total distress rating score was 17. At 12 months follow-up, the highest observed total distress rating score was 24, and at 24 months follow-up, the highest observed total distress rating score was 25, 8 points greater than the highest observed score at baseline. Repeated measures ANOVA was again used to compare mean total distress scores across baseline, 12 months, and 24 months follow-up. Mean total distress score at baseline was significantly different from mean total distress score at 24 months follow-up ($p < 0.05$). Mean total distress score at 12 months follow-up was also significantly different from mean total distress score at 24 months follow-up ($p < 0.05$). Figure 9 illustrates the marginal means for mean total distress score from baseline through 24 months follow-up for the entire sample.

Effects of Patient Demographics on Baseline Caregiver Distress

Pearson product-moment correlation coefficients (Pearson's r) were generated between continuous patient demographic variables (age, education level, baseline residual temporal lobe volumes, and baseline ADAS-cog score) and baseline caregiver distress. The correlation between patient's age and baseline caregiver distress was $r = -0.03$ ($p > 0.05$), and the correlation between patient's education level and baseline caregiver distress was $r = -0.18$ ($p < 0.05$). The correlation between baseline residual whole brain volume and baseline caregiver distress was $r = -0.13$ ($p > 0.05$).The correlation between baseline residual hippocampus volume and baseline caregiver

distress was $r = -0.10$ ($p > 0.05$). The correlation between baseline residual entorhinal cortex volume and baseline caregiver distress was $r = -0.13$ ($p > 0.05$), and the correlation between residual middle temporal gyrus volume and baseline caregiver distress was $r = -0.04$ ($p > 0.05$). The correlation between baseline ADAS-cog score and baseline caregiver distress was $r = 0.21$ ($p < 0.05$). Table 2 lists Pearson's r values and p-values for the correlations described above.

One-way analysis of variance (ANOVA) was used to examine the effects of categorical patient demographic variables (gender, marital status, race, and baseline diagnosis) on baseline caregiver distress. Patient race and baseline diagnosis were found to significantly affect baseline caregiver distress ($p < 0.05$); the remaining variables were found not to significantly affect baseline caregiver distress. Post hoc comparisons using the Tukey Honestly Significant Different (HSD) test revealed that baseline caregiver distress was significantly lower for caregivers of cognitively normal patients compared to caregivers of patients with mild cognitive impairment or AD. Post hoc comparisons could not be conducted for patient race because one category (Hawaiian/Pacific Islander) consisted of only 1 participant. Table 3 lists F statistics and p-values for the four one-way ANOVA analyses described above.

Effects of Baseline Caregiver Distress on Future Alzheimer's disease Severity

Hierarchical linear regression was used to examine the effects of baseline caregiver distress on cognitive and neuroanatomical indicators of AD severity. Entering baseline caregiver distress as a predictor significantly improved the model when ADAS-cog score was used as the outcome variable for both 12 months and 24 months follow-up

($p < 0.05$), suggesting that variance in baseline caregiver distress does account for variance in future cognitive dysfunction. Significant results at both 12 and 24 months follow-up suggest that this effect does hold over time. Entering baseline caregiver distress as a predictor did not significantly improve the model when residual whole brain or temporal lobe volumes were used as the outcome variables for neither 12 months nor 24 months follow-up. However, results did trend towards significance when comparing 12 months to 24 months follow-up. Consequently, it may be that effects on future neuroanatomical atrophy do arise as a result of baseline caregiver distress, but these effects may be extremely subtle and manifest at a much slower rate. Results of the regression analyses are presented in Tables 4a through 4j.

CHAPTER IV

DISCUSSION

The purpose of this study was to take the first steps towards understanding the possible adverse effects of caregiver distress on patient AD severity. Results indicated that entering baseline caregiver distress as a predictor significantly improved the model when ADAS-cog score was used as the outcome variable for both 12 months and 24 months follow-up, suggesting that variance in baseline caregiver distress does account for variance in future cognitive dysfunction. Significant results at both 12 and 24 months follow-up suggest that this effect does hold over time. Entering baseline caregiver distress as a predictor did not significantly improve the model when residual whole brain on temporal lobe volumes were used as the outcome variables for neither 12 months nor 24 months follow-up. However, results did trend towards significance, as indicate by considerable declines in p-values, when comparing 12 months to 24 months follow-up. Consequently, it may be that effects on future neuroanatomical atrophy do arise as a result of baseline caregiver distress, but these effects may be extremely subtle and manifest at a much slower rate.

The mechanism through which baseline caregiver distress in response to neuropsychiatric symptoms predicts future cognitive status (as characterized by ADAS-cog scores) is unclear. Based on preliminary findings discussed previously in the introduction, it may be the case that increased caregiver distress leads to reduced social connectedness, which has been found to be a protective factor against incidence of dementia (Fratiglioni et al., 2000) and cognitive dysfunction secondary to AD pathology

(Bennett et al., 2006). Alternatively, caregiver distress may compromise the quality of care that an AD patient receives, which may facilitate faster decline. For example, caregivers who become increasingly distressed without adequate tools to manage their distress may become despondent or detached. This in turn may reduce the degree of interpersonal connectedness (described above) between caregiver and patient. Furthermore, it may increase feelings of distress in the patient, which in turn may result in impaired cognitive function.

While we did not encounter significant effects for predicting future residual temporal lobe volumes from baseline caregiver distress, our results did trend towards significance when comparing 12 months to 24 months follow-up. This trend is noteworthy as it suggests that prolonged longitudinal follow-up of patients may reveal that baseline caregiver distress does in fact impact neuroanatomy over time, albeit very slowly and minimally. Nonetheless, such a finding may have meaningful clinical implications, including diagnosis and treatment planning, but further investigation of this potential effect is needed.

While these preliminary findings are intriguing, limitations of this study (largely based in data availability and design) likely impacted the results. First, a larger sample size would have increased our power in detecting a statistically significant effect. Our small sample size (N = 184) was derived after eliminating participants for whom there was missing or incomplete key data across the three time points (baseline, 12, 24 months follow-up). Additionally, the probability of detecting an effect may have increased had we included data from additional time points, such as 36 or 48 months follow-up.

However, given the population, participants were at increased risk of mortality as time went on; as such, in order to maximize our sample size, we did not extend our data mining beyond 24 months follow-up. In regards to study design, our list of indicators to operationalize disease severity was not exhaustive, nor were they perfect. However, we extrapolated based on the research and included indicators that are strongly linked to AD pathology. Finally, we were unable to examine the effect of the nature of the caregiver-patient relationship as this data was not included in the ADNI dataset. Future research should address all of these limitations by utilizing a larger sample with more extensive longitudinal follow-up and operationalization of AD severity across multiple measurable indicators, such as functional status and neurophysiology.

CHAPTER V

SUMMARY AND CONCLUSIONS

Results from this study may help us understand the role that caregiver distress plays when considering the global impact of AD within a dyad. Understanding the reciprocal effects that caregiver distress and AD severity may have on each other has many clinical implications. Identifying patient demographic variables that affect caregiver distress, such as age or gender, can help clinicians proactively monitor patients who are at risk to elicit increased distress from their caregivers. Furthermore, because baseline caregiver distress was found to significantly predict cognitive status over time, there may be incentive to treat caregiver distress to indirectly mitigate this aspect of AD progression. Additionally, if a feedback loop exists wherein caregiver distress contributes to future AD severity, which in turn causes increased caregiver distress, this preliminary study may facilitate future research into this cyclical model of the distress/severity relationship. Consequently, we will have greater understanding of the nature of AD pathology, as well as socio-structural risk factors for and protective factors against increased disease severity. Finally, identifying groups of caregivers who are more likely to experience elevated levels of distress may allow for more tailored psychotherapeutic interventions and psychoeducation to reduce caregiver distress and improve caregiving outcomes.

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APPENDIX A

TABLES

Page

APPENDIX B

FIGURES

Page

Table 1a

NPI rating schemas for symptom frequency

Rating	Descriptor	Operational Definition
1	Rarely	Less than once a week
2	Sometimes	Roughly once a week
3	Often	Many times a week but less than every day
4	Very often	At least once or more daily

Table 1b

NPI rating schemas for symptom severity

Rating	Descriptor	Operational Definition
1	Mild	Symptom is present but appears harmless and produces minimal distress
2	Moderate	Symptom is distressing and disruptive
3	Severe	Symptom is very distressing and extremely disruptive

Table 1c

NPI rating schemas for caregiver distress

Rating	Descriptor	Operational Definition
0	Not at all	---
1	Minimally	Symptom causes virtually no change in routine
2	Mildly	Symptom causes almost no change in routine but minimal time rebudgeting is necessary
3	Moderately	Symptom disrupts routine and time rebudgeting is necessary
4	Severely	Symptom disrupts routine, upsets others, and is a major time infringement
5	Very severely or extremely	Symptom is very disruptive, a major source of distress for others, and requires time usually devoted to other people or tasks

Table 2

Correlations between continuous patient demographic variables and baseline caregiver distress

Correlated Variables	Pearson's r Value	p-value
Age *x* Baseline Caregiver Distress	-0.03	0.71
Education *x* Baseline Caregiver Distress	-0.18	0.01*
Baseline ADAS-cog *x* Baseline Caregiver Distress	0.21	0.00*
Baseline Residual Whole Brain Volume *x* Baseline Caregiver Distress	-0.13	0.07
Baseline Residual Hippocampus Volume *x* Baseline Caregiver Distress	-0.10	0.18
Baseline Residual Entorhinal Cortex Volume *x* Baseline Caregiver Distress	-0.13	0.08
Baseline Residual Middle Temporal Gyrus Volume *x* Baseline Caregiver Distress	-0.04	0.60

Note: Significant correlations ($p < 0.05$) designated with an asterisk (*)

Table 3

One-way analysis of variance (ANOVA) results between categorical patient demographic variables and baseline caregiver distress

Variable	F	p-value
Patient Gender	1.25	0.27
Patient Race	2.86	0.04*
Marital Status	1.05	0.37
Baseline Diagnosis	11.48	0.00*

Note: Significant differences between groups ($p < 0.05$) designated with an asterisk (*)

Table 4a

Hierarchical regression predicting effects of baseline caregiver distress on cognitive indicators of AD severity (ADAS-cog score) at 12 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.04	0.04	2.16	0.09
2	Baseline Diagnosis	0.36	0.33	46.17	0.00
3	Race	0.38	0.01	1.20	0.31
4	Marital Status	0.39	0.01	1.09	0.35
5	Baseline ADAS-cog	0.66	0.27	135.69	0.00
6	Baseline residual temporal lobe volumes	0.67	0.01	2.08	0.11
7	**Baseline caregiver distress**	**0.68**	**0.01**	**5.01**	**0.03***

Note: Significant model ($p < 0.05$) designated with an asterisk (*)

Table 4b

Hierarchical regression predicting effects of baseline caregiver distress on cognitive indicators of AD severity (ADAS-cog score) at 24 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.05	0.05	2.80	0.04
2	Baseline Diagnosis	0.34	0.30	40.17	0.00
3	Race	0.35	0.01	0.88	0.45
4	Marital Status	0.36	0.01	0.67	0.57
5	Baseline ADAS-cog	0.65	0.29	139.76	0.00
6	Baseline residual temporal lobe volumes	0.68	0.03	5.25	0.00
7	**Baseline caregiver distress**	**0.69**	**0.01**	**5.51**	**0.02***

Note: Significant model ($p < 0.05$) designated with an asterisk (*)

Table 4c

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the hippocampus) at 12 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.00	0.00	0.27	0.85
2	Baseline Diagnosis	0.25	0.25	29.65	0.00
3	Race	0.25	0.00	0.06	0.98
4	Marital Status	0.26	0.00	0.18	0.91
5	Baseline ADAS-cog	0.33	0.06	19.22	0.00
6	Baseline residual temporal lobe volumes	0.94	0.61	570.34	0.00
7	Baseline caregiver distress	0.94	0.00	0.43	0.52

Table 4d

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the hippocampus) at 24 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.01	0.01	0.35	0.79
2	Baseline Diagnosis	0.27	0.27	32.54	0.00
3	Race	0.28	0.00	0.24	0.87
4	Marital Status	0.28	0.00	0.26	0.85
5	Baseline ADAS-cog	0.38	0.10	26.76	0.00
6	Baseline residual temporal lobe volumes	0.92	0.55	398.15	0.00
7	Baseline caregiver distress	0.92	0.00	0.96	0.33

Table 4e

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the entorhinal cortex) at 12 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.03	0.03	1.61	0.19
2	Baseline Diagnosis	0.17	0.14	15.16	0.00
3	Race	0.18	0.01	1.03	0.38
4	Marital Status	0.19	0.01	0.39	0.76
5	Baseline ADAS-cog	0.27	0.08	19.78	0.00
6	Baseline residual temporal lobe volumes	0.84	0.57	198.59	0.00
7	Baseline caregiver distress	0.84	0.00	0.00	0.96

Table 4f

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the entorhinal cortex) at 24 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.02	0.02	1.50	0.22
2	Baseline Diagnosis	0.17	0.15	16.16	0.00
3	Race	0.18	0.00	0.16	0.92
4	Marital Status	0.18	0.01	0.37	0.78
5	Baseline ADAS-cog	0.27	0.09	20.10	0.00
6	Baseline residual temporal lobe volumes	0.80	0.54	153.66	0.00
7	Baseline caregiver distress	0.81	0.00	0.75	0.39

Table 4g

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the middle temporal gyrus) at 12 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.00	0.00	0.06	0.98
2	Baseline Diagnosis	0.10	0.09	9.30	0.00
3	Race	0.10	0.01	0.51	0.67
4	Marital Status	0.11	0.01	0.70	0.55
5	Baseline ADAS-cog	0.19	0.07	14.92	0.00
6	Baseline residual temporal lobe volumes	0.92	0.74	544.04	0.00
7	Baseline caregiver distress	0.92	0.00	0.06	0.81

Table 4h

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the middle temporal gyrus) at 24 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.01	0.01	0.28	0.84
2	Baseline Diagnosis	0.13	0.12	12.57	0.00
3	Race	0.13	0.01	0.43	0.73
4	Marital Status	0.14	0.01	0.65	0.59
5	Baseline ADAS-cog	0.23	0.09	18.83	0.00
6	Baseline residual temporal lobe volumes	0.90	0.67	374.31	0.00
7	Baseline caregiver distress	0.90	0.00	0.52	0.47

Table 4i

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the whole brain) at 12 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.02	0.02	1.12	0.34
2	Baseline Diagnosis	0.04	0.02	1.94	0.15
3	Race	0.06	0.02	1.39	0.25
4	Marital Status	0.08	0.02	0.93	0.43
5	Baseline ADAS-cog	0.11	0.04	6.71	0.01
6	Baseline residual whole brain volume	0.98	0.87	7629.03	0.00
7	Baseline caregiver distress	0.98	0.00	0.05	0.82

Table 4j

Hierarchical regression predicting effects of baseline caregiver distress on neuroanatomical indicators of AD severity (residual MRI volume of the whole brain) at 24 months follow-up

	Model	R^2	ΔR^2	F	p-value
1	Sex; Education; Age	0.02	0.02	1.16	0.33
2	Baseline Diagnosis	0.05	0.03	2.77	0.07
3	Race	0.07	0.02	1.10	0.35
4	Marital Status	0.09	0.02	1.17	0.32
5	Baseline ADAS-cog	0.13	0.05	9.68	0.00
6	Baseline residual whole brain volume	0.97	0.83	4185.45	0.00
7	Baseline caregiver distress	0.97	0.00	1.41	0.24

Figure 1

Hierarchical regression examining downstream effects of baseline caregiver distress on future AD severity

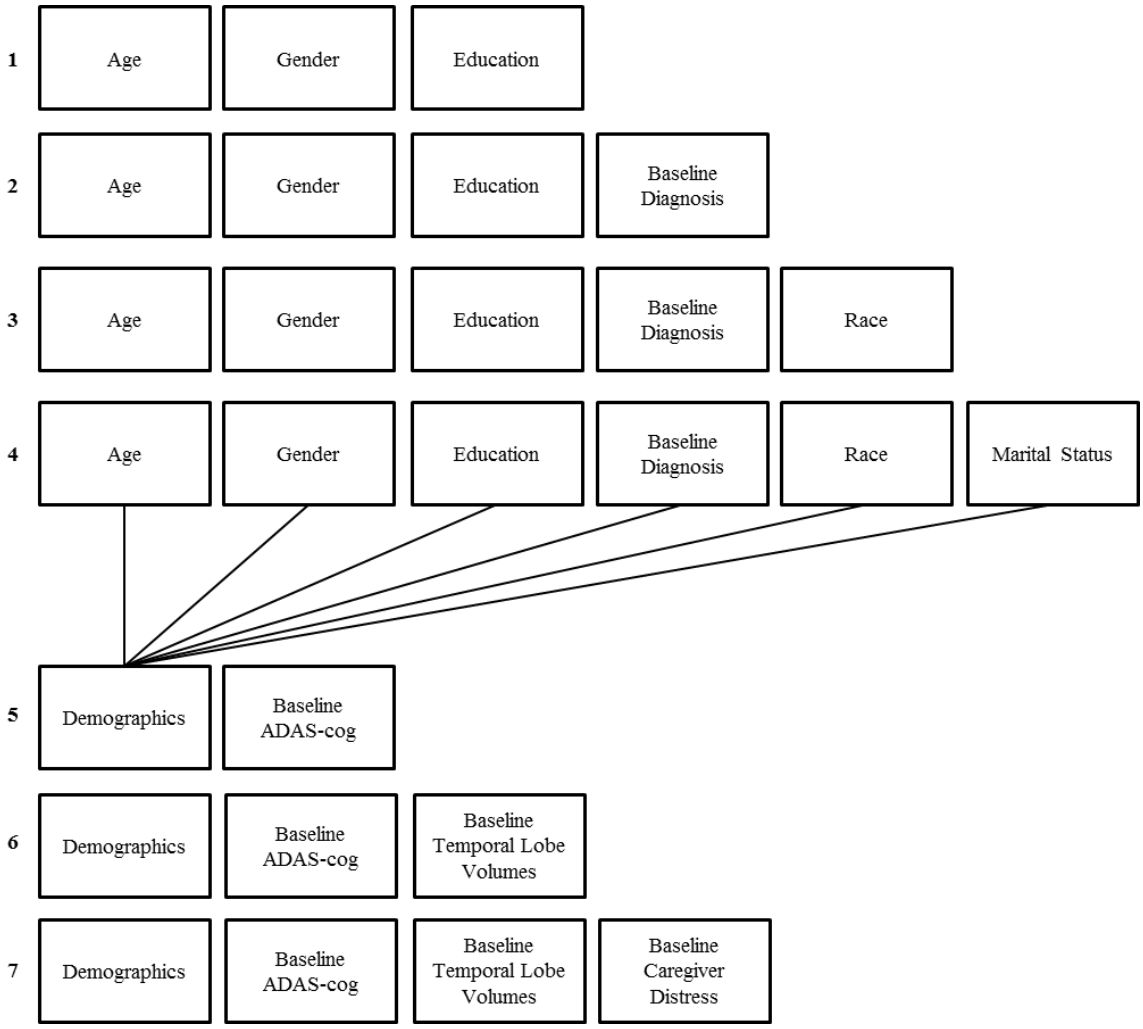


Figure 2

Outcome variable changes in each model to reflect the selected indicators of AD severity (cognitive impairment and neurodegeneration)

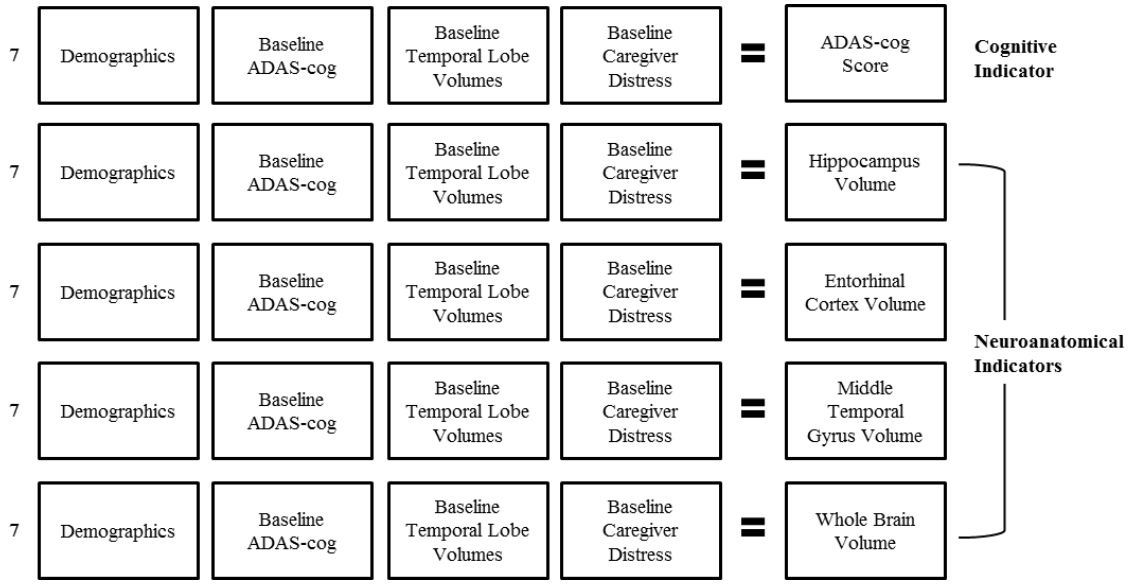


Figure 3

Replication of the third and final step of the hierarchical regression to reflect outcome data from 12 and 24 months follow-up

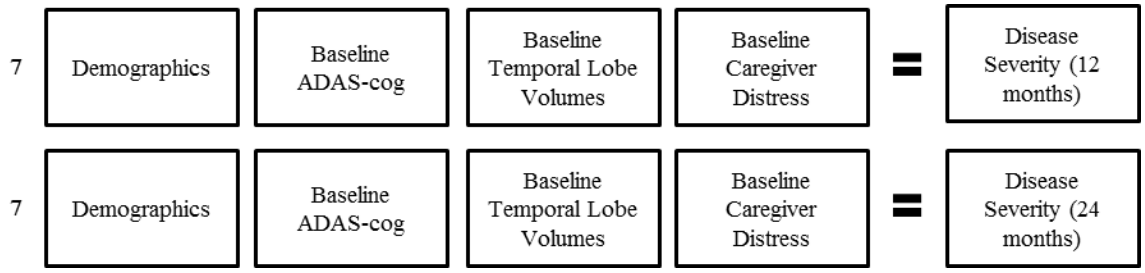


Figure 4

Seventh and final steps for each of the eight main regression models reflecting different indicators of disease severity and time points

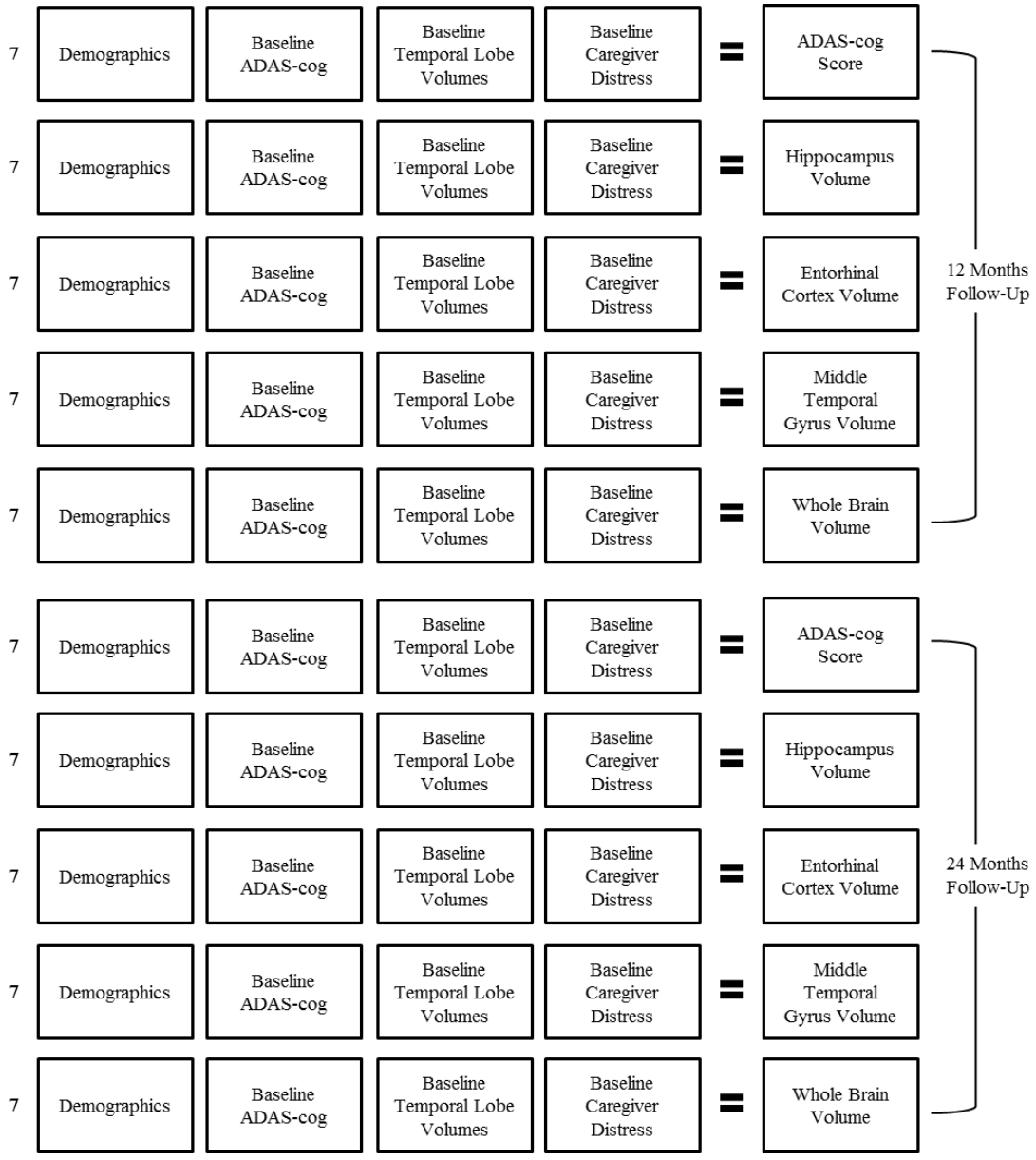


Figure 5

Marginal means of total NPI score from baseline through 24 months follow-up

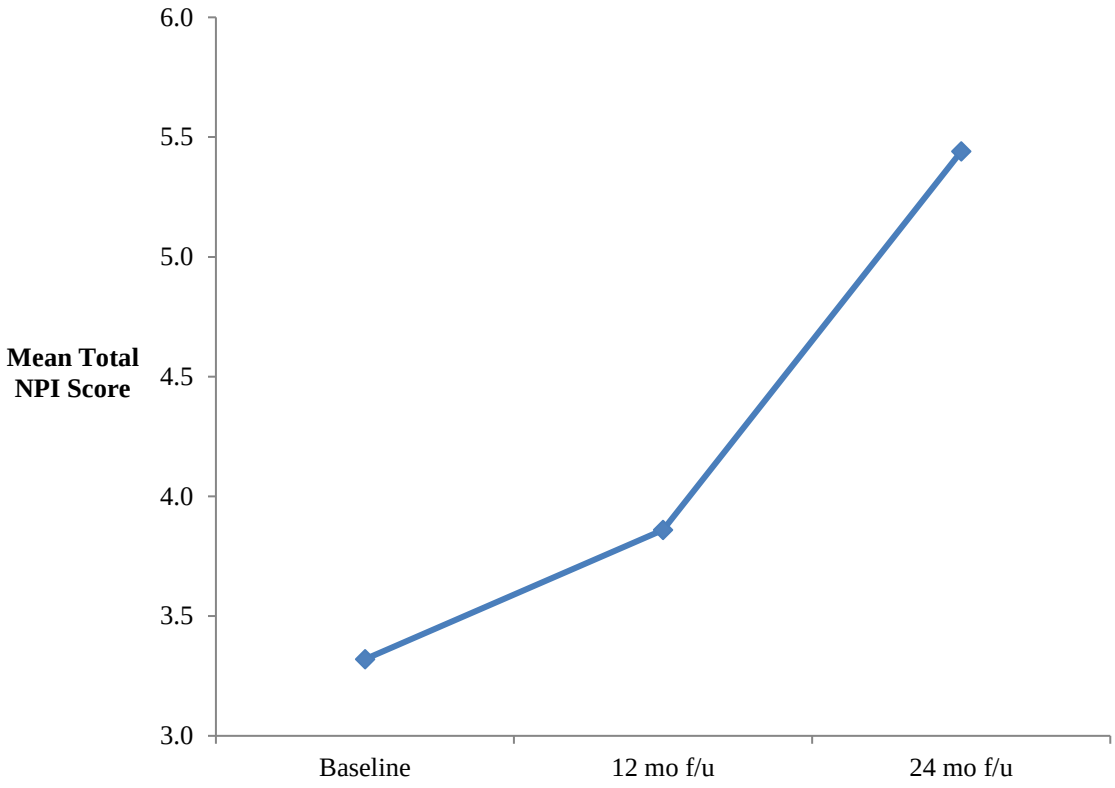


Figure 6a

Frequency of symptom endorsement by caregivers from baseline through 12 and 24 months follow up (grouped by time point)

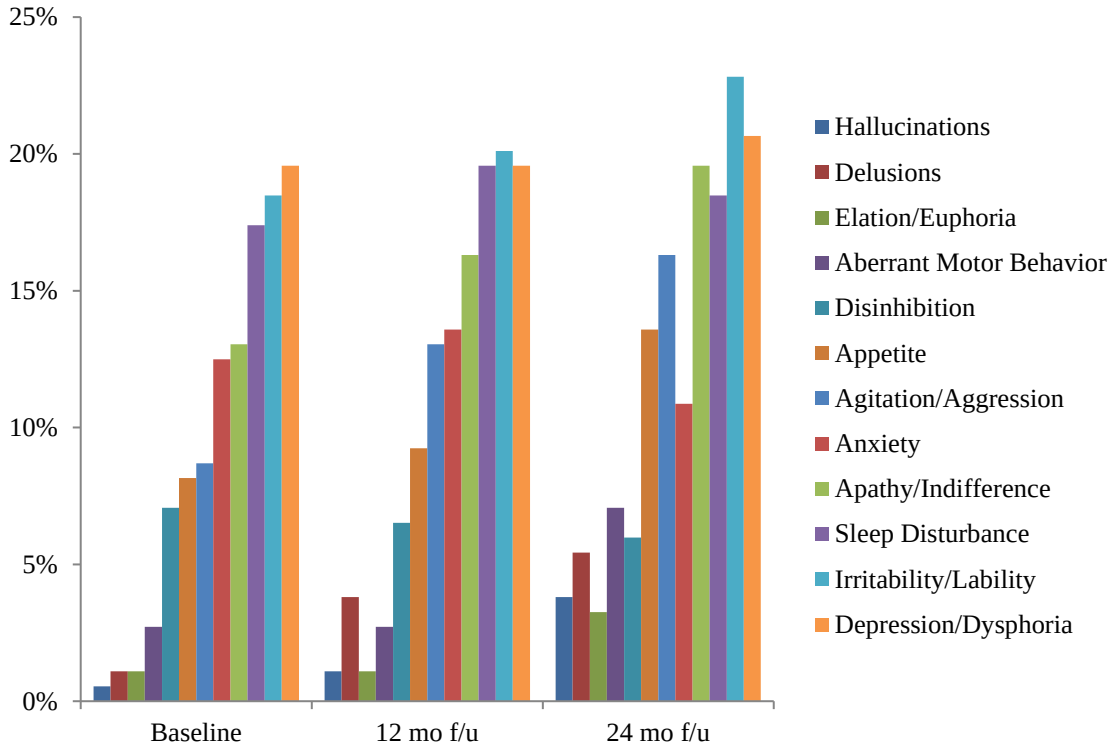


Figure 6b

Frequency of symptom endorsement by caregivers from baseline through 12 and 24 months follow up (grouped by symptom)

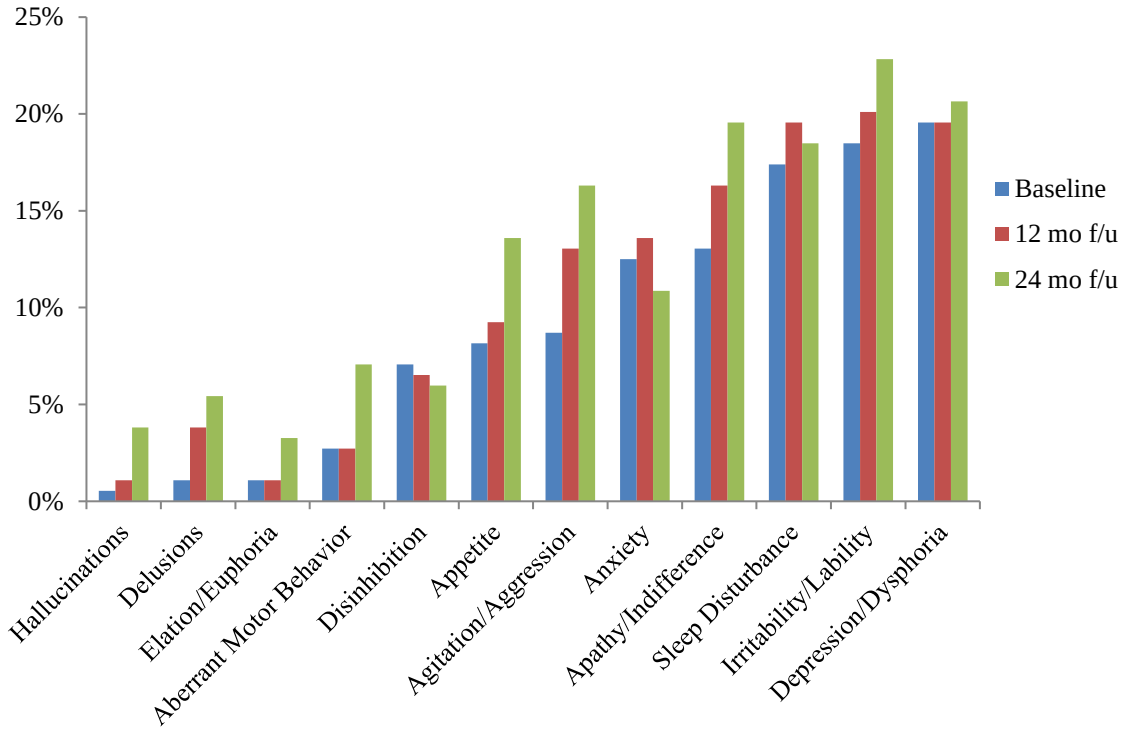
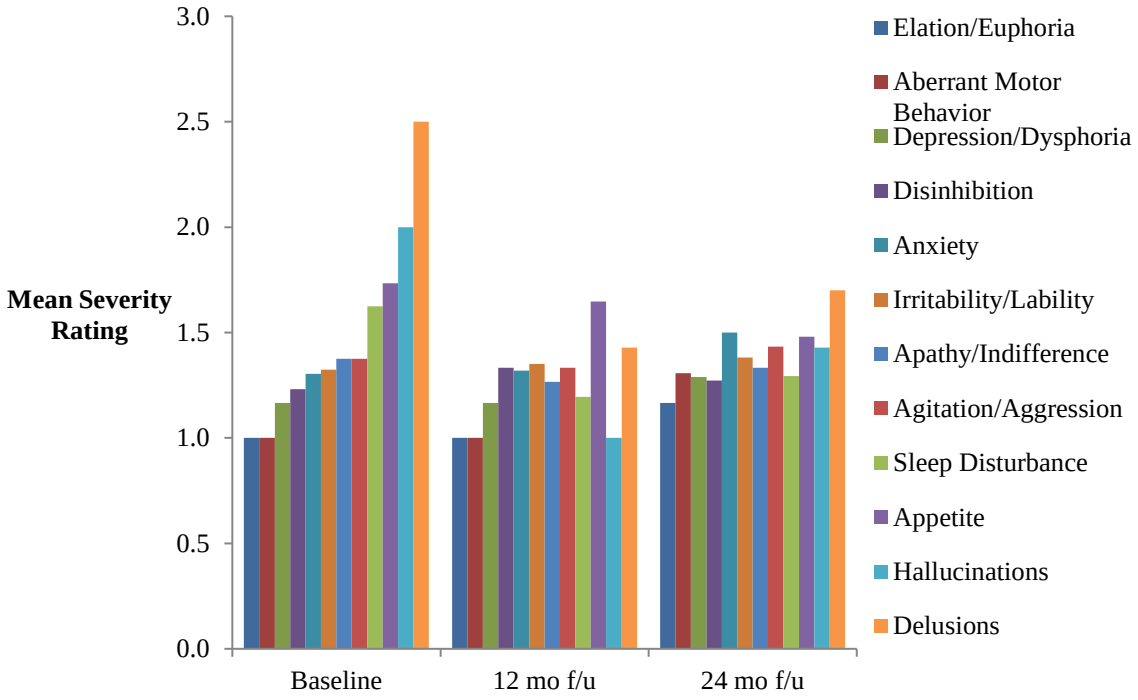


Figure 7a

Mean symptom severity ratings from baseline through 12 and 24 months follow-up (grouped by time point)

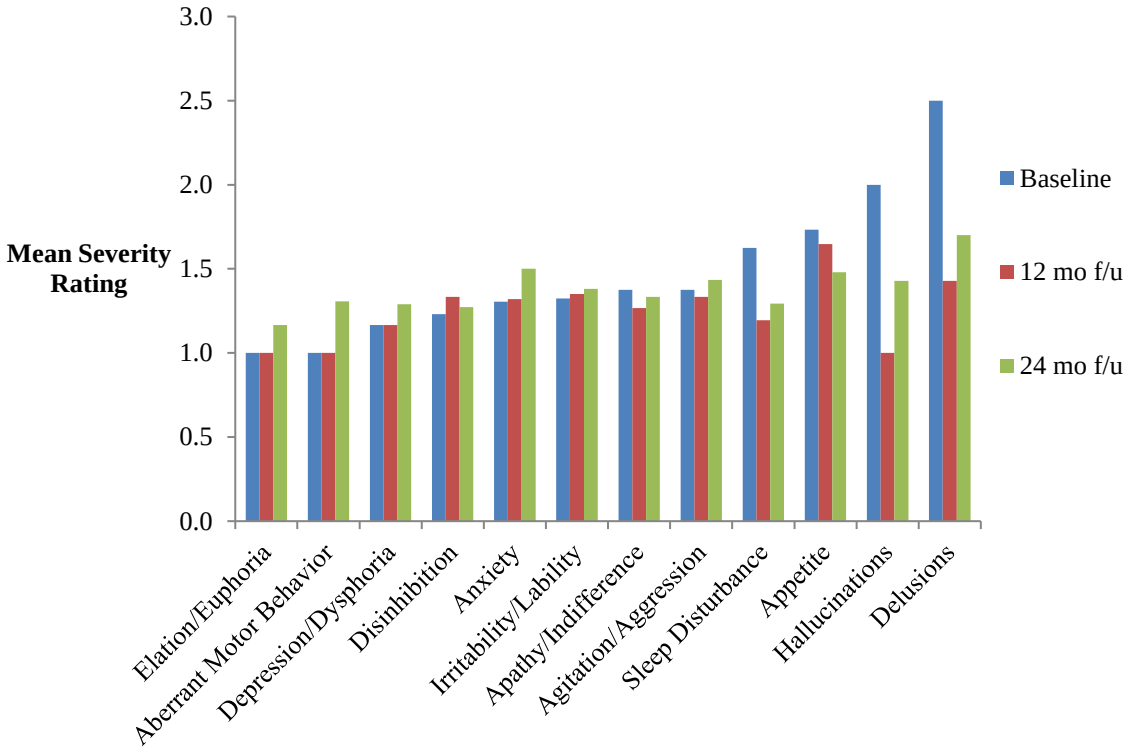


Number of ratings assessed for each symptom at each time point (n)

Symptom	Baseline	12 months	24 months
Elation/Euphoria	2	2	6
Aberrant Motor Behavior	5	5	13
Depression/Dysphoria	36	36	38
Disinhibition	13	12	11
Anxiety	23	25	20
Irritability/Lability	34	37	42
Apathy/Indifference	24	30	36
Agitation/Aggression	16	24	30
Sleep Disturbance	32	36	34
Appetite	15	17	25
Hallucinations	1	2	7
Delusions	2	7	10

Figure 7b

Mean symptom severity ratings from baseline through 12 and 24 months follow-up (grouped by symptom)

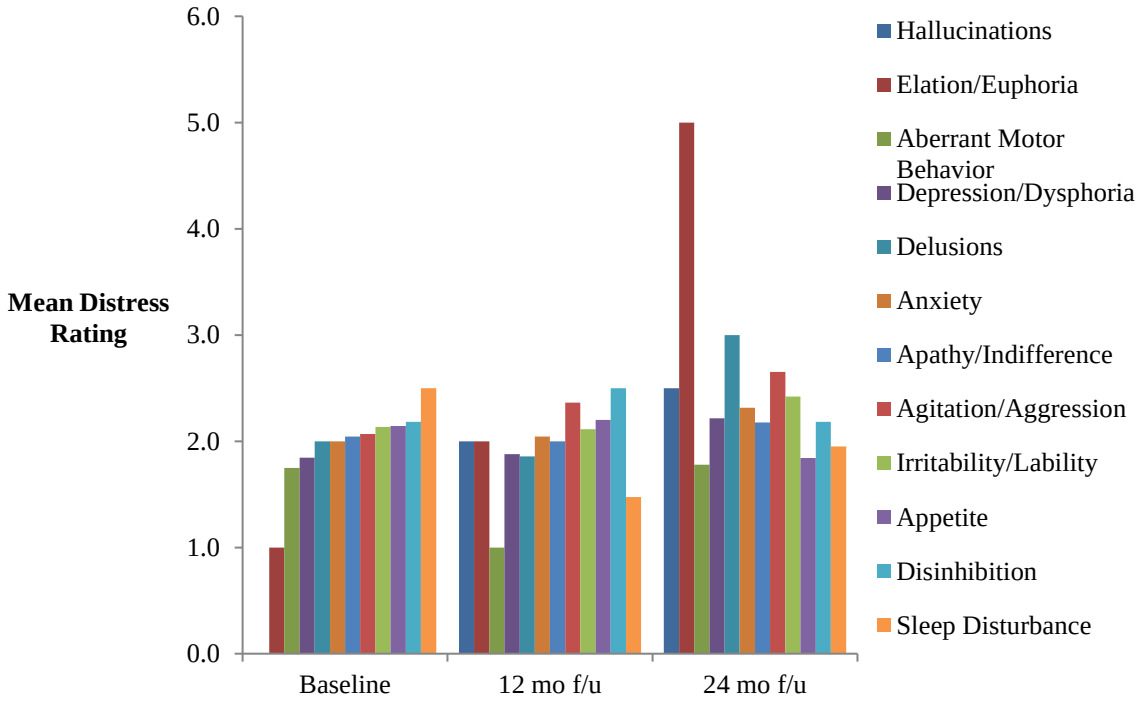


Number of ratings assessed for each symptom at each time point (n)

Symptom	Baseline	12 months	24 months
Elation/Euphoria	2	2	6
Aberrant Motor Behavior	5	5	13
Depression/Dysphoria	36	36	38
Disinhibition	13	12	11
Anxiety	23	25	20
Irritability/Lability	34	37	42
Apathy/Indifference	24	30	36
Agitation/Aggression	16	24	30
Sleep Disturbance	32	36	34
Appetite	15	17	25
Hallucinations	1	2	7
Delusions	2	7	10

Figure 8a

Mean caregiver distress ratings per symptom from baseline through 12 and 24 months follow-up (grouped by time point)

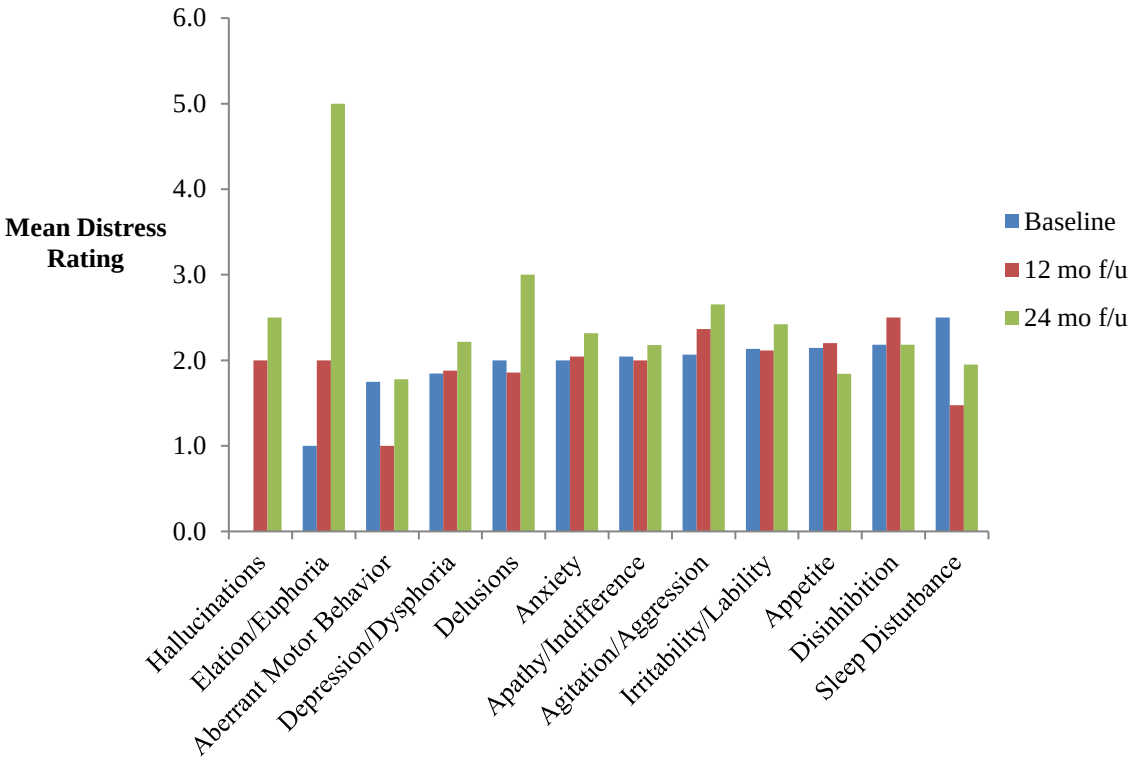


Number of ratings assessed for each symptom at each time point (n)

Symptom	Baseline	12 months	24 months
Hallucinations	0	1	6
Elation/Euphoria	2	2	5
Aberrant Motor Behavior	4	4	9
Depression/Dysphoria	32	33	37
Delusions	2	7	9
Anxiety	22	23	19
Apathy/Indifference	23	28	34
Agitation/Aggression	15	22	26
Irritability/Lability	30	35	38
Appetite	14	10	19
Disinhibition	11	12	11
Sleep Disturbance	22	21	20

Figure 8b

Mean caregiver distress ratings per symptom from baseline through 12 and 24 months follow-up (grouped by symptom)



Number of ratings assessed for each symptom at each time point (n)

Symptom	Baseline	12 months	24 months
Hallucinations	0	1	6
Elation/Euphoria	2	2	5
Aberrant Motor Behavior	4	4	9
Depression/Dysphoria	32	33	37
Delusions	2	7	9
Anxiety	22	23	19
Apathy/Indifference	23	28	34
Agitation/Aggression	15	22	26
Irritability/Lability	30	35	38
Appetite	14	10	19
Disinhibition	11	12	11
Sleep Disturbance	22	21	20

Figure 9

Marginal means of mean total NPI distress score from baseline through 24 months follow-up