ANALYZING TRAJECTORIES OF CAREGIVER PSYCHOLOGICAL DISTRESS OVER TIME USING GROUP-BASED MODELING METHODS

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Group-based trajectory analysis is an innovative statistical method to identify distinct populations over time. We used this approach to characterize patterns of change in distress using shortened scales (depressive symptoms (CESD), anxiety (POMS), and caregiver burden (CRA)) in caregivers (CG) of persons with primary malignant brain tumors. In an ongoing longitudinal study, 99 CGs were interviewed within a month of their care recipients' diagnosis and at 4, 8, and 12- months afterwards. We used SAS Proc Traj to select models based on clinical criteria and statistical judgment. We identified 2 trajectories for depressive symptoms, 2 for anxiety, and 3 for caregiver burden. An estimated 61.2% of CGs had low CESD (range: 0-30) scores at baseline (mean (M)=5.3, standard deviation (SD) = 3.6) and remained low (M=2.7, SD=2.8) at 12-months (p=0.06 for trajectory slope); the remaining CGs (38.8%) had high scores at baseline (M=14.4, SD=5.3) that significantly decreased by 12-months (M=9.1, SD=4.6; p=0.01). An estimated 20.4% of CGs had low POMS (range: 3-18) scores at baseline (M=6.0, SD=2.2) that decreased significantly (M=4.0, SD=1.1) at 12-months (p=0.002); the remaining CGs (79.6%) had high scores at baseline (M=10.2, SD=2.1) that decreased significantly by 12-months (M=7.8, SD=1.5; p=0.001). An estimated 20.4% of CGs had low CRA (range: 5-25) scores at baseline (M=10.5, SD=2.7) that decreased significantly (M=6.4, SD=1.3) at 12-months (p<0.001); the moderate trajectory included 26.5% of CGs with consistent scores at baseline (M=14.2, SD=2.0) and 12 months (M=11.0, SD=1.4; p=0.51); the majority of CGs (53.1%) had consistently high

scores at baseline (M=19.7, SD=2.1) and (M=20.0, SD=2.4) at 12 months (p=0.85). Logistic and multinomial regression results revealed that CGs with low emotional stability were more likely to belong to the high depressive symptoms (p=0.007) and anxiety (p=0.002) trajectory groups. CGs were more likely to belong to the moderate to high caregiver burden trajectory group if their care recipients had more aggressive tumor types (p=0.004) or lower constructional ability (p=0.05). The public health significance of this work is that trajectory analysis provides a way to identify CGs at risk of increasing psychological distress so that suitable interventions can be developed and targeted.

TABLE OF CONTENTS

LIST OF TABLES

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1.0 INTRODUCTION

Some of the following paragraphs are summarized from the Mind Body Interactions in Neuro-Oncology Caregivers grant (P. Sherwood, et al., 2007). In 2006, approximately 18,600 Americans were diagnosed with a primary malignant brain tumor (PMBT) ("Fast Stats: An interactive tool for access to SEER cancer statistics," Accessed on 12/18/2009). Only 3.4% of individuals diagnosed with a glioblastoma, the most common type of PMBT, will survive within five years of diagnosis (CBTRUS, 2008). Those who do survive can suffer from debilitating and severe physical and neurological dysfunction and may never achieve full recovery. Patients are unable to resume normal daily activities and these roles and responsibilities often fall to family members to assume.

Taking on the role of family caregiver has been associated with emotional distress for family members. In addition to caring for a disabled loved one, the caregiver, typically the spouse often assumes primary responsibility for tasks such as managing household finances, ensuring employment and insurance coverage, and childcare. Caregiver studies have shown an association between caregiving and negative psychological effects (Rogers, Given, Remer, & Sherwood, 2004; P. R. Sherwood, Given, Doorenbos, & Given, 2004). After a period of time, these negative emotions can affect the caregiver's ability to provide good care.

Several studies have shown the relationship between negative emotional distress and poor physical health in family caregivers (Carter, 2002; Picot & Genet, 1998; Schulz & Beach, 2000; Vitaliano, Zhang, & Scanlan, 2003). Caregiver physical health is important to providing good care because an ailing caregiver can lack the ability to perform daily functions for themselves and for their care recipient, and also may be more likely to die younger (Schulz & Beach, 1999). In addition, psychologically distressed caregivers may be less likely to seek medical attention for their physical ailments because of a need to care for their loved ones.

How and when caregiver negative emotional reactions occur and vary throughout the time following the care recipient's diagnosis is important in designing effective interventions to provide timely and appropriate care (P. R. Sherwood, et al., 2008). Hypotheses of how caregivers cope with stress over time include the 1) adaptation hypothesis (Helson, 1964) and the 2) "wear-and-tear hypothesis" (Townsend, Noelker, Deimling, & Bass, 1989). The adaptation hypothesis proposes that upon diagnosis of the care recipient, the caregiver must learn to cope with the devastating diagnosis of their loved one. As a result, caregivers experience high levels of psychological distress at the point of diagnosis. However, with time, the initial caregiving demands wear off as the caregiver learns to adjust to the situation and experience less feelings of psychological distress. The "wear and tear" theory proposes the opposite. At the point of diagnosis, caregivers have low levels of psychological distress as they immediately employ coping strategies and resources to deal with life changes such as managing new responsibilities and family roles. However, as time passes, the caregiver's coping strategies may become less effective, leading to increasing feelings of depression, anxiety and burden.

Current research has been unable to describe changes over time in caregiver emotional health because of methodologic limitations. The majority of research in family caregiving,

particularly in oncology, has been cross-sectional, providing only a snapshot of the caregiver's emotional response instead of a progression of change over time (M.P. Lawton, M. Moss, C. Hoffman, & M. Perkinson, 2000; P. R. Sherwood, et al., 2008). In the longitudinal studies that have been performed, analytic limitations have prevented a clear understanding of both varying changes in emotional reactions over time as well as the variables that predict specific trajectories. This data is vital for designing and implementing tailored interventions that target specific caregivers at risk for distress at the time when they are most likely to exhibit that distress.

1.1 THE PARENT STUDY

Mind Body Interactions in Neuro-Oncology Caregivers is an ongoing descriptive longitudinal study (NCI; R01 CA118711, PI Sherwood) that motivated this analysis. This study was approved by the Institutional Review Board (IRB) of the University of Pittsburgh and caregiver-care recipient dyads provided informed consent. As of September 2009, a sample of 99 caregiver-care recipient dyads of persons with a primary malignant brain tumor was collected from a suburban neuro-oncology clinic in Western Pennsylvania. Data collection began in 2006 on the date of the patient's diagnosis, and 4, 8, and 12 months after diagnosis. Each dyad received questionnaires specific to the caregiver: measures of socio-demographic characteristics, personal characteristics, psychological responses, behavioral responses, biologic responses, and overall physical health; and questionnaires specific to the care recipient: measures of tumor grade, functional and neurological ability, and symptom status.

1.1.1 Recruitment and data collection

Dyads were recruited through the neuro-oncology clinic at the University of Pittsburgh Cancer Institute by research team members of the parent study. Caregiver and care recipient data collection were administered in private examination rooms during routine clinical appointments. Caregivers were not required to be legally related to, or live with the care recipient but were required to be a nonprofessional, non-paid caregiver, over 21 years of age, English-speaking and not a primary caregiver for anyone else other than children under 21 years of age. Care recipients were required to be over 21 years of age and newly (within 1 month) diagnosed with a PMBT, which was verified by a pathology report to be a glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, medulloblastoma, or anaplastic ependymoma.

Questionnaires for the caregiver were administered by a trained interviewer separately from the care recipient, in order to encourage candid answers from each member of the dyad. Upon signing all consent forms, baseline data from the caregiver was collected. If questionnaires could not be completed, interviewers continued the session over the telephone within 72 hours of the original data collection session. Care recipients' data were collected during their routine clinic examinations by a registered nurse.

Measures of care recipient disease characteristics, caregiver sociodemographic information, caregiver personal characteristics, caregiver psycho-behavioral responses, biologic responses and overall physical health were measured with established instruments at baseline, 4, 8 and 12 months after diagnosis with similar procedures at each time point. For care recipients

who passed away, instruments adjusted for bereaved caregivers were used if caregivers agreed to remain in the study.

1.1.2 Caregiver Measures

Caregiver sociodemographic information collected at baseline included their age, gender, relationship to care recipient, and years of education. Personal characteristics of the caregiver measured included mastery, emotional stability, and social support. Psychobehavioral characteristics of the caregiver measured included depression, anxiety and caregiver burden (see appendix A.1).

Mastery was measured using the Master scale (Pearlin & Schooler, 1978), an 11-item instrument that uses a scale from 1 to 4 to rate the degree of caregiver mastery over important life outcomes and control of things that happen to them. An overall score was produced by summing all items, with higher scores indicating higher levels of mastery.

Emotional stability was measured using the modified Goldberg Adjective Scale (GLB) to measure caregiver level of neuroticism. Caregivers rate on scale of 0 to 4 how accurately they would describe themselves based on traits of feeling resentful, irritable, tense, nervous, or depressed. An overall sum score was produced after reverse-scoring each item, with higher scores indicating higher emotional stability and lower neuroticism (Goldberg, 1990, 1992).

Social support was measured using the Interpersonal Evaluation List (ISEL) (Nato Advanced Research Workshop on Social Support: Theory, Applications, Sarason, Sarason, & North Atlantic Treaty Organization. Scientific Affairs), a 14-item instrument measuring the

caregiver's perception of their social support. Sum scores of each subscale and the overall measure were produced with higher scores indicating more social support.

Caregiver psychological responses were also measured using self-report instruments. Depressive symptoms were measured using the shortened version of the Center for Epidemiologic Studies-Depression scale (CES-D) (Radloff, 1977), a 10-item questionnaire rating the subject's experience of various symptoms such as feeling lonely, fearful, and sad on a 4-point scale. An overall sum score was produced, with higher scores indicating higher levels of depressive symptoms.

Anxiety was measured using a shortened version of the anxiety subscale of the Profile of Moods States (POMS) scale (Usala & Hertzog, 1989), a 3-item questionnaire which rated the subject's experience of various symptoms, specifically feeling on edge, nervous and tense on a 5-point scale. An overall sum score was produced, with higher scores indicating higher levels of anxiety.

Caregiver burden was measured using the Caregiver Reaction Assessment (CRA) scale, which measures the subject's perception of the impact providing care has on five areas of life: self-esteem, schedule, finances, feelings of abandonment and health (Given, et al., 1992; Stommel, Wang, Given, & Given, 1992) on a 5-point scale. Subscale and overall sum scores were produced, with higher scores indicating greater levels of caregiver burden.

1.1.3 Care Recipient Measures

Care recipients' sociological, demographic and clinical characteristics were collected at baseline, and measures on care recipient disease characteristics, functional, neurological and symptom

status were collected at every time point. To identify disease characteristics, the care recipient's medical records and pathology reports were examined to note the tumor type, grade and treatment trajectory. Tumor type was categorized as: astrocytoma grades I, II, III, or IV (glioblastoma multiforme), oligodendroglioma, or other. Care recipient cognitive functions were assessed using the Neurobehavioral Cognitive Status Examination (NCSE) (Kiernan, Mueller, Langston, & Van Dyke, 1987) instrument, which measures cognitive ability in the domains: level of consciousness, orientation, attention, language (comprehension, naming, repetition), constructional ability, memory, calculations, and reasoning (similarities and judgment). Subjects were required to answer questions and perform tasks that demonstrated ability in each cognitive domain; for example, constructional ability measures the patient's functional and cognitive ability to assemble shapes in order to replicate a 2-dimensional drawing. Each question was measured on a 4-point scale; higher scores indicate greater neuropsychological dysfunction.

Care recipient symptom severity and impact on daily functioning was measured using the M.D. Anderson Symptom Inventory Brain Tumor module (MDASI-BT), a 22-item instrument that assesses severity of multiple symptoms with additional items unique to the brain tumor population (Armstrong, et al., 2006). A total symptom score is summed over all items with higher scores indicating greater symptom severity and interference (see Appendix A.2).

1.2 USE OF TRAJECTORY ANALYSIS

Initially, we attempted to develop a simplified composite index of psychological distress (simultaneously measuring depressive symptoms, anxiety, and caregiver burden), that could be

administered at several time points to identify caregivers in need. However, an exploratory factor analysis failed to reduce the three scales used to measure depressive symptoms (CES-D), anxiety (POMS), and caregiver burden (CRA Schedule) respectively, since they had already been shortened by similar procedures. This provided motivation to focus on alternative approaches to identify caregivers most at risk for psychological distress rather than composite measures of psychological distress. We wanted to 1) describe the variations of caregiver psychological distress over time and 2) examine relationships between these patterns of change with care recipients' neurological, biologic, and clinical characteristics. Identifying specific patterns of caregiver psychological distress change and their associated characteristics would help design and implement interventions to target caregivers most in need.

Ways to analyze longitudinal data include modeling the population average: (i) repeated measures analysis of variance models time-based data via pre-identified groups, and (ii) standard latent growth curve analysis models the mean population growth curve and individual variation about the mean. Trajectory analysis, or group-based modeling, developed by Nagin and colleagues is a semi-parametric model that combines aspects of both (i) and (ii). It allows subgroup population trajectories, which are unidentifiable on measurable characteristics, to be estimated even though they are not observed (D. S. Nagin, 2005). Unlike other methods, trajectory analysis defines groups to approximate the underlying phenomena. Subsequent modeling can identify factors that predict group membership.

The use of trajectory analysis is spreading from its origination in criminology to other research areas. Over 80 studies in the U.S. and abroad, between 1993 and 2005, have implemented group-based modeling methods (Piquero, 2008). We are aware of no caregiver

studies to date that have used trajectory analysis to analyze psychological distress over time in family caregivers of persons with a PMBT.

1.3 STATEMENT OF THE PROBLEM

The purpose of this analysis is to use group-based trajectory analysis to 1) characterize patterns of change over time in caregiver psychological distress throughout the course of caregiving and 2) identify the caregiver and care recipient characteristics that are associated with caregiver psychological distress trajectories over time.

2.0 LITERATURE REVIEW

In the United States 44.4 million caregivers are involved in caregiving to persons over 18 years of age ("Caregiving in the U.S.," 2004). Of these, surveys have shown family caregiving to be associated with higher mortality rate (Schulz & Beach, 1999), decreased immune response (Kiecolt-Glaser, et al., 2003), higher risk of depression and anxiety (Cannuscio, et al., 2002), premature aging (Epel, et al., 2004), and increased rate of developing chronic illness ("Informal Caregiving: Compassion in Action," 1998). The negative physical, emotional and long-term consequences have been demonstrated in family caregivers of different populations, i.e. Alzheimer's, dementia, cancer, geriatrics, and severe disability.

2.1 SUMMARY OF CONCEPTUAL MODEL

Caregivers for persons with a PMBT constitute a distinct subset of the caregiving population because the care recipient has both neurological and oncological impairment. Unlike caregivers of persons with Alzheimer's, dementia or other long-term chronic illnesses, caregivers of persons with a PMBT must face the multiple stages of crisis that start with cancer diagnosis, and continues throughout the care situation with the ongoing distress of sudden shifts in roles and responsibilities, and finally to the end-of-life decisions that arise with a short-term terminal

illness (Schubart, Kinzie, & Farace, 2008). In addition, the caregiver must also adjust to functional, cognitive and neuropsychiatric changes in the care recipient depending on tumor location in the brain.

Caregiver psychological distress response depends on a combination of factors instead of just the presence of the stressor. Care recipient disease characteristics describe the severity of the deterioration of the care recipient, which will lead to greater distress for the caregiver. The attitude caregivers form toward the care situation and the presence of available outside support will influence the caregiver psychological and emotional distress response to the care situation. The parent study is based on the Adapted Pittsburgh Mind-Body Model to describe the relationships between factors associated with the emotional and physical stress response in caring for someone with a PMBT (P. Sherwood, et al., 2007).

The sudden and traumatic diagnosis of a PMBT triggers the caregiver response to the care situation. Following diagnosis, the demands of the care situation will be dependent on the care recipient's functional, neurologic, symptom and tumor status. Tumor grade, location and treatment options are associated with aggressiveness of tumor recurrence, mortality and physical, cognitive, and functional changes in the care recipient. Care recipients with lower functionality and cognitive ability generally require more help with activities of daily living and make more demands on the caregiver (P. R. Sherwood, et al., 2008).

Caregiver personal and social characteristics will indicate the type of attitudes caregivers will have towards the care situation, and the amount of outside support they will have. Caregiver personal attributes describe their personality type, or distinctive traits of mind and behavior. For example, neuroticism is as a personality type that is a consistent predictor of psychological distress. High neuroticism has been associated with greater risk for depressive symptoms for

care recipients with poor neurological status and to greater caregiver burden (Bookwala & Schulz, 1998; Nijboer, Tempelaar, Triemstra, van den Bos, & Sanderman, 2001). Mastery describes the level of caregiver perceived control or ability to fulfill the role and challenge of the care situation. Caregivers with high levels of mastery generally feel more prepared and ready to face the care demands and challenges ahead and are less likely to have poor psychological response to the care situation (Bookwala & Schulz, 1998; Li, Seltzer, & Greenberg, 1999; Skaff, Pearlin, & Mullan, 1996).

Caregiver social attributes describe the level of outside support available to assist in caring for the patient. Social support describes the perceived availability and willingness of friends and family to provide emotional support to the caregiver, and has been associated with caregiver burden and depressive symptoms in the presence of care recipient neurological status (Ergh, Hanks, Rapport, & Coleman, 2003; Pinquart & Sorensen, 2005). Greater social support may provide the caregiver with relief when care demands are high.

Caregiver sociodemographic characteristics will also play a part in how one responds to the challenges of caregiving. Being female, younger, have a low income, or caring for a spouse have been associated with greater risk of caregiver burden, depressive symptoms, anxiety and sleep pattern changes (P. R. Sherwood, et al., 2008). The care situation is dynamic and constantly changing since caregiver and care recipient factors must be reappraised throughout the course of providing care.

2.2 FACTORS RELATED TO PSYCHOLOGICAL DISTRESS

2.2.1 Depressive Symptoms

Depressive symptoms in caregivers are defined as loss of interest or pleasure in activities, feelings of low self-worth, low energy, and/or poor concentration (Radloff, 1977). Previous studies have shown depressive symptoms in caregivers of persons with dementia, oncology and other chronic illnesses have been closely linked to care recipients' disease characteristics; care recipients with neurological dysfunction are associated with caregivers with higher levels of depressive symptoms (Pinquart & Sorensen, 2003), especially in Caucasian caregivers (Pinquart & Sorensen, 2005).

2.2.2 Anxiety

Caregiver anxiety is defined as feeling nervous, on edge and tense. A direct relationship has been shown between care recipients' functional ability and anxiety in caregivers of persons with chronic illnesses (Beach, Schulz, Yee, & Jackson, 2000). Caregiver anxiety can also depend on the relationship to the care recipient; daughter caregivers were more likely to experience greater anxiety, depressive symptoms and caregiver strain than husband caregivers of breast cancer patients (Bernard & Guarnaccia, 2003). Caregivers who seek social support and practice coping methods were also related to anxiety in caregivers of dementia patients (Beach, et al., 2000).

2.2.3 Caregiver Burden

Caregiver burden is defined as the physical, emotional and psychological impact of caregiving on the various aspects of life (schedule, finances, self-esteem, health and feelings of abandonment) for the person providing care (Given, et al., 1992). Caregiver burden has been shown to be associated with care recipient disease characteristics: tumor type (Gaugler, et al., 2005), symptom status (Andrews, 2001), neurological function (Marsh, Kersel, Havill, & Sleigh, 2002; Pinquart & Sorensen, 2003; Rymer, et al., 2002), and functional status (Chio, Gauthier, Calvo, Ghiglione, & Mutani, 2005; Cohen, Colantonio, & Vernich, 2002; Gaugler, et al., 2005). However some studies have been unable to replicate this link (Meyers & Gray, 2001; Morimoto, Schreiner, & Asano, 2003; Rymer, et al., 2002).

2.3 GROUP-BASED TRAJECTORY ANALYSIS

A literature search was conducted in November 2009 using PubMed to search for publications of the theory, validity, extensions, or criticisms of group-based modeling analysis. The search terms included: “group-based trajectory analysis”, “semi-parametric group-based modeling”, “group-based modeling”, “proc traj”, or “Nagin, Daniel [full author name]”. A total of 32 articles were displayed in the initial search. Of these 2 did not use trajectory analysis, 29 were applications of the technique and 1 discussed an extension of trajectory analysis (Haviland, Nagin, Rosenbaum, & Tremblay, 2008). References from a book chapter (Piquero, 2008) provided 19 methodology publications not listed in PubMed.

2.3.1 History

The development of group-based trajectory analysis emerged from criminology research. Criminology is the study of the development and causes of criminal activity in humans, and is primarily concerned with the behavioral, sociological, and psychological factors that lead an individual to begin, maintain, and/or end their criminal careers. Therefore, criminology studies frequently collect longitudinal data to capture when misbehavior begins in the life course and to identify the factors associated with the development of criminal activity. Studies have charted the life course of criminal activity persistence; however, few have examined desistance of criminal activity since several studies do not follow individuals once they turn 30 years old. In addition, it is difficult to operationalize "desistance" because of the intermittent nature of criminal activity over time (Piquero, 2008).

Avi-Itzhak and Shinnar sparked the criminal careers debate with their hypothesis of criminal activity onset and termination. By analyzing whether incapacitation affected criminal activity onset, active offending, and termination, they assumed criminal activity could be started and stopped, and that individuals could be categorized as criminals and non-criminals (Avi-Itzhak & Shinnar, 1973). Along similar lines, Moffitt supported the conventional criminal careers theory, that criminals and non-criminals were distinct groups marked by specific points of career onset, activity, and termination (Moffitt, 1993). In contrast, Gottfred and Hirschi proposed the criminal propensity theory, describing criminal activity as a continuum of self-control instead of distinct subgroups in the population. Children with low levels of self-control would be more likely to offend in adolescence or adulthood, whereas children with higher levels of self-control would be at lower risk of criminal behavior (Gottfredson & Hirschi, 1990).

Available statistical models were based on the criminal propensity theory, and assumed that the rate of offending followed a Poisson process and that the population distribution of this rate could follow the gamma distribution (Greenberg, 1991) or the lognormal distribution (Rowe, Osgood, & Nicewander, 1990). Nagin and Land developed the first group-based modeling approach using a nested mixed Poisson model to analyze individual criminal careers. Standard maximum likelihood procedures were used to estimate parameters at the individual level, and the individual rate of offending was set to follow a Poisson distribution. The model controlled for individual-level demographic and social characteristics, and accounted for random error.

When applied to empirical data, Nagin and Land concluded that both aspects of the criminal career theory were plausible (D. S. Nagin & Land, 1993). The model was subsequently revised to the "semi-parametric" group-based modeling approach to describe a model that has both parametric and nonparametric components (K. C. Land, P. L. McCall, & D. S. Nagin, 1996b). Further developments allowed the model to accommodate distributions for binary, count, and censored normal data (D. Nagin & Tremblay, 1999; D. S. Nagin, 2005).

2.3.2 Rationale

Ongoing disagreement and debate revealed the need for modeling techniques that could explore, identify, and chart out distinct groups of criminal careers across sampled individuals to answer two main criminal career questions: 1) are criminals and non-criminals distinct subsets of the population? and 2) what does the age-crime curve look like? If analyzed cross-sectionally, cluster analysis would be a logical technique to identify two distinct subgroups of criminals or non-criminals in the population. Cluster analysis identifies subgroups of similar individuals by

minimizing variation within groups and maximizing variation between groups (Tryon, 1939). However, cluster analysis would not be ideal in identifying subgroups of individuals with repeated measurements.

The age-crime curve could be analyzed as the regression of age on crime in a sample of individuals to detect trends or associations with increasing age (Land, et al., 1996b). Exponents can be added to accommodate curvature in trajectories and additional covariates can be adjusted for. Maximum likelihood estimation can provide the basis for hypothesis testing. However, regression analysis cannot account for subgroups within the population without assuming them to be known a priori. Using subjective cut-offs or incorrectly assumed grouping schemas can lead to underestimated standard errors, inflated t-statistics, and spurious p-values (Land, et al., 1996b).

Group-based modeling combines the above two techniques to simultaneously identify groups of homogenous trajectories of change over time in the population, and to estimate trends in the outcome over time. The model assumes that the underlying population is composed of distinct groups defined by their trajectories. This strategy of approximating an unknown distribution using nonparametric "groups" originates from finite mixture modeling, a technique to model distributions that may not be sufficiently approximated with a parametric distribution (McLachlan & Peel, 2000).

Statistical techniques that also model trajectories of change over time are hierarchical linear modeling (HLM) (Raudenbush & Bryk, 2002) and latent growth curve modeling (LGM) (McArdle & Epstein, 1987). Both HLM and LGM 1) assume trajectories follow a continuous distribution in the population, 2) model individual-level heterogeneity in trajectories, and 3) identify factors that account for individual variability about the population mean trajectory of

change (D. Nagin & Tremblay, 1999; D. S. Nagin, 2005). The group-based modeling approach differs because it assumes the population is composed of a mixture of distinct groups defined by their trajectories. Nagin recommends the use of group-based modeling for data with inherent distinct subgroup population trajectories. When the effect is assumed to change as a population average, or growth, with no assumptions of trajectory subgroup mixtures in the population, then LGM or HLM would be a better modeling technique (D. S. Nagin, 2005).

2.3.3 Censored normal trajectory analysis model

Group-based modeling approximates unknown distributional shapes using the methods of finite mixture modeling. The population is composed of a sum of discrete groups that have parametric forms. The general form of the likelihood function for a given set of longitudinal observations can be defined as the sum of each parametric density of the mixture weighted by the corresponding mixing proportion, over the number of mixture groups (McLachlan & Peel, 2000). The following derivation of the general likelihood function follows Nagin's notation and process (D. S. Nagin, 2005).

In a given population, let $Y_i = \{y_{i1}, y_{i2}, \ldots, y_{iT}\}$ denote the sequence of outcome measurements observed in individual *i* from time 1, 2, …, *T* periods of time, and $P(Y_i)$ as the probability of observing this sequence. In order to find the set of parameters that will maximize $P(Y_i)$, it is assumed that the model is composed of *j* underlying "trajectory groups". These groups are finite sets of polynomial functions over time. The $P(Y_i)$ can be written as

$$P(Y_i) = \sum_{j}^{J} \pi_j P^j(Y_i),$$

(eqn.1)

where π_j represents the probability of membership in trajectory group *j* and $P^j(Y_i)$ represents the probability of Y_i given membership in group *j*. The probabilities of trajectory group membership, π_j, *j=1,…, J,* are estimated indirectly using the multinomial logit function:

$$\pi_j = \frac{e^{\theta_j}}{\sum_j^J e^{\theta_j}},$$

(eqn. 2)

where θ_1 is normalized to zero for identifiability purposes. To simplify an already complex model, conditional independence is assumed between random variables y_{it}, given membership in trajectory group *j*. In other words, for individuals within trajectory group *j,* outcomes over time and individual-level deviations from the group trend are independent. Given this assumption, the probability of observing Y_i given membership in group *j* is,

$$P^j(Y_i) = \prod_{t}^{T} p^j(y_{it}),$$

(eqn. 3)

where $p^j(y_{it})$ is selected to conform to the distribution of the data analyzed. The model is able to accommodate count, binary and censored normal data. For count data, $p^j(y_{it})$ is assumed to follow a Poisson distribution or a zero-inflated Poisson. For dichotomous data, $p^j(y_{it})$ is assumed to follow the binary distribution. For normally distributed data, $p^j(y_{it})$ is assumed to

follow the censored normal distribution, which is especially designed for psychometric data by accounting for clustering of data at the scale minimum and maximum.

When y_{it} follows a censored normal distribution, y_{it}^{*j} represents a latent variable, or an unobserved construct that links the course of outcome over a time period x_{it}, given trajectory group j:

$$y_{it}^{*j} = \beta_0^j + \beta_1^j x_{it} + \beta_2^j x_{it}^2 + \beta_3^j x_{it}^3 + \varepsilon_{it},$$

(eqn. 4)

where ε_{it} is normally distributed with mean zero and standard deviation, σ. If $\beta^j X_{it}$ denotes the linear prediction, then $y_{it}^{*j} = \beta^j X_{it} + \varepsilon_{it}$, and y_{it}^{*j} is normally distributed with mean, $\beta^j X_{it}$ and standard deviation σ.

To account for censoring of psychometric data, let S_{min} and S_{max} denote the scale minimum and maximum scores, such that,

$$y_{it} = S_{min}\ if\ y_{it}^{*j} < S_{\min}$$

$$y_{it} = y_{it}^{*j} if\ S_{min} \leq y_{it}^{*j} \leq S_{max}$$

$$y_{it} = S_{max}\ if\ y_{it}^{*j} > S_{\max}$$

Under the censored normal model, the probability of y_{it} given membership in group j equals:

$$p^j(y_{it} = S_{min}) = \Phi\left(\frac{S_{min} - \beta^j x_{it}}{\sigma}\right),$$

(eqn. 5a)

$$p^j(y_{it}) = \frac{1}{\sigma}\varphi\left(\frac{y_{it} - \beta^j x_{it}}{\sigma}\right) for S_{min} \leq y_{it} \leq S_{max},$$

(eqn. 5b)

$$p^j(y_{it} = S_{max}) = 1 - \Phi\left(\frac{S_{max} - \beta^j x_{it}}{\sigma}\right),$$

(eqn. 5c)

where φ represents the standard normal distribution and Φ represents the cumulative distribution function of a normal random variable with mean $\beta^j X_{it}$ and standard deviation σ. Equation 5a-5c constrains the predicted scores to be between the range of the scale.

The likelihood function for the entire sample of N individuals is,

$$L = \prod_i^N P(Y_i),$$

(eqn. 5)

between $S_{min} \leq y_{it} \leq S_{max}$:

$$L = \prod_i^N \sum_j^J \pi_j P^j(Y_i),$$

$$L = \prod_i^N \sum_j^J \pi_j \prod_t^T p^j(y_{it}),$$

$$L = \prod_i^N \sum_j^J \pi_j \prod_t^T \frac{1}{\sigma} \varphi\left(\frac{y_{it} - \beta^j x_{it}}{\sigma}\right),$$

(eqn. 6)

which is maximized using a general quasi-Newton procedure (Dennis, 1981; Dennis, 1979) that specifies multiple starting parts to locate the global maximum. An inverse observed information matrix is evaluated at the maximum likelihood parameter estimates to obtain the variance-covariance matrix (Jones & Nagin, 2007).

2.3.4 Model Selection

Model selection is a 2-stage process:

1. Estimate the number of trajectory groups
2. Estimate the shape/order of each trajectory group

Finding the most parsimonious model is an iterative process and incorporates both statistical and subjective knowledge. The maximum number of trajectory groups in model selection is the total number of individuals in the sample population, N. However this large number of potential models and the exponential possibilities of new models when order and number of groups are considered, provide good reason to incorporate subjective knowledge to limit the set of models considered. For example, a 3-group quadratic model could have 3 parameters in each group: the intercept, the linear term, and the quadratic term, generating 27 (=3^3) possible models. Instead of testing all possible models, the researcher can stop model selection with the maximum number of possible groups based on theoretical knowledge and judgment (D. S. Nagin, 2005).

Nagin recommends the use of the Bayesian Information Criteria (BIC) as a basis for selecting the best model. The general form of the BIC is:

$$BIC = \log(L) - 0.5k\log(N),$$

where L is the value of the model's maximized likelihood, k is the number of parameters in the model, and N represents the sample size. The model with the largest (or least negative) BIC score is selected. The BIC is the difference between the measured improvement in model fit ($\log(L)$) and the penalty for additional parameters and sample size. According to Nagin, the number of parameters, k, includes the number of beta coefficients used for each group j, and the number of group membership probability parameters minus one. Therefore, a 2-group linear

model has a total of 5 parameters:$\beta_0^1, \beta_1^1 x_{it}$,$\beta_0^2, \beta_1^2 x_{it}$, and π_1. The intercept and linear slope for the first and second trajectory group is represented by $\beta_0^1, \beta_1^1 x_{it}$,and $\beta_0^2, \beta_1^2 x_{it}$ respectively. The probability of group membership in trajectory group 1 is denoted byπ_1. In the software used to perform model fitting, two values of the BIC is calculated based on 1) the number of individuals and the 2) total number of observations across time. The true BIC lies within these two BIC values (D. S. Nagin, 2005).

In addition to the BIC, the performance of two commonly suggested alternative fit statistics have been evaluated. The Akaike Information Criteria (AIC) (Akaike, 1974) and the Integrated Classification Likelihood-BIC (ICL-BIC) (McLachlan & Peel, 2000) were evaluated on mixture models of simulated count data. Brame et al. found the AIC to be similar to the BIC, but more likely to select a model with an extra (or unnecessary) group than the BIC. The ICL-BIC performed most poorly, almost consistently selecting the wrong model (Brame, Nagin, & Wasserman, 2006). To assist in model selection, other likelihood-based statistics can be evaluated in addition to the BIC, AIC, and ICL-BIC: the sample-size adjusted BIC (ssBIC) (Sclove, 1987), the consistent AIC (CAIC) (Bozdogan, 1987), the classification likelihood information criteria (CLC) (McLachlan & Peel, 2000; Ramaswarmy, DeSarbo, Reibstein, & Robinson, 1997), and entropy (Ramaswarmy, et al., 1997).

The AIC, BIC, ssBIC and CAIC are fit statistics based on the log-likelihood. The form of each statistic differs by the degree of penalty given to the number of estimated model parameters. The CLC, ICL-BIC and entropy are based on the classification maximum likelihood function (CML). CML evaluates mixture models based on how likely an individual belongs to group *j* conditional on their observed outcomes. Entropy is a scaled statistic of the degree of separation between mixture groups. The CLC combines entropy and the log-likelihood function,

and similarly, the ICL-BIC adjusts the BIC statistic with the measure of entropy. For these fit statistics based on log-likelihood, classification maximum likelihood, or a combination of both, smaller fit statistics and larger entropy would indicate better model fit (Henson, Reise, & Kim, 2007). Statistically, the model with a majority of smaller fit statistics would be the better choice. In situations where the fit statistics do not give strong evidence for a specific model, judgment based on prior research and clinical expertise should be used to choose the model with the best number of groups.

After estimating the number of groups, trajectory shape can be evaluated. Nagin suggests a systematic stepwise procedure, fixing the order to quadratic for each group, starting with a one group, then fitting a two-group quadratic model (2,2), a three-group quadratic model (2,2,2), until the maximum number of groups determined a priori have been fitted. The process is repeated by setting the order to linear or cubic for each model and evaluating BIC at each step. The estimated trajectory shape and substantive knowledge are used to estimate the order of each group (D. S. Nagin, 2005). Trajectory order can vary between groups. For example, if a population consists of one group that is consistently unchanging over time and another that rises and falls, then the first group can be a linear shape and the second a quadratic order. Trajectory beta estimates also can be tested formally; therefore significant beta coefficients provide additional evidence for the specified order in each group. The model with the largest BIC is selected.

An alternative method for estimating trajectory shape begins with a two-group quadratic model (2,2). This (2,2) model is compared with a three-group quadratic (2,2,2) model and the BIC is used to choose the best model. Given this "best" model, a lower-order model is fitted, for example, if the (2,2) model had a smaller BIC than the (2,2,2) model, a (1,1) model would be

tested next. If the (1,1) model has a smaller BIC than the previous (2,2) model, then the model fitting process stops and the (1,1) model is the selected. Trajectory shape can also be modified for each group depending on the charted trajectory for each group and the statistical significance of the beta coefficient significance. The first-order trajectory is recommended over the zero-order model since the zero-order model does not preserve beta parameter estimates that describe trajectory shape and direction (Henson, et al., 2007).

In addition to model fit statistics, model selection can also depend on the estimated number of individuals in each trajectory group. If the sample size in each group is too small to appropriately be identified as a "group" then fewer groups may be used to increase the number of individuals in each group. Given a small population size, the number of groups will automatically be reduced, regardless of the maximum number of theoretically possible groups. The plotted trajectory of each group shows how the trajectory behaves. The number of time points may also limit trajectory shape possible since data with two time points can only change linearly.

Model fit statistics and/or group sample size do not definitively determine the final model. Statistical criteria can be used as guides to narrow down the possible model choices, but professional and subjective judgment also should be incorporated in the model selection process. Research theories and published literature may provide reason to choose a certain model, regardless of statistical criteria.

2.3.5 Model Parameters

Trajectory analysis produces parameter estimates to represent the trajectory shape (using beta coefficients) and the p-values from hypothesis testing of each beta coefficient. The beta coefficients ${\beta_0}^j, {\beta_1}^j, {\beta_2}^j$ describe the shape of the trajectory for each modeled group *j*. Trajectory analysis can model shapes that range from flat (and unchanging) to linear (either increasing or decreasing), to curved with points of inflection (e.g. quadratic, cubic, or quartic) depending on the sign and exponential order given to each coefficient (see Table 1).

Table 1. Trajectory Shape by Beta Coefficients in Group j

$\beta_1 x$	$\beta_2 x^2$	**Trajectory Shape**
>0	<0	Single-peaked trajectory
0	0	Constant over time
>0	>0	Steadily accelerating
<0	<0	Steadily decelerating
<0	>0	Parabolic

Because the parameters are estimated by maximum likelihood, they can be tested using t-statistics. The null hypothesis is that the beta coefficients are zero. A significant p-value would imply the rate of change in the trajectory shape is significantly different from zero (D. S. Nagin, 1999, 2005).

The mean squared error of the model is denoted by sigma in the model output. Nagin describes this as the persistent 'unobserved heterogeneity' or random error for each individual by

time. Only the error term does not vary by group and therefore is not denoted with *j* in equation 4 (K. C. Land, P. McCall, & D. S. Nagin, 1996a).

Posterior probabilities of group membership are some of the most important and valuable parameters estimated by the trajectory analysis model (D. S. Nagin, 2005). Posterior probabilities measure the likelihood that a specific individual to belong to each of the trajectory groups given their observed data. The posterior probability is not the same as the probability of group membership (π_j), but is calculated using Bayes' Theorem:

$$\hat{P}(j|Y_i) = \frac{\hat{P}(Y_i|j)\hat{\pi}_j}{\sum_j \hat{P}(Y_i|j)\hat{\pi}_j},$$

(eqn 7.)

where $P(Y_i|j)$ is the predicted probability of observing individual *i*'s actual behavior trajectory, Y_i, given membership in group *j*, and π_j is the estimated population probability of being in group *j* (D. S. Nagin, 1999, 2005). It is computed from the estimated model parameters, and can be used to assess the quality of model fit by examining how distinct the posterior probabilities for each individual are because individuals are assigned to the trajectory group with the highest posterior probability.

Posterior probabilities can also be used as sampling weights to account for the inherent group uncertainty, and can be used with other approaches for follow-up data analysis. For example, trajectory group membership can be treated as an outcome variable, and risk factors other than time can be tested for association with trajectory group membership, weighting by the posterior probabilities to account for uncertainty (D. S. Nagin, 1999, 2005). The maximum of

the posterior probabilities generated for each trajectory group is used as a weight because this probability represents the actual trajectory group the individual has been assigned to.

2.3.6 Proc TRAJ Software

The SAS Procedure TRAJ was developed to perform model fitting and trajectory plotting (B. L. Jones, Nagin, & Roeder, 2001). The macros and documentation can be downloaded and installed from the website: www.andrew.cmu.edu/~bjones. Proc TRAJ requires three statements: MODEL, VAR and INDEP. The MODEL statement identifies the dependent variable distribution: censored normal (cnorm), zero-inflated poisson (zip), and binary distribution (logit). The VAR statement identifies the dependent variable measured over time. The INDEP statement identifies the independent variables at the point when the dependent variables were measured. ID identifies the subjects in the population, MIN and MAX are options of the censored normal model that allow the user to specify the minimum and maximum value of the outcome scale or instrument. ORDER identifies trajectory shape by assigning the exponential order given in the regression equation (intercept, linear, quadratic, cubic or quartic). NGROUPS specifies the number of groups to be modeled.

The Proc TRAJ output displays a set of parameter estimates for each model. The beta coefficients and standard errors for each trajectory group, the group membership probabilities and standard errors for the population, model fit statistics (two BICs, AIC, and the log-likelihood value), the mean square error variance, and the t-statistics and p-values for each parameter estimate. Each parameter is tested according to the student's t-distribution based on the null hypothesis that the parameter is equal to zero. Separate output datasets are produced and can be

used for further exploration or plotting of the trajectories. The OUTPLOT statement produces a dataset of the average observed and fitted values of each trajectory by time point. The output also contains the upper and lower 95% confidence bounds for each trajectory at each time point if the SAS macro for adding 95% confidence bands is used. The OUTSTAT statement produces a dataset containing the parameter estimates and the group membership probabilities at the population level for each trajectory group. The OUT statement produces a dataset containing all the variables used in the analysis, the group assignments and the posterior subject specific group membership probabilities (Bobby L. Jones).

Three SAS macros (trajplot, trajplotnew, and trajtest) have been developed in recent years as extensions in Proc TRAJ. The 'trajplot' statement uses the dataset produced by OUTPLOT and OUTSTAT to plot a line graph of the estimated and average observed change over time in the dependent variable by trajectory group. The 'trajplotnew' statement produces the same line graph with plotted confidence interval bands around each line. Lastly, the 'trajtest' statement can be used to conduct Wald tests of equality across coefficient estimates (B. L. Jones, et al., 2001; B. L. Jones & Nagin, 2007).

An additional SAS macro was developed to produce mixture fit statistics. The 'mixturefit' macro requires specification of the OUT dataset, the group identifying variable, the subject specific group membership probabilities, the log-likelihood value of the model, and the number of parameters. A total of seven mixture fit statistics are produced (entropy, AIC, BIC, CAIC, ssBIC, CLC, and ICL-BIC). The average posterior probability of group membership also is produced in a table between the trajectory groups (Henson, et al., 2007).

2.3.7 Strengths and Weaknesses of Trajectory Analysis

The weaknesses of trajectory analysis have been associated with the use of groups to approximate an underlying continuous distribution. Since the model assumes that a discrete or multinomial probability distribution can describe the unobserved heterogeneity in the data, the model may be mispecified if this distribution is actually continuous. The number of trajectory groups also may vary with increasing sample size (Piquero, 2008). Longitudinal data with few time points may limit identification of parameter estimates. A sensitivity analysis examining the influence of length of follow-up (as well as missing data) on trajectory analysis in a criminology study revealed that length of follow-up did not drastically change the number of trajectory groups; however, trajectory shape, group membership and peaks were affected. Individuals in trajectory groups also shifted to other groups with increased follow-up time, demonstrating poor group stability under these conditions (Eggleston, Laub, & Sampson, 2004).

Despite these limitations, the strengths of trajectory analysis still lie in its unique ability to concisely and easily summarize complex longitudinal data. Nagin reiterates that trajectory groups are not fixed realities, and individuals are not expected to follow these trajectories permanently. Trajectory groups are simply clusters of individuals with approximately similar patterns of change. In response to the sensitivity analysis conducted by Eggelston and colleagues, Nagin asserted that the issue of missing data and extended follow-up time periods are not specific to group-based modeling, but apply to all forms of longitudinal analysis methods; accordingly, sensitivity analyses should be conducted on other forms of longitudinal data analysis to evaluate properly the relative sensitivity of the group-based model. The influence of follow-up length on trajectory shape, membership, and stability would be expected, especially if

trajectory groups are limited by an incomplete time period. If the follow-up length is too short, it will fail to capture the full life-course of the outcome (D. S. Nagin, 2004). Simulation studies have also found sample sizes greater than 300 to 500 individuals to be robust to number of trajectory groups (Sampson, Laub, & Eggleston, 2004).

Group-based modeling has advantages over other longitudinal data analysis techniques, i.e. principal hierarchical modeling and latent growth curve modeling, because it does not assume a monotonic and regularly varying growth in the overall population. Group-based modeling assumes the opposite – the population is not normally or continuously distributed but composed of a discrete and distinct set of varying "growths" or trajectories of change (D. S. Nagin, 2005; Piquero, 2008). The strengths of group-based modeling methods are in its ability to estimate a distribution when there is no empirical or theoretical basis, especially for populations that behave irregularly.

2.4 BINARY AND MULTINOMIAL LOGISTIC REGRESSION

Binary and multinomial logistic regressions predict a categorical outcome variable while adjusting for one or more explanatory variables. In binary logistic regression, the outcome variable is dichotomous. The explanatory variables can be continuous or dummy-coded discrete variables. Logistic regression models the conditional mean of the regression equation bounded between zero and 1, with errors distributed binomially. The parameters are estimated using maximum likelihood. The model output includes slope coefficients, standard errors, Wald test statistics, and the corresponding p-values. The significance of each variable can be assessed

using the likelihood ratio test or the Wald test. The exponentiation of the slope coefficients produces odds ratios (ORs), i.e., ratio of odds that an outcome occurs when the explanatory variable is 1 compared to the odds that the outcome occurs when the explanatory variable is 0 (for binary predictors).

Multinomial logistic regression models outcomes with more than 2 levels and no natural ordering. For example, a three-level outcome will result in two sets of binary logistic regression equations, each one comparing one level of the outcome with the referent group. Multinomial logistic regression of a 3-level outcome produces slope coefficients, standard errors, Wald tests statistics, and corresponding p-values for each regression equation. Exponentiation of the slope coefficients produces relative risk ratios (RRs), i.e., the ratio of the predicted probabilities of a given level of the outcome versus the referent level for a one unit difference in the predictor. Multi-parameter tests the two risk ratios for a given predictor can jointly test whether the two predictors are equal to each other in the two models, or both equal to 0. Nagelkerke's R^2 is often referred to as a pseudo R^2 because it attempts to imitate the R^2 from linear regression as a measure of association. (Hosmer & Lemeshow, 2000).

2.5 TRAJECTORY GROUPS AND RISK FACTORS

Once the final trajectory model is identified, predictors of group membership can be examined using binary logistic or multinomial regression, depending on the number of identified groups. Similar approaches (Cote, et al., 2009; Yeates, et al., 2009) do not account for the classification error problem induced by treating trajectory groups as fixed and without error. Trajectory

groups are identified based on probability, but statistical methods like logistic regression do not assume classification error. Failure to account for classification error can lead to incorrect inferences and erroneous parameter variances (D. S. Nagin, 2005). One solution is to use weighted logistic or multinomial regression to adjust for uncertainty. Weights are calculated as products of trajectory group posterior probabilities. Combining trajectory groups with weighted regression methods can provide risk profiles for individuals most likely to follow certain trajectories over time.

3.0 METHODOLOGY

The analysis was based on the caregiver and care recipient dataset collected as of June 19, 2009. Specific dates for each collection period were recorded at baseline (diagnosis), 4 months, 8 months and 12 months after diagnosis.

3.1 EXPLORATORY DATA ANALYSIS METHODS

3.1.1 Computing Sum Scores

The measures of depressive symptoms, anxiety and caregiver schedule burden were chosen for this analysis. An overall score was computed for each subject by summing all the items (after reverse-coding appropriate items). These scales were chosen to represent caregiver psychological distress because they are widely used and have been validated as reliable measures of emotional health. All sum scores were calculated using SPSS version 16.0.

3.1.2 Univariate Analysis

Frequency tables were run for categorical risk factors (caregiver gender, relationship to care recipient, care recipient tumor type) and summary statistics (mean, standard deviation, minimum and maximum) were run for continuous covariates (caregiver age, baseline score of caregiver mastery, emotional stability, social support; baseline score of care recipient neuropsychological domain scores and symptoms score. As a potential covariate to predicting caregiver psychological and physical health, a time-dependent indicator for the death of a care recipient was created and coded as bereaved (yes or no) for caregivers who remained in the study.

3.1.3 Exploring the distribution

To explore the distribution of depressive symptoms, anxiety, and caregiver burden scores histograms and boxplots were created at baseline based on an initial sample of N=75 as of March 24, 2009. To examine distributions by time point, boxplots were graphed across time points and raw observations were graphed using spaghetti plots and individual profile plots (to examine patterns of change in the data). All distributional plots were created using STATA version 9.0.

3.2 PRELIMINARY DATA ANALYSIS METHODS

3.2.1 Data Setup and SAS Code

In order to apply Proc Traj, repeated measurements and covariate data must be set up in "wide" format, where only one row of data exists per subject and each repeated measurement is a separate variable. Repeated measures of the same outcome must have identical names with consecutive numbering to represent the time of measurement. Variables that hold the date of each repeated measure must also be identified in the dataset; as for outcome measures, time variables must have identical names and consecutive numbering. This naming convention also applies to time-varying covariates (see Table 2 and 3).

Table 2. Sample Data Organization for Proc Traj

ID	Gender	Age	CESD1	CESD2	CESD3	CESD4	T1	T2	T3	T4
1	1	52	3	10	14	12	0	4	8	12
2	0	54	11	10	14	15	0	4	8	12
3	0	44	8	9	10	9	0	4	8	12

Table 3. Variable Description of Sample Data

Variable Name	Description
ID	Caregiver ID
Gender	Caregiver gender
Age	Caregiver age
CESD1	Overall score of depressive symptoms at baseline

Table 3. Continued

CESD2	Overall score of depressive symptoms at 4 months
CESD3	Overall score of depressive symptoms at 8 months
CESD4	Overall score of depressive symptoms at 12 months
T1	Months from first visit (approximately 0 months)
T2	Months from first visit (approximately 4 months)
T3	Months from first visit (approximately 8 months)
T4	Months from first visit (approximately 12 months)

Since follow-up visits were conducted within two weeks of caregiver's follow-up date, time variables were computed by calculating the duration between dates of follow-up and baseline date of measurement in months. As advised by Nagin, each time variable was scaled to be between 0 and 10 by dividing each duration time by 10. Scaling time variables decreases processing time in Proc Traj (D. S. Nagin, 2005).

The following is an example of the syntax used in Proc Traj to test and plot a censored normal two-group linear model for depression from baseline to one year:

```
proc traj data=traj.cg out=oput outstat=cesdstat outplot=cesdplot ci95m;
id id;
var CESD1-CESD4;
indep t1-t4;
model cnorm;
min 0;
max 30;
order 1 1;
run;
%trajplot(cesdplot,cesdstat,'Depression over Time','cnorm model(1 1)-
2group','CESD','Time/10');
%trajplotnew(cesdplot,cesdstat,'Depression over Time','cnorm model(1 1)-
2group','CESD','Time/10');
```

The censored normal model was used for all measures with minimum and maximum values determined by the scale range (CESD: 0-30; POMS: 3-15; CRA Schedule: 5-25).

3.3 TRAJECTORY ANALYSIS METHODS

3.3.1 Model Selection

The method proposed by Henson, et al. (Henson, et al., 2007) and non-statistical considerations were used for choosing the best trajectory model. Models with smaller mixture fit statistics and larger entropy were preferred. Three separate censored normal trajectory models were analyzed using SAS Proc Traj for each measure of psychological distress: depressive symptoms, anxiety, and caregiver burden. Trajectory plots, trajectory plots with confidence intervals, and mixture fit statistics were produced in addition to the SAS Proc Traj parameter output to aid in model selection. For each measure, a two-group quadratic model (2,2) was first tested as the base or referent model. A two-group model was selected based on previous hypotheses of caregiver psychological distress change following cancer diagnosis of the care recipient - caregivers may follow the "adapation hypothesis" or the "wear and tear" hypothesis of change.

Trajectory order was estimated after the number of trajectory groups was estimated. Two guidelines were implemented because of model and data limitations. In all models, the lowest trajectory order tested was the linear order, even if the slope was not significantly different from zero. The linear order was still retained in the model to preserve parameter estimates revealing slope information about trajectory shape; trajectory orders of zero or less were not considered. The highest trajectory order tested was the quadratic order because the current data limitations (i.e., only four points of measurement) precluded testing for higher order trajectory shapes.

Final model decisions were based on both statistical and clinical criteria. Trajectory plots with non-overlapping confidence intervals, a general consensus of small mixture fit statistics,

appropriate estimated sample size of each trajectory group, and distinct average posterior probabilities per group all were considered. Clinical criteria consisted of examining available clinical cutoffs for each measurement scale and incorporating previous research on the identification of sub-groups specific to the measurement scale, i.e. normal vs. abnormal, or low, medium, vs. high.

3.3.2 Exploring Relationships between Trajectory Groups

After choosing the final model for each outcome scale, the relationships between trajectory groups were explored for each outcome using cross-tabulation tables, Fisher's exact, and Pearson chi-square exact tests. Phi (φ) and Cramer's *V* were calculated to measure effects sizes for 2 x 2 and 2 x 3 cross-tabulations respectively. To account for trajectory group uncertainty, cross-tabulation was done using average weights calculated from posterior probabilities. Both weighted and unweighted tables were compared and used to aid in interpretation. P-values less than or equal to 0.05 were considered to be statistically significant.

3.4 BINARY AND MULTINOMIAL LOGISTIC REGRESSION ANALYSIS METHODS

Predictors or risk factors of each trajectory group were tested using weighted binary logistic regression for outcome measures with two trajectory groups. For the outcome measures with three trajectory groups, weighted multinomial logistic regression was used. Caregiver risk

factors included in the model were: age, gender, relationship to care recipient (spouse vs. other), years of education, and baseline level of mastery, emotional stability, and social support. Care recipient risk factors included tumor type (astrocytoma III-IV vs. other), cognitive function, and symptom status. To reduce correlation between predictors, mean composite scores of the language (composition, repetition, and naming scores) and reasoning (judgment and similarities scores) subscale were computed from the NCSE domain scores, and continuous predictors (caregiver age, emotional stability, social support, mastery, years of education and symptoms score) were centered at the median.

To build an overall prediction model for caregiver psychological distress, factors related to the caregiver and care recipient were first tested as separate models. Block testing was used to select factors important to the each model. Block 0 included factors clinically important to the model (caregiver: age, gender, relationship to care recipient, years of education and emotional stability; care recipient: tumor type), Block I included exploratory factors (caregiver: baseline levels of social support and mastery; care recipient: cognitive function domain scores and symptoms score). Subsequent blocks were tested after selecting significant variables in each model. Criteria for selecting important variables consisted of significant Wald's and multi-parameter tests at p-values < 0.05 and/or a standardized beta coefficient>0.3. The final model was built by combining significant variables from the caregiver and care recipient models.

Collinearity diagnostics were calculated for each model and assumptions were checked by calculating predicted probabilities, standardized Pearson residuals and Cook's distance for binary outcomes. Additionally, orthogonalization analysis was conducted to adjust for collinearity and examine the contribution of certain variables to the model. Index plots of the residuals and Cook's distance were created to identify poorly fit and influential observations

respectively; Cook's distance was plotted vs. residuals, and residuals were plotted by predicted probabilities. In sensitivity analyses, the impact of influential observations was assessed by refitting the model without these observations. The Hosmer & Lemeshow goodness-of-fit test was used to assess model adequacy. Binary and multinomial logistic regression analyses were conducted using SAS proc logistic (see Appendix B).

4.0 RESULTS

As of June 19, 2009, a total of 99 caregiver-care recipient dyads were recruited with data up to six time points (baseline (at diagnosis), 4 months, 8 months, 12 months, 18 months and 24 months after diagnosis). The total number of caregivers at each time point and the observed average score for each outcome are listed in table 4. The reduced sample size at each time point is a result of caregivers who have not reached their follow-up time point yet at the time the analysis was conducted (at baseline, n=1; 4 months, n=9; 8 months, n=14; 12 months, n=15) and caregiver attrition. The reasons for caregiver attrition throughout the course of caregiving were: dropped out before baseline assessment for unknown reasons (n=14), loss to follow-up (n=5), death of the care recipient (n=2), overwhelmed (n=5), caregiving relationship ended (n=1), and care recipient ineligible diagnosis (n=1). Additionally, this analysis also included pilot data with no 8 month and 12 month assessments (n=12).

Table 4. Summary Statistics of Outcome Measures over Time

	Depressive symptoms		Anxiety		Caregiver Burden	
Time Point	N	M (SD)	N	M (SD)	N	M (SD)
Baseline	82	9.5 (6.3)	80	9.1 (2.8)	81	15.8 (4.4)
4 months	61	7.6 (5.9)	61	8.0 (2.8)	59	15.1 (5.0)
8 months	34	6.6 (6.0)	34	7.6 (2.7)	30	13.7 (4.9)
12 months	19	5.4 (4.8)	19	6.2 (2.3)	14	13.7 (4.9)
18 months	8	3.8 (3.3)	8	6.8 (2.7)	6	10.0 (6.6)
24 months	3	7.0 (4.4)	3	8.0 (3.0)	--	--

4.1 EXPLORATORY DATA ANALYSIS RESULTS

4.1.1 Socio-demographic and Clinical Characteristics

The majority of the sample collected at baseline were female caregivers (n=63, 75.9%) with an average age of 51 years, who completed 14 years of education on average, were not bereaved (n=86, 87.8%), and were caring for spouses (n=61, 75.3%) (see table 5).

Table 5. Baseline Descriptives of Caregiver Sample

	N (%) **M (SD)**
Caregiver Characteristics	
Gender	
Male	20 (24.1%)
Female	63 (75.9%)
Relationship to Care Recipient	
Spouse or significant other	61 (75.3%)
Parent	9 (11.1%)
Daughter/son	5 (6.2%)
Sister/brother	1 (1.2%)
Niece/nephew	1 (1.2%)
Other	1 (1.2%)
Friend/companion	3 (3.7%)
Bereaved	12 (12.2%)
Age	51.4 (11.4)
Years of Education	14.3 (2.5)
Mastery	20.6 (2.6)
Emotional Stability	14.7 (3.4)
Social Support	35.5 (4.5)

In the care recipients, the most common tumor type was a glioblastoma (n=52, 58.4%). On average, care recipients scored low on symptom status (M=32.3, SD=29.6). Cognitive

functioning was relatively high for the orientation and language repetition domains, and low for the calculations domain (see Table 6).

Table 6. Baseline Descriptives of Care Recipient Sample

Care Recipient Characteristics	**N (%)** **M (SD)**
Tumor type (n=89)	
Astrocytoma I-II	5 (5.6%)
Glioblastoma	52 (58.4%)
Oligodendroglima	14 (15.7%)
Other	12 (13.5%)
Symptoms (N=65)	32.3 (29.6)
Cognitive functions	
Orientation (n=85)	11.6 (1.1)
Attention (n=85)	6.9 (1.7)
Language (n=84)	
Comprehension	5.5 (0.8)
Repetition	11.6 (1.2)
Naming	7.7 (0.8)
Constructional ability score (n=84)	4.4 (1.9)
Memory (n=84)	7.5 (3.4)
Calculations (n=83)	3.5 (0.9)
Reasoning	
Similarities (n=83)	6.7 (1.7)
Judgment (n=82)	4.7 (1.4)

4.1.2 Psychological Distress Distribution and Change over time

The distribution of depressive symptoms score was right-skewed, and the majority of caregivers scored between 5 and 14 (see Appendix C.1). The distribution of anxiety scores was left-skewed, and the majority of caregiver scored between 8 and 11 (see Appendix C.2). The distribution of caregiver burden scores was slightly right skewed, and the majority of caregivers scored between 15 and 18 (see Appendix C.3).

Individual profile plots over time for each outcome show the actual raw trajectories for each person, and provided evidence of heterogeneity of trajectories within each scale. The plots indicate that at most 50% of caregivers have complete data on all four time points (see Appendix D.4).

The boxplots over time shows the majority of caregiver scores below the clinical cutoff of depression (=10) at baseline and remains low over time with large variation at each time point. For Anxiety score, the median score decreases over time, starting at approximately 9.0 at baseline to 7.0 at one year, with similarly large variation. Caregiver burden scores are similar at baseline and 4 months, with a higher median value at 1 year.

4.2 PRELIMINARY DATA ANALYSIS RESULTS

In this analysis, four time points were analyzed: at diagnosis (baseline), 4 months, 8 months, and 12 months following diagnosis. The 8 caregivers at 18 months and 3 caregivers at 24 months were excluded. The number of months between each date of measurement was calculated to obtain more exact estimates of duration in days between follow-up visits. The time variables were divided by 10 to scale the time values between 0 and 1.

Spaghetti plots between baseline and 4 months plot fitted slopes between time and the outcome scale. These fitted lines reveal potential groups of change, specifically, trajectories increasing, decreasing, or remaining the same from baseline to 4 months. The thick red line represents the population average, which shows a generally unchanging and constant slope and hides the heterogeneity present in the data (see Appendix D.4).

4.3 TRAJECTORY ANALYSIS RESULTS

4.3.1 Model Selection

From baseline to one year following diagnosis, a two-group linear model was estimated for both depressive symptoms and anxiety, and a three-group linear model was estimated for caregiver's feeling of burden on the schedule subscale. Appendix D contains the SAS Proc Traj output parameters and trajectory plots.

4.3.1.1 Depressive Symptoms

The (2,2) model had a higher entropy and lower values for the AIC, BIC, CAIC, CLC, and ICL-BIC compared to the (2,2,2) model (see Table 7). Therefore, a two-group model linear model was selected and tested. The (1,1) model had lower values for the AIC, BIC, CAIC, ssBIC, and ICL-BIC, but the entropy was the same as the (2,2) model. The linear trajectory slope parameters for both groups in the (1,1) model were borderline or significantly different from zero, whereas the (2,2) model did not have significant quadratic or linear trajectory slope parameters. The lower mixture fit statistic values and significant trajectory slope parameters provide statistical evidence supporting the two-group linear trajectory model.

Table 7. Mixture Fit Statistics for Depressive Symptoms Trajectory Model

Models	Entropy	AIC	BIC	CAIC	ssBIC	CLC	ICL-BIC
(2,2)	0.53	1147.50	1170.77	1179.77	1142.34	1192.91	1234.17
(2,2,2)	0.47	1149.06	1182.67	1195.67	1141.61	1236.55	1296.15
(1,1)	0.53	1145.10	1163.24	1170.24	1141.13	1194.57	1226.67

A patient with a score of 10 or greater on the CESD scale is considered to be clinically depressed. This clinical cutoff provided additional evidence to choose the two-group linear model because the model identified two groups of patients: 1) those clinically depressed (intercept=13.9) and 2) those not clinically depressed (intercept=5.1) at baseline. The three-group trajectory model further divided the clinically depressed group into two groups, those severely depressed (intercept=15.3) and those moderately depressed (intercept=11.3), and retained a group of caregivers who were not clinically depressed (intercept=4.5).

The final two-group linear trajectory model estimated that 61.2% of caregivers had low depressive symptoms at baseline (mean (M) = 5.3) and remained low (M=2.7) at 12-months (p=0.06 for trajectory slope); the remaining caregivers (38.8%) had high scores at baseline (M=14.4) that decreased significantly by 12-months (M=9.1; p=0.01). See Appendix D.1 for parameter estimates.

4.3.1.2 Anxiety

Similar to the depressive symptoms model, the (2,2) model for anxiety score had higher entropy and lower values for the AIC, BIC, CAIC, CLC, and ICL-BIC compared to the (2,2,2) model (see Table 8). Therefore, a two-group model linear model was selected and tested. The (1,1) model had lower values for the AIC, BIC, CAIC, and ICL-BIC compared to the (2,2) model. The linear trajectory slope parameters for both groups in the (1,1) model were significantly different from zero, whereas the (2,2) model did not have significant quadratic or linear trajectory slope parameters. Since the majority of the mixture fit statistics for the (1,1) model were lower than that of the (2,2) model, and trajectory slope parameters were significantly

different from zero, the two-group linear trajectory model was selected as the final model for POMS.

Table 8. Mixture Fit Statistics for Anxiety Trajectory Model

Models	Entropy	AIC	BIC	CAIC	ssBIC	CLC	ICL-BIC
(2,2)	0.58	863.14	886.41	895.41	857.98	902.63	943.89
(2,2,2)	0.56	856.40	890.01	903.01	848.95	925.63	985.23
(1,1)	0.57	859.34	877.44	884.44	885.33	903.40	935.50

The final two-group linear model estimated that 20.4% of caregivers had low anxiety scores at baseline (M=6.0) that decreased significantly (M=4.0) by 12-months (p=0.002); the remaining caregivers (79.6%) had high scores at baseline (M=10.2) that decreased significantly by 12-months (M=7.8; p=0.001).

4.3.1.3 Caregiver Burden

The (2,2) model for caregiver burden scores had higher entropy and lower values for the CAIC, CLC, and ICL-BIC compared to the (2,2,2) model (see Table 9). However since the AIC and BIC were smaller for the (2,2,2) model, a three-group linear model was tested. The (1,1,1) model had lower values for the AIC, BIC, CAIC, ssBIC, and ICL-BIC compared to the (2,2,2) model, which provided support for a linear model. A two-group linear model was compared to the (1,1,1) model. The (1,1) model had a higher entropy and lower values for only the CLC and ICL-BIC. The mixture fit statistics predominantly support the (1,1,1) model, because it had the lowest values on four (the AIC, BIC, CAIC, ssBIC) out of seven statistics compared to the other trajectory models tested.

Table 9. Mixture Fit Statistics for Caregiver Burden Trajectory Model

Models	Entropy	AIC	BIC	CAIC	ssBIC	CLC	ICL-BIC
(2,2)	0.63	970.46	993.73	1002.73	965.30	1002.91	1044.18
(2,2,2)	0.61	956.62	990.23	1003.23	949.17	1014.83	1074.43
(1,1,1)	0.60	952.64	978.49	988.50	946.91	1018.50	1064.35
(1,1)	0.63	967.90	986.00	993.00	963.89	1004.57	1036.67

The (1,1,1) model estimated three distinct groups of caregivers experiencing different levels of caregiver burden across the caregiver burden scale. These three groups had low (intercept=10.7), moderate (intercept=14.0), and high (intercept=19.3) scores on the Caregiver burden at baseline and showed clear separation of trajectories when plotted with 95% confidence interval bands. The (1,1) model grouped 18 caregivers from the moderate group into the low (intercept=12.3) group and 8 caregivers into the high (intercept=18.7) group. Since the caregiver burden scale does not have clear cutoff values that support the presence of two distinct groups of caregivers experiencing either severe or mild schedule burden, the allowance of three latent groups of caregivers is reasonable.

An estimated 20.4% of caregivers had low caregiver burden scores at baseline (M=10.5) that decreased significantly (M=6.4) by 12-months ($p<0.001$); the moderate trajectory included 26.5% of caregivers with consistent scores at baseline (M=14.2) and 12 months (M=11.0; $p=0.51$); the majority of caregivers (53.1%) had consistently high scores at baseline (M=19.7) and (M=20.0) at 12 months($p=0.85$). See Appendix D.3 for parameter estimates and plots.

4.3.2 Relationships between Trajectory Groups

Pairwise weighted cross-tabulations revealed significant relationships between trajectory groups for depressive symptoms and anxiety (Φ=0.45, $\chi^2(1)$=17.0, p<0.001), and anxiety and caregiver burden (Cramer's V=0.31, $\chi^2(2)$=6.0, p=0.05). There was no significant association between depressive symptoms and caregiver burden (Cramer's V=0.09, $\chi^2(2)$=0.52, p=0.77). Of the caregivers in the low depressive symptoms trajectory group, an estimated 62.0% were in the high anxiety group and an estimated 38.0% were in the low anxiety group (see table 10). All of the caregivers in the high depressive symptoms group were also in the high anxiety group. Therefore, the caregiver sample includes of three latent groups representing depressive symptoms and anxiety patterns of change over time: 1) 20.4% (n=20) of caregivers did not experience high levels of depression or anxiety, 2) 40.8% (n=40) of caregivers experience low depression but high anxiety, and 3) 38.8% (n=38) of caregivers experience both high depression and high anxiety from diagnosis to one year afterwards (not shown in table).

Table 10. Weighted Cross-tabulation Between Trajectory Groups

	Caregiver Burden				**Anxiety**	
Depressive Symptoms	**Low**	**Moderate**	**High**		**Low**	**High**
Low	11.8 (30.5%)	13.3 (34.4%)	13.6 (35.2%)		18.5 (38.0%)	30.3 (62.0%)
High	5.4 (22.7%)	8.3 (34.9%)	10.0 (42.4%)		0 (0.0%)	34.8 (41.6%)
Anxiety						
Low	5.6 (36.3%)	7.7 (50.0%)	2.1 (13.8%)		--	--
High	11.9 (24.5%)	13.2 (27.1%)	23.5 (48.4%)		--	--

Caregivers in the high anxiety group were also likely to be in the high caregiver burden trajectory group (48.4%). The remaining caregivers in the high anxiety group divide evenly

between the low and moderate caregiver burden trajectory groups (24.5% and 27.1% respectively).

Table 11 shows the weighted cross tabulation between caregiver burden and anxiety group stratified by depressive symptoms (high or low trajectory groups). Of the caregivers in the low depressive symptoms group, a significant association was observed between anxiety and caregiver burden (Cramer's V=0.42, $\chi^2(2)=8.6$, $p=0.01$). Caregivers in the low depressive symptoms and anxiety group also tended to be in the low (31.6%) and moderate (47.2%) caregiver burden group rather than the high (21.2%) group. The majority of caregivers in the high anxiety group also were also in the high caregiver burden group (63.0% of the subgroup with low depressive symptoms and 57.8% of the subgroup with high depressive symptoms). No caregivers were classified in both the low anxiety group and the high depressive symptoms group.

Table 11. Weighted Cross-tabulation Between Anxiety and Caregiver Burden by Depressive Symptoms Trajectory Group

Depressive Symptoms	Anxiety	Caregiver Burden		
		Low	Moderate	High
Low	Low	5.8 (31.6%)	8.6 (47.2%)	3.8 (21.2%)
	High	6.3 (20.6%)	5.0 (16.5%)	19.2 (63.0%)
High	Low	0.0	0.0	0.0
	High	6.3 (18.0%)	8.8 (25.2%)	19.9 (57.8%)

4.4 BINARY AND MULTINOMIAL LOGISTIC REGRESSION RESULTS

4.4.1 Depressive Symptoms Trajectory Group

The initial binary logistic regression results from the first block of caregiver factors (age, gender, relationship to care recipient, years of education and emotional stability at baseline) suggested an association between caregiver gender and relationship to care recipient. A cross tabulation revealed that a majority (69%) of female caregivers care for spouses instead of non-spouses (φ=-0.26, Fisher's Exact test, p=0.01). To reduce multicollinearity between predictors, relationship to care recipient was excluded from further analyses, and gender was used.

In the caregiver model, Block 0 ($\chi^2(4)=15.2$, p=0.004, Nagelkerke R^2=0.25) and Block I ($\chi^2(6)=17.8$, p=0.007, Nagelkerke R^2=0.28) significantly predicted depressive symptoms trajectory group. Emotional stability was the only significant predictor in each block ($\chi^2(1)=8.8$, p=0.003; $\chi^2(1)=6.7$, p=0.01 respectively) (see Appendix E.1). The exploratory factors in Block I were not significant to the model and were excluded from the final caregiver model.

In the care recipient model, tumor type did not significantly predict depressive symptoms group, nor did symptoms status or any of the cognitive functions (see Appendix E.1). Since cognitive functions scores may be highly correlated, predictors (symptoms inventory and calculations score) with standardized coefficients > 0.3 were refit with the fixed factor, tumor type, in Block II. However, none of these variables were significant to the overall care recipient model ($\chi^2(3)=3.6$, p=0.31). The final caregiver-care recipient model of the fixed factors from Block I significantly predict depressive symptoms trajectory group ($\chi^2(5) = 22.13$, p=0.0005, Nagelkerke R^2=0.36). Caregivers with higher levels of emotional stability were less likely to be

in the high depressive symptoms trajectory group (*B*=-0.36, *OR*=0.70 per unit difference in emotional stability, $\chi^2(1) = 11.5$, p=0.0007), while controlling for caregiver age, gender, education, and care recipient tumor type.

There was no significant difference between observed and predicted depressive symptom trajectory group membership (Hosmer & Lemeshow test $\chi^2(8)$=2.4, p=0.97). Influence plots identified two observations with Cook's distance > 0.10 (see Appendix E.1). Estimates changed very little when the model was refit with these observations excluded.

4.4.2 Anxiety Trajectory Group

In the caregiver model, emotional stability significantly predicted anxiety trajectory group in both Block 0 ($\chi^2(4)$=10.9, p=0.03, Nagelkerke R^2=0.22) and Block I ($\chi^2(6)$=13.7, p=0.03, Nagelkerke R^2=0.27) (see Appendix E.2). In Block II, neither social support nor mastery contributed significantly to the caregiver model, and were excluded.

In the care recipient model, tumor type did not significantly predict anxiety trajectory group ($\chi^2(1)$=0.003, p=0.96). The presence of symptoms and cognitive function domain scores also did not contribute to the overall model in Block I ($\chi^2(9)$=13.8, p=0.13). The predictors (orientation, language, constructional ability, calculations) with standardized coefficients > 0.3 and tumor type were tested in Block II. However, none of these contributed significantly to the overall model ($\chi^2(5)$=7.1, p=0.21).

The combined caregiver-care recipient model consisting of Block 0 variables was borderline significant in predicting anxiety trajectory group ($\chi^2(5) = 10.2$, p=0.07, Nagelkerke R^2=0.22). Caregivers with higher emotional stability were less likely to be in the high anxiety

trajectory group (*B*=-0.27, *OR*=0.76 per unit difference in emotional stability, $\chi^2(1) = 5.7$, *p*=0.02), controlling for caregiver age, gender, years of education, and care recipient tumor type.

There was no difference between observed and predicted anxiety group membership, (Hosmer & Lemeshow ($\chi^2(8)=9.2$, *p*=0.32), indicating no lack of model fit. Influence plots identified one observation with Cook's distance > 0.25 (see Appendix E.2 for plot). Upon removal of this observation, the overall model p-value achieved statistical significance ($\chi^2(5) = 15.8$, *p*=0.008, Nagelkerke R^2=0.30). The caregiver-care recipient model with and without the influential observation is shown under Block 0 and I respectively, in Appendix E.2. The influential case was a 44 year old female caregiver with 17 years of education, whose care recipient has an astrocytoma grades III-IV. However, her emotional stability score of 7 was somewhat low for a typical person classified in the low anxiety group.

4.4.3 Caregiver Burden Trajectory Group

A multinomial logistic regression was used to estimate caregiver burden trajectory group membership. The overall caregiver model for caregiver burden trajectory group was not significant for Block 0 ($\chi2(8)=7.9$, *p*= 0.45) or Block I ($\chi2(12)=11.1$, *p*=0.53) (see Appendix E.3).

In the care recipient model, tumor type was a significant predictor in Block 0 ($\chi^2(2)=11.4$, *p*=0.003, Nagelkerke R^2=0.15). Tumor type continued to be significant in the presence of the symptoms and cognitive function domain scores of Block I ($\chi2(18)=36.6$, *p*=0.006, Nagelkerke R^2=0.54). In Block II variables with standardized coefficient estimates >0.3 (language and constructional ability) were retained. In Block III, the language domain score was removed, and

the final care recipient model was predicted by tumor type and language (χ2(4)=22.8, p=0.001, Nagelkerke R^2=0.30) (not shown in table).

The caregiver-care recipient model combined the caregiver Block I variables with the care recipient Block III variables. Caregiver education was significantly correlated with age (r=-0.3, p=0.02) and constructional ability score (r=0.3, p=0.007). Orthogonal versions of these variables were created to assess their relative contributions to the prediction. Constructional ability was the stronger independent predictor, and caregiver education was not significant when constructional ability was in the model.

The final model was still significant (χ^2(10)=26.6, p=0.003, Nagelkerke R^2=0.35), with significant multi-parameter tests for tumor type (χ^2(2)=8.5, p=0.01) and borderline significant test for constructional ability score (χ^2(2)=4.7, p=0.10). Care recipients with astrocytoma III-IV were almost ten times more likely to have caregivers assigned to the high caregiver burden group (B=2.3, RR=9.8, χ^2(1)=8.5, p=0.004) and six times more likely to have caregivers in the moderate trajectory group (B=1.8, RR=5.8, χ^2(1)=4.5, p=0.03) than to have caregivers assigned to the low caregiver burden group. Additionally, for every one unit increase in care recipient constructional ability score, caregivers were 0.4 times less likely to belong to the moderate trajectory group (B=-1.0, RR=0.44 , χ^2(1)=5.5, p=0.03) or to the high caregiver burden group (B=-0.9, RR=0.39, χ^2(1)=4.3, p=0.04), adjusting for caregiver demographic variables.

5.0 DISCUSSION

Group-based trajectory modeling revealed significantly different patterns of change in psychological distress over time for caregivers of patients with a primary malignant brain tumor within 12 months of diagnosis. Baseline scores of depressive symptoms trajectory groups started either high (above clinical cutoff for depression) or low (below the cutoff), and decreased on average, by 4 and 2 points respectively, over time. Similarly, anxiety scores started either high or low at baseline, and significantly decreased by 2 and 3 points respectively, over time. Caregiver burden scores behaved in different ways. Caregivers who scored low at baseline continued to decrease significantly over time, but caregivers who scored moderate to high at baseline experienced no significant change in caregiver burden over time.

Prospective research on caregiving is rare or based on studies of small sample sizes (M. P. Lawton, M. Moss, C. Hoffman, & M. Perkinson, 2000). To our knowledge, no other caregiver study has used group-based modeling of longitudinal caregiving data, nor has estimated distinct trajectories of depressive symptoms, anxiety scores, and caregiver burden score over time. Our results to date lend support to the adaptation hypothesis, suggesting that caregivers learn to adjust and cope with the demands of the care situation. However, clinical interpretation is important to evaluate whether caregivers actually experience less psychological distress, because statistically significant improvement, may not be clinically important if the

caregiver has not crossed the cutoff for normal levels of psychological distress. These trajectories not only allow the researcher to easily examine patterns of change over time, but also give the researcher power to analyze relationships between trajectory groups. Trajectory groups can be used as outcome or predictor variables in other analyses (provided the appropriate weights are used to control for trajectory group uncertainty in the trajectory group classification). Emotional stability score was the primary risk factor identified for high levels of depressive symptoms and anxiety. Caregivers with lower emotional stability were more likely to experience high levels of depressive symptoms and anxiety at diagnosis that decreased over time.

A recent study using random-effects growth curve modeling on caregivers of Alzheimer's patients reported similar results (Jang, Clay, Roth, Haley, & Mittelman, 2004). Caregiver emotional stability was a significant risk factor for increased levels of caregiver depression one year following intervention. These authors add that although emotional stability and depressive symptoms are highly correlated, they are two separate constructs. In our data, caregiver emotional stability was significantly correlated with depressive symptoms trajectory group (r=-0.4, p=0.002) and baseline depressive symptoms score (r=-0.6, p<0.0001).

Emotional stability score of the caregiver was not associated with caregiver burden. Caregiver burden was predicted only by care recipient characteristics, specifically tumor type and cognitive function. Care recipients with more aggressive tumor types will most likely have more frequent doctor's visits, treatment appointments and shorter survival time, which may explain why caregivers feel burden on their schedules. In addition, poor performance on constructional activity (i.e., the inability to assemble shapes to copy a 2-dimensional drawing) suggests that care recipients have both cognitive and functional limitations, specifically in the use of tools, and will be more likely to require help from the caregiver in performing activities of

daily living, such as dressing, bathing, and eating. This places a greater burden on the caregiver since the care recipient requires constant attention and help.

Our findings suggest that caregiver personality disposition (e.g. emotional stability) is associated with caregiver psychological responses in the depressive symptoms and anxiety trajectory groups. Only the caregiver burden trajectory group is predicted by care recipient disease characteristics. Contrary to our expectations, our analysis failed to identify significant associations between risk factors that have been shown to be associated with depressive symptoms and anxiety in caregivers (e.g. age, gender, relationship to care recipient, care recipient tumor type) when emotional stability score was included in the overall prediction model. The contribution of emotional stability score may have over-adjusted for the other risk factors. Future studies can estimate the independent contributions of emotional stability score to each risk factor in the model by using orthogonalization. The relatively small sample size also limits our power to detect associations.

5.1 LIMITATIONS

One of the limitations of this analysis was the limited number of measurement time points assessed. As mentioned in chapter 2.3.7, the number of time points can influence trajectory shape, group membership, and peaks. In this analysis length of follow up spanned over one year across only four points of assessment. Therefore, trajectory shapes were limited to linear, and sample sizes at the 8-month and 12-month time points were small. The assessment period to date may not be sufficiently long and/or the assessments may not be sufficiently frequent to represent

the true trajectory of change in care recipients. However 12 months post-diagnosis, follow-up assessments continue for every six months up to 5 years in this ongoing study, and recruitment also is continuing.

Another limitation in this analysis is potential selection bias. Caregivers who experience higher levels of demands and psychological distress may be more likely to leave the study, be lost to follow-up, have a deceased care recipient, or refuse because they are unable to cope with the demands of the care situation. If the caregivers who drop out of the study tend to be those who are experiencing caregiver burnout and can no longer handle extraneous responsibilities (such as participating in longitudinal research), then the remaining sample would be biased in favor of an adaptation hypothesis, because caregivers who remain in the study are those who have learned to manage and provide care as a family caregiver. In this analysis, 14 caregivers dropped out of the study after consenting but before baseline measurements could be assessed. These caregivers could be more highly stressed at baseline than others. Five caregivers dropped out of the study because of feeling "overwhelmed", and 5 caregivers were lost to follow-up. One of the limitations of the parent study is the inability to distinguish specific reasons for caregiver dropout, and informative drop-out could provide biased results.

Although there were no significant differences between observed and predicted groups in the Hosmer-Lemeshow tests, the overall classification rate was not assessed. There is a possibility for misclassification. Future studies also should analyze the overall classification rate (using ROC area under the curve) and the rate of false positives and negatives (using Youden's Index). Distance measures can be used to minimize false positives and negatives.

5.2 FUTURE DIRECTIONS

In this analysis, questions were raised that will be pursued in future work. With the development of group-based trajectory analysis, several extensions have been proposed; one of them is the combination of propensity scores and trajectory analysis to make causal inferences from non-experimental longitudinal data (Haviland, Nagin, & Rosenbaum, 2007; Haviland, et al., 2008). For example, in our analysis we did not evaluate the effect of death of the care recipient on caregiver psychological distress outcomes. This event of caregiver bereavement may be causally associated with lower caregiver burden and greater depressive symptoms and anxiety. A propensity score would estimate the conditional probability of bereavement given observed covariates. These estimated scores can match pairs of bereaved and not bereaved caregivers with similar propensity scores. The effect of bereavement on psychological distress can then be estimated with a causal interpretation.

Another extension of trajectory modeling that Nagin is currently working on is a method that accounts for nonrandom subject attrition, which may be of great importance to this caregiver analysis, given the potentially informative drop out. As recruitment in this caregiver study progresses, a prospective validation component can be conducted to test whether trajectory groups can be extrapolated to new caregiver and care recipient dyads, and to assess whether the patterns observed within 12 months persist over longer periods of time.

The use of trajectory analysis in caregiving is a powerful way to discover and display trajectories of psychological distress over time. These distinct trajectory groups can be used as a screening tool to identify caregivers who appear to be at increased risk of psychological distress over time. Our findings suggest caregiver emotional stability scores and care recipient disease

and cognitive status are important factors to consider when designing an intervention for targeting caregivers at risk of psychological distress.

5.3 PUBLIC HEALTH SIGNIFICANCE

For the 44.4 million family caregivers in the U.S., current healthcare systems lack the financial resources to offer interventions to help these individuals adjust to the psychological and physical demands of caregiving. Additionally, caregiver interventions that have been shown to be the most effective are time- and personnel-intensive, and consequently, will require greater financial resources. If interventions cannot be provided for all family caregivers, a screening tool can be devised to identify specific caregivers who are most at risk of distress, which can allow interventions to be designed according to the needs of the caregiver, providing more effective therapy. Studies have shown that caregivers of Alzheimer's patients benefitted most from personalized and enhanced intervention of direct care (Jang, et al., 2004).

The public health significance of group-based trajectory analysis modeling on longitudinal data is its ability to estimate trajectories of caregiver psychological distress over time, the probability of membership in each trajectory group, and the use of these groups to estimate associated risk factors, that can be used to create a risk profile or screening tool to distinguish caregivers most in need of intervention or care.

6.0 CONCLUSION

The estimation of distinct trajectories of longitudinal caregiver psychological distress outcomes can provide deeper understanding and new approaches for the advancement of neuro-oncological caregiving research. Where current methodologies have been lacking, group-based modeling methods enable researchers to comprehend, model, and test data-defined rather than researcher-defined subgroups. In this study, over the course of caregiving, caregivers typically followed a steadily decreasing trajectory within 12 months, lending support to the adaptation hypothesis. Two linear trajectory groups were identified for depressive symptoms and anxiety, and three for caregiver burden. Caregiver emotional stability was highly associated with depressive symptoms and anxiety. Care recipient disease characteristics were highly associated with moderate to high caregiver burden trajectory group. Our findings demonstrate the use of group-based modeling and logistic regression analysis/multinomial modeling to create a screening tool that can identify caregiver and/or care recipient characteristics associated with psychological distress trajectory group membership.

APPENDIX A: CAREGIVER AND CARE RECIPIENT QUESTIONNAIRES

A.1 CAREGIVER QUESTIONINAIRES

Caregiver Reaction Assessment

"I will now read a number of statements about your feelings about caregiving over the past month. Please answer according to the following 5 point scale where 1 equals strongly disagree, 2 equals disagree, 3 equals neither agree nor disagree, 4 equals agree, and 5 equals strongly agree."

	Strongly disagree (1)	Disagree (2)	Neither disagree nor agree (3)	Agree (4)	Strongly agree (5)
1. I feel privileged to care for (patient's name).					
2. Others have dumped caring for (patient's name) onto me.					
3. My family left me alone to care for (patient's name)					
4. My activities are centered around care for (patient's name).					
5. It is very difficult to get help from my family in taking care of (patient's name).					
6. I resent having to take care of (patient's name).					
7. I have to stop in the middle of work to help (patient's name).					
8. I really want to care for (patient's name).					
9. I visit family and friends less since I've been caring for (patient's name).					
10. I will never be able to do enough caregiving to repay (patient's name).					
11. My family works together at caring for (patient's name).					
12. I have eliminated things from my schedule since caring for (patient's name).					
13. Since caring for (patient's name), I feel my family has abandoned me.					
14. Caring for (patient's name) makes me feel good.					
15. Caring for (patient's name) is important to me)					
16. I enjoy caring for (patient's name)					
17. The constant interruptions make it difficult to find time for relaxation.					

Shortened CES-D

Interviewer:

"Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the past week."

	Rarely or None of the time (Less than 1 day) (0)	Some or a Little or the time (1-2 Days) (1)	Occasionally or a Moderate Amount of Time (3-4 days) (2)	Most or all of the Time (5-7 days) (3)
1. I was bothered by things that usually do not bother me.				
2. I had trouble keeping my mind on what I was doing.				
3. I felt depressed.				
4. I felt that everything I did was an effort.				
5. I felt hopeful about the future.				
6. I felt fearful.				
7. My sleep was restless.				
8. I was happy.				
9. I felt lonely.				
10. I could not get "going".				

Modified GLB- Neuroticism

Interviewer:

"Please indicate how accurately each trait describes you, using this scale. Describe yourself as you see yourself in the present time, not as you wish to be in the future. Describe yourself as you are GENERALLY or TYPICALLY, as compared with other persons you know of the same sex and roughly the same age."

	Not at all accurate (0)	A little accurate (1)	Moderately accurate (2)	Quite a bit accurate (3)	Extremely accurate (4)
1. Resentful					
2. Tense					
3. Irritable					
4. Nervous					
5. Depressed					

Modified ISEL

Interviewer:

"I am going to read a list of statements each of which may or may not be true about you. For each statement please indicate how true that statement is about you, using the following scale."

	Definitely False (1)	False (2)	True (3)	Definitely True (4)
1. If I wanted to go on a trip for a day (for example, to the country or mountains), I would have a hard time finding someone to go with me.				
2. I feel that there is no one I can share my most private worries and fears with.				
3. If I were sick, I could easily find someone to help me with my daily chores.				
4. There is someone I can turn to for advice about handling problems with my family.				
5. If I decided one afternoon that I would like to go to a movie that evening, I could easily find someone to go with me.				
6. When I need suggestions on how to deal with a personal problem, I know someone I can turn to.				
7. I don't often get invited to do things with others.				
8. If I had to go out of town for a few weeks, it would be difficult to find someone who would look after my house or apartment (the plants, pets, garden, etc.)				
9. If I wanted to have lunch with someone, I could easily find someone to join me.				
10. If I was stranded 10 miles from home, there is someone I could call who could come and get me.				

11. In the past month, how often have others made too many demands on you?
    a. Never (0)
    b. Once in a while (1)
    c. Fairly often (2)
    d. Very often (3)
    e. Unknown (4)
    f. Refused (5)

12. In the past month, how often have others been critical of you?
    a. Never (0)
    b. Once in a while (1)
    c. Fairly often (2)
    d. Very often (3)
    e. Unknown (4)
    f. Refused (5)
13. In the past month, how often have others pried into your affairs?
    a. Never (0)
    b. Once in a while (1)
    c. Fairly often (2)
    d. Very often (3)
    e. Unknown (4)
    f. Refused (5)
14. In the past month, how often have others taken advantage of you?
    a. Never (0)
    b. Once in a while (1)
    c. Fairly often (2)
    d. Very often (3)
    e. Unknown (4)
    f. Refused (5)

Mastery

Interviewer:

"Please answer the following questions about yourself by indicating the extent to which you agree or disagree with each statement, using the above scale."

	Strongly disagree (1)	Disagree (2)	Agree (3)	Strongly agree (4)
1. I feel that I have a number of good qualities.				
2. I am able to do things as well as most other people.				
3. I feel that I'm a person or worth, or at least on an equal basis with others.				
4. I take a positive attitude toward myself.				
5. There is really no way I can solve some of the problems that I have.				
6. Sometimes I feel that I am being pushed around in life.				
7. I have little control over the things that happen to me.				
8. I can do just about anything I really set my mind to.				
9. I often feel helpless in dealing with problems of life.				
10. What happens to me in the future mostly depends on me.				
11. There is little I can do to change many of the important things in my life.				

Shortened POMS – Anxiety

Interviewer:

"I am going to read a list of words that describe feelings people have. I would like you to decide how often you felt this way during the PAST WEEK. Don't answer according to how you usually feel, but rather how you felt during the past week, using the following scale. DURING THE PAST WEEK, HOW OFTEN DID YOU FEEL…."

	Never (1)	Rarely (2)	Sometimes (3)	Frequently (4)	Always (5)
1. On edge					
2. Nervous					
3. Tense					

A.2 CARE RECIPIENT QUESTIONNAIRES

The Neurobehavioral Cognitive Status Examination

I. Level of consciousness:	Alert	
	Lethargic	
	Fluctuating	
Describe patient's condition:		
II. Orientation (Score 2,1,0)		
A. Person		
1. Name (0 points)	Response	Score
2. Age (2 points)	Response	Score
B. Place		
1. Current location (2 points)	Response	Score
2. City (2 points)	Response	Score
C. Time		
1. Date: month(1 point) day(1 point) year(2 points)	Response	Score
2. Time of day within one hour (1 point)	Response	Score
3. Day of week	Response	Score Total Score
III. Attention		
A. Digit Repetition	Graded digit repetition (Score 1 or 0; discontinue after 2 misses at one	

	level).	
Level 1		
3-7-2	Response	Score
4-9-5	Response	Score
Level 2		
5-1-4-9	Response	Score
9-2-7-4	Response	Score
Level 3		
8-3-5-2-9	Response	Score
6-1-7-3-8	Response	Score
Level 4		
2-8-5-1-6-4	Response	Score
9-1-7-5-8-2	Response	Score
		Total Score
B. Four Word Memory Task	Give the four unrelated words robin, carrot, piano, green. Have patient repeat the four words twice correctly and record the number of trials required to do this_____.	
B. Comprehension	(Be sure to have at least 3 other objects in front of the patient for this test). If a, b, and c are successfully completed, praxis for these tasks is assumed normal.	
Metric	(Score 1 or 0). If incorrect, describe behavior.	
a. Pick up then pen.	Response	Score
b. Point to the floor.	Response	Score
c. Hand me the keys.	Response	Score

d. Point to the pen and pick up the keys.	Response	Score
e. Hand me the paper and point to the coin.	Response	Score
f. Point to the keys, hand me the pen, and pick up the coin.	Response	Score Total Score:
C. Repetition		
Metric	(Score 2 if first try is correct, 1 if second try is correct, 0 is incorrect).	
a. Out the window.	Response	Score
b. He swam across the lake.	Response	Score
c. The winding road led to the village.	Response	Score
d. He left the latch open.	Response	Score
e. The honeycomb drew a swarm of bees.	Response	Score
f. No ifs, ands, or buts.	Response	Score Total Score:
D. Naming		
Metric	(Score 1 or 0).	
a. Shoe	Response	Score
b. Bus	Response	Score
c. Ladder	Response	Score
d. Kite	Response	Score
e. Horseshoe	Response	Score
f. Anchor	Response	Score

g. Octopus	Response	Score
h. Xylophone	Response	Score
		Total Score:
V. Construction Ability		
Metric	Design Constructions (Score 2 if correct in 0-30 seconds; 1 if correct in 31-60 seconds; 0 if correct in greater than 60 seconds or incorrect)..	
Design 1	(Record incorrect attempts). Time:_____	Score
Design 2	(Record incorrect attempts). Time:_____	Score
Design 3	(Record incorrect attempts). Time:____	Score Total Score:
VI. Memory		
(Score 3 if recalled without prompting; 2 if recalled with category prompt; 1 if recognized from list; 0 if not recognized)		
Words	Robin	
	Carrot	
	Piano	
	Green	
		Score
Category Prompt	Bird	
	Vegetable	
	Musical Instrument	
	Color	
		Score
List	Sparrow, robin, bluejay	

	Carrot, potato, onion	
	Violin, guitar, piano	
	Red, green, yellow	
		Score
		Total Score
VII. Calculations		
Metric	(Score 1 point if correct within 20 seconds). Problems may be repeated, but time runs continuously from first presentation.	
1. How much is 5+3?	Response	
	Time	Score
2. How much is 15+7?	Response	
	Time	Score
3. How much is 39/3?	Response	
	Time	Score
4. How much is 31-8?	Response	
	Time	Score Total Score
VIII. Reasoning		
Similarities	(Explain: "A hat and a coal are alike because they are both articles of clothing." If a patient does not respond, encourage; if patient gives differences, score 0). (Score 2 if abstract; 1 if imprecisely abstract or concrete; 0 if incorrect).	
Metric		
a. Rose-Tulip	Flowers	
	Other Responses	Score
b. Bicycle-Train	Transportation	

	Other Responses	Score
c. Watch-Ruler	Measurement	
	Other Responses	Score
d. Corkscrew-Hammer	Tools	
	Other Responses	Score
		Total Score
B. Judgment		
Metric	(Score 2 if correct; 1 if partially correct; 0 if incorrect).	
a. What would you do if you woke up one minute before 8:00 am and remembered an important appointment downtown at 8:00?	Response:	Score
b. What would you do if you were walking beside a lake and saw a 2-year-old child playing alone at the end of a pier?	Response:	Score
c. What would you do if you came home and found that a broken pipe was flooding the kitchen?	Response:	Score
		Total Score
	End Time: _____	

MDASI-BT

I. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been **in the last 24 hours**. Please fill in the box below from **0 (symptom has not been present)** to **10 (symptom was as bad as you can imagine it could be)** for each item.

1. Your difficulty understanding at its WORST?

0 1 2 3 4 5 6 7 8 9 10

2. Your difficulty speaking at its WORST?

0 1 2 3 4 5 6 7 8 9 10

3. Your problem with remembering at its WORST?

0 1 2 3 4 5 6 7 8 9 10

4. Your difficulty concentrating at its WORST?

0 1 2 3 4 5 6 7 8 9 10

5. Your feeling distressed at is WORST?

0 1 2 3 4 5 6 7 8 9 10

6. Your irritability at is WORST?

0 1 2 3 4 5 6 7 8 9 10

7. Your disturbed sleep at is WORST?

0 1 2 3 4 5 6 7 8 9 10

8. Your feeling sad at is WORST?

0 1 2 3 4 5 6 7 8 9 10

9. Your fatigue (tiredness) at its WORST?

0 1 2 3 4 5 6 7 8 9 10

10. Your seizures at its WORST?

0 1 2 3 4 5 6 7 8 9 10

11. Your numbness at its WORST?

0 1 2 3 4 5 6 7 8 9 10

12. Your weakness at its WORST?

0 1 2 3 4 5 6 7 8 9 10

13. Your pain at its WORST?

0 1 2 3 4 5 6 7 8 9 10

14. Your drymouth at its WORST?

0 1 2 3 4 5 6 7 8 9 10

15. Your drowsiness (sleepy) at its WORST?

0 1 2 3 4 5 6 7 8 9 10

16. Your lack of appetite at its WORST?

0 1 2 3 4 5 6 7 8 9 10

17. Your change in appearance at its WORST?

0 1 2 3 4 5 6 7 8 9 10

18. Your vision at its WORST?

0 1 2 3 4 5 6 7 8 9 10

19. Your change in bowel pattern at its WORST?

0 1 2 3 4 5 6 7 8 9 10

20. Your shortness of breath at its WORST?

0 1 2 3 4 5 6 7 8 9 10

21. Your nausea at its WORST?

0 1 2 3 4 5 6 7 8 9 10

22. Your vomiting at its WORST?

0 1 2 3 4 5 6 7 8 9 10

II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items **in the past 24 hours**: **(0-Did not interfere, 10- interfered completely)**

General Activity?

0 1 2 3 4 5 6 7 8 9 10

Mood?

0 1 2 3 4 5 6 7 8 9 10

Work (including work around the house)?

0 1 2 3 4 5 6 7 8 9 10

Relations with other people?

0 1 2 3 4 5 6 7 8 9 10

Walking?

0 1 2 3 4 5 6 7 8 9 10

Enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10

APPENDIX B: PROGRAMMING CODE

B.1 SPSS PROGRAMMING CODE

```
** CESD **.
RECODE
  future
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  afuturerc .
RECODE
  happy
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  ahappyrc .
COMPUTE aCESD = afuturerc + ahappyrc + bother + trblemin + dep + effort +
  fearful + restless + lonely + getgoing .

RECODE
  bfuture
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  bfuturerc .
RECODE
  bhappy
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  bhappyrc .
EXECUTE .
COMPUTE bCESD = bfuturerc + bhappyrc + bbother + btrblemi + bdep + beffort +
  bfearful + brestles + blonely + bgetgoin .

RECODE
  cfuture
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  cfuturerc .
RECODE
  chappy
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  chappyrc .
COMPUTE cCESD = cfuturerc + chappyrc + cbother + ctrblemi + cdep + ceffort +
  cfearful + crestles + clonely + cgetgoin .
RECODE
  dfuture
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  dfuturerc .
RECODE
  dhappy
  (0=3)  (1=2)  (2=1)  (3=0)  INTO  dhappyrc .
COMPUTE dCESD = dfuturerc + dhappyrc + dbother + dtrblemi + ddep + deffort +
  dfearful + drestles + dlonely + dgetgoin .
```

```
*** CRA SCHEDULE **.
COMPUTE aCRASCHED = activ + stopwork + visitles + elimsch + diffrela .
COMPUTE bCRASCHED = bactiv + bstopwor + bvisitle + belimsch + bdiffrel .
COMPUTE cCRASCHED = cactiv + cstopwor + cvisitle + celimsch + cdiffrel .
COMPUTE cCRAFINAN = cfinstra + cdiffpay + cfinanrerc .
COMPUTE cCRAABANDON = cdump + cdiffhel + caband +calonecr + cfamtogrc .
COMPUTE dCRASCHED = dactiv + dstopwor + dvisitle + delimsch + ddiffrel .

** POMS **
COMPUTE aPOMS = onedge + nervous + tensepm .
COMPUTE bPOMS = bonedge + bnervous + btensepm .
COMPUTE cPOMS = conedge + cnervous + ctensepm .
COMPUTE dPOMS = donedge + dnervous + dtensepm .

** Calculate duration times between dates of assessment.
COMPUTE Time_Baseline=0.

* Date and Time Wizard: Time_4mos.
COMPUTE  Time_4mos=(bdate - adate) / (30.4375 * time.days(1)).
VARIABLE LABEL  Time_4mos.
VARIABLE LEVEL  Time_4mos (SCALE).
FORMATS  Time_4mos (F8.2).
VARIABLE WIDTH  Time_4mos(8).
EXECUTE.

* Date and Time Wizard: Time_8mos.
COMPUTE  Time_8mos=(cdate - adate) / (30.4375 * time.days(1)).
VARIABLE LABEL  Time_8mos.
VARIABLE LEVEL  Time_8mos (SCALE).
FORMATS  Time_8mos (F8.2).
VARIABLE WIDTH  Time_8mos(8).
EXECUTE.

* Date and Time Wizard: Time_12mos.
COMPUTE  Time_12mos=(ddate - adate) / (30.4375 * time.days(1)).
VARIABLE LABEL  Time_12mos.
VARIABLE LEVEL  Time_12mos (SCALE).
FORMATS  Time_12mos (F8.2).
VARIABLE WIDTH  Time_12mos(8).
EXECUTE.

DESCRIPTIVES VARIABLES=Time_Baseline Time_4mos Time_8mos Time_12mos
  /STATISTICS=MEAN STDDEV MIN MAX.

temp.
select if time_4mos < 0 or time_8mos <0.
list id# adate bdate cdate edate time_4mos time_8mos.
```

B.2 STATA EXPLORATORY PLOTS

```
/* Psychological Distress Thesis Analysis */
/* Dataset: CG dataset 3.24.09 */

mvencode _all, mv(.a =99)
/* 1. Baseline Simple Descriptives */
/* a. Univariate descriptives of scale and item */
/** i. boxplots and histograms **/

graph box aCESD, name(boxcesd)
graph box aPOMS, name(boxpom)
graph box aCRASCHED, name(boxsched)

hist aCESD, name(histcesd)
hist aPOMS, name(histpom)
hist aCRASCHED, name(histsched)

/* Spaghetti plots for each scale over 2 timepoints */
findit spagplot
use "C:\Users\Jean Kuo\Desktop\MS Thesis\Analysis Files\CG dataset 3.24.09
long.dta", clear
/* Time variable needs to be numeric*/
encode time, generate(timeAB)
replace timeAB=. if timeAB>2

set autotabgraphs on, permanently
spagplot CESD timeAB, id(id)name(CESD_AB)
spagplot POMS timeAB, id(id) name(POMS_AB)
spagplot CRASCHED timeAB, id(id) name(CRASCHED_AB)
graph combine CESD_AB POMS_AB CRASCHED_AB, name(spagcombo)
```

B.3 SAS PROGRAMMING CODE

```
options nofmterr ls=80 ps=55 nodate; /*formatting for 8 by 11 paper */

/** Trajectory Analysis*/
/** All caregivers*/

proc import out=cgfull datafile = "C:\Users\Jean Kuo\Desktop\MS
Thesis\Analysis Files\6.10.09\Caregiver Analysis File 6.10.09_corrected.sav";
run;
proc import out=cgfull datafile = "F:\MS Thesis\Analysis
Files\6.10.09\Caregiver Analysis File 6.10.09_corrected.sav";
run;
```

```
libname traj 'C:\Users\Jean Kuo\Desktop\MS Thesis\Analysis Files\6.10.09';
libname traj 'C:\Documents and Settings\cjk28\Desktop\MS Thesis\to add';
libname traj 'F:\MS Thesis\Trajectory Analysis\6.19.09 Traj Analysis';

/* Kevin Kim's Macro */
%include 'C:\Users\Jean Kuo\Desktop\MS Thesis\Trajectory Analysis\6.19.09
Traj Analysis\mixturefit.sas';
%include 'C:\Documents and Settings\cjk28\Desktop\MS Thesis\to
add\mixturefit.sas';
%include 'F:\MS Thesis\Trajectory Analysis\6.19.09 Traj
Analysis\mixturefit.sas';

data traj.cgfull; set work.cgfull;run;

proc contents data=traj.cgfull;run;

data traj.cg (rename=(id_=id) keep= id_ age sex relat2cr race adate bdate
cdate ddate edate fdate  aCRASCHED bCRASCHED cCRASCHED dCRASCHED eCRASCHED
fCRASCHED aCESD bCESD cCESD dCESD eCESD fCESD aPOMS bPOMS cPOMS
dPOMS ePOMS fPOMS  aMSF36 bMSF36 cMSF36 dMSF36 time_baseline time_4mos
time_8mos time_12mos time_18mos time_24mos);
set traj.cgfull;run;

/* Scale Time to be near 1*/
data traj.cg (drop=t0); set traj.cg;
t1=time_baseline/10;
t2=time_4mos/10;
t3=time_8mos/10;
t4=time_12mos/10;
t5=time_18mos/10;
t6=time_24mos/10;
run;

data bereaved; set traj.cg;
bereaved=0;
if id=19 then bereaved=1 ; /* died before A */
if id=2 | id=8 | id=26 | id=76 | id=37 then bereaved=2 ; /* died A-B */
if id=20 | id=39 | id=52 | id=54 then bereaved=3 ; /* died B-C */
if id=33 then bereaved=4 ; /*died C-D */
if id=22 then bereaved=5; /* died D-E */
run;

data bereaved; set bereaved;
ber1=0;     ber2=0; ber3=0; ber4=0; ber5=0; ber6=0;
if bereaved=1 then do;
ber1=1; ber2=1; ber3=1; ber4=1; ber5=1; ber6=1;end;
if bereaved=2 then do;
ber2=1; ber3=1; ber4=1; ber5=1; ber6=1;end;
if bereaved=3 then do;
ber3=1; ber4=1; ber5=1; ber6=1;end;
if bereaved=4 then do;
ber4=1; ber5=1; ber6=1;end;
if bereaved=5 then do;
ber5=1; ber6=1;end;
run;
```

```
proc freq;
tables bereaved*ber1-ber5; run;

data traj.cg; set bereaved;run;

data a ; set traj.cg;
  rename aCESD=CESD1 bCESD=CESD2 cCESD=CESD3 dCESD=CESD4 eCESd=CESD5
fCESD=CESD6;
  rename aPOMS=POMS1 bPOMS=POMS2 cPOMS=POMS3 dPOMS=POMS4 ePOMS=POMS5
fPOMS=POMS6;
  rename aCRASCHED=CRASCHED1 bCRASCHED=CRASCHED2 cCRASCHED=CRASCHED3
dCRASCHED=CRASCHED4 eCRASCHED=CRASCHED5;
  rename aMSF36=MSF1 bMSF36=MSF2 cMSF36=MSF3 dMSF36=MSF4;
run;
proc contents data=a;run;

data traj.cg; set a;run;

data traj.cg;set traj.cg;
if crasched3>25 then crasched3='.';
if crasched4>25 then crasched4='.';
if crasched5>25 then crasched5='.'; run;

/* Trajectory Analysis for each outcome*/
proc means data=traj.cg;
var t1-t4 CESD1-CESD4 POMS1-POMS4 CRASCHED1-CRASCHED4;
run;

title 'Depression from t1-t4 (1 1)';
proc traj data=traj.cg out=oput outstat=cesdstat outplot=cesdplot ci95m;
id id;
var CESD1-CESD4;
indep t1-t4;
model cnorm;
min 0;
max 30;
order 1 1;
run;
%trajplot(cesdplot,cesdstat,'Depression over Time','cnorm model(1 1)-
2group','CESD','Time/10');
%trajplotnew(cesdplot,cesdstat,'Depression over Time','cnorm model(1 1)-
2group','CESD','Time/10');
%mixturefit(data = oput, group = group, prob = grp1prb grp2prb, logl =  -
565.57, param = 7);

/****** POMS **********/
title 'POMS from t1-t4 (1 1)';
proc traj data=traj.cg out=oput outstat=pomsstat outplot=pomsplot ci95m ;
id id;
var POMS1-POMS4;
indep t1-t4;
model cnorm;
min 3;
max 15;
```

```
order 1 1;
run;
%trajplot(pomsplot,pomsstat,'Anxiety over Time','cnorm model(1 1)-
2group','POMS','Time/10');
%trajplotnew(pomsplot,pomsstat,'Anxiety over Time','cnorm model(1 1)-
2group','POMS','Time/10');
%mixturefit(data = oput, group = group, prob = grp1prb grp2prb, logl =  -
422.67, param = 7);

proc means data=traj.cg;
var crasched1-crasched5;run;

/****** crasched **********/
title 'crasched from t1-t4 (1 1 1)';
proc traj data=traj.cg out=oput outstat=craschedstat outplot=craschedplot
ci95m ;
id id;
var crasched1-crasched4;
indep t1-t4;
model cnorm;
min 5;
max 25;
order 1 1 1;
run;
%trajplot(craschedplot,craschedstat,'CRA Burden over Time','cnorm model(1 1
1)-3group','crasched','Time/10');
%trajplotnew(craschedplot,craschedstat,'CRA Burden over Time','cnorm model(1
1 1)-3group','crasched','Time/10');
%mixturefit(data = oput, group = group, prob = grp1prb grp2prb grp3prb, logl
= -466.32, param = 10);

title 'crasched from t1-t4 (1 1)';
proc traj data=traj.cg out=oput outstat=craschedstat outplot=craschedplot
ci95m ;
id id;
var crasched1-crasched4;
indep t1-t4;
model cnorm;
min 5;
max 25;
order 1 1;
run;
%trajplot(craschedplot,craschedstat,'CRA Burden over Time','cnorm model(1 1)-
2group','crasched','Time/10');
%trajplotnew(craschedplot,craschedstat,'CRA Burden over Time','cnorm model(1
1)-2group','crasched','Time/10');
%mixturefit(data = oput, group = group, prob = grp1prb grp2prb, logl = -
476.95, param = 7);

proc traj data=traj.cg out=oput outstat=craschedstat outplot=craschedplot
ci95m ;
id id;
var crasched1-crasched4;
indep t1-t4;
model cnorm;
```

```
tcov ber1-ber4;
min 5;
max 25;
order 1 1;
run;

/* Create new file with group probabilities of each scale*/
/* CESD 2 group (1 1)*/
title 'Depression from t1-t4 (1 1)';
proc traj data=traj.cg out=cesdoput outstat=cesdstat outplot=cesdplot ci95m;
id id;
var CESD1-CESD4;
indep t1-t4;
model cnorm;
min 0;
max 30;
order 1 1;
run;
/* POMS 2 group (1 1)*/
title 'POMS from t1-t4 (1 1)';
proc traj data=traj.cg out=pomsoput outstat=pomsstat outplot=pomsplot ci95m ;
id id;
var POMS1-POMS4;
indep t1-t4;
model cnorm;
min 3;
max 15;
order 1 1;
run;
/* CRASCHED 3 group (1 1 1)*/
title 'crasched from t1-t4 (1 1 1)';
proc traj data=traj.cg out=craoput outstat=craschedstat outplot=craschedplot
ci95m ;
id id;
var crasched1-crasched4;
indep t1-t4;
model cnorm;
min 5;
max 25;
order 1 1 1;
run;
title 'Crasched from t1-t4 (1 1)';
proc traj data=traj.cg out=oput outstat=craschedstat outplot=craschedplot
ci95m ;
id id;
var crasched1-crasched4;
indep t1-t4;
model cnorm;
min 5;
max 25;
order 1 1;
run;

/* exported to SPSS and merged files there*/
```

```
proc import out=merged datafile = "C:\Users\Jean Kuo\Desktop\MS
Thesis\Analysis Files\oput files\MergedGroups.sav";
run;
proc import out=merged datafile = "F:\MS Thesis\Analysis Files\oput
files\MergedGroups.sav";
run;

data traj.merged; set merged;
proc contents data=traj.merged;run;

title 'Group Frequencies';
proc freq data=traj.merged;
table cesdgp pomsgp cra_3gp cra_2gp;
run;

data mean;set traj.merged;
cesd_pomswt=(maxcesd+maxpoms)/2;
cesd_cra3wt=(maxcesd+maxcra_3)/2;
poms_cra3wt=(maxpoms+maxcra_3)/2;
cesd_cra2wt=(maxcesd+maxcra_2)/2;
poms_cra2wt=(maxpoms+maxcra_2)/2;
run;

data mean1;set traj.merged;
allwt=(maxcesd+maxpoms+maxcra_2)/3;
run;

data traj.merged; set mean1;run;
proc contents data=traj.merged;run;

title 'Crosstabs of CESD vs. POMS';
proc freq data=traj.merged;
table cesdgp*pomsgp/chisq;
weight cesd_pomswt;
run;
title 'Crosstabs of CESD vs. CRA_3groups';
proc freq data=traj.merged;
table cesdgp*cra_3gp/chisq;
weight cesd_cra3wt;
run;
title 'Crosstabs of POMS vs. CRA_3groups';
proc freq data=traj.merged;
table pomsgp*cra_3gp/chisq;
weight poms_cra3wt;
run;

title 'Crosstabs of CESD vs. CRA_2groups';
proc freq data=traj.merged;
table cesdgp*cra_2gp/chisq;
weight cesd_cra2wt;
run;
title 'Crosstabs of POMS vs. CRA_2groups';
proc freq data=traj.merged;
table pomsgp*cra_2gp/chisq;
weight poms_cra2wt;
```

```
run;

title 'Crosstabs of POMSxCESDxCRA_2gps';
proc freq data=traj.merged;
table cra_2gp*cesdgp*pomsgp/fisher chisq;
run;
title 'Crosstabs of POMSxCESDxCRA_2gps';
proc freq data=traj.merged;
table cesdgp*pomsgp*cra_2gp/fisher chisq;
run;
title 'Crosstabs of POMSxCESDxCRA_2gps';
proc freq data=traj.merged;
table pomsgp*cesdgp*cra_2gp/fisher chisq;
run;

title 'Crosstabs of POMSxCESDxCRA_2gps WEIGHTED';
proc freq data=traj.merged;
table cra_2gp*cesdgp*pomsgp/fisher chisq;
weight allwt;
run;
title 'Crosstabs of POMSxCESDxCRA_2gps WEIGHTED';
proc freq data=traj.merged;
table cesdgp*pomsgp*cra_2gp/fisher chisq;
weight allwt;
run;
title 'Crosstabs of POMSxCESDxCRA_2gps WEIGHTED';
proc freq data=traj.merged;
table pomsgp*cesdgp*cra_2gp/fisher chisq;
weight allwt;
run;

title 'Crosstabs of POMSxCESDxCRA_3gps';
proc freq data=traj.merged;
table cra_3gp*cesdgp*pomsgp/fisher chisq;
run;
title 'Crosstabs of POMSxCESDxCRA_3gps';
proc freq data=traj.merged;
table cesdgp*pomsgp*cra_3gp/fisher chisq;
run;
title 'Crosstabs of POMSxCESDxCRA_3gps';
proc freq data=traj.merged;
table pomsgp*cesdgp*cra_3gp/fisher chisq;
run;

/* Cross tabs of combo group by CRA 3 group*/
title 'Crosstabs of depanx by CRA_3gps';
proc freq data=traj.cg;
table depanx*cra_3gp/fisher chisq;
run;
title 'Crosstabs of depanx by CRA_2gps';
proc freq data=traj.cg;
table depanx*cra_2gp/fisher chisq;
run;
title 'Crosstabs of CRA_2gp by CRA_3gps';
proc freq data=traj.cg;
```

```
table cra_2gp*cra_3gp/fisher chisq;
run;

/* Merge with main dataset*/
data test; merge traj.cg traj.merged;
by id;
run;
proc print data=test (obs=6);run;
data traj.cg; set test;run;

data traj.cg; set work.test;
depanx=10*CESDgp+POMSgp;
depsched=10*cesdgp+cra_2gp;
schedanx=10*cra_2gp+pomsgp;
run;

/* Cross tabs of Groups with Bereaved*/
title "Cross tabulation of combo groups with bereaved";
proc freq data=traj.cg;
table depanx*bereaved/fisher chisq;
run;
proc freq data=traj.cg;
table depsched*bereaved/fisher chisq;
run;
proc freq data=traj.cg;
table schedanx*bereaved/fisher chisq;
run;

/* Recode bereaved to yes/no variable*/
proc freq data=traj.cg;
table bereaved;
run;
data alive; set traj.cg;
ber_yes = 0;
if bereaved >0 then ber_yes=1;
run;
proc freq data=alive;
table bereaved*ber_yes;
run;
data traj.cgalive; set traj.cg;
if ber_yes=0;
run;

/* Cross tabs of Groups with Bereaved*/
title "Cross tabulation of combo groups with bereaved";
proc freq data=traj.cg;
table depanx*ber_yes/fisher chisq;
run;
proc freq data=traj.cg;
table depsched*ber_yes/fisher chisq;
run;
proc freq data=traj.cg;
table schedanx*ber_yes/fisher chisq;
run;
```

```
/* Rerun cross tabs without bereaved*/
title 'Crosstabs of depanx by CRA_3gps';
proc freq data=traj.cgalive;
table depanx*cra_3gp/fisher chisq;
run;
title 'Crosstabs of depanx by CRA_2gps';
proc freq data=traj.cgalive;
table depanx*cra_2gp/fisher chisq;
run;

/* Create graph in SPSS*/
proc export data=traj.test1 outfile = "F:\MS Thesis\Analysis Files\oput
files\CGMergedGroups.sav";
run;

proc print noobs data =traj.cg;
var id cesdgp maxcesd pomsgp maxpoms cra_2gp maxcra_2 depanx depsched
schedanx;
run;

/* Demographic Frequencies*/
/* Use traj.logreg as primary dataset*/
/* 11/30/09 */

libname traj 'F:\MS Thesis\Trajectory Analysis\6.19.09 Traj Analysis';

/*Calculate MDASI at baseline*/
data traj.cgcr;set traj.cgcr;
  if difundwst = 99 then difundwst=.a;
  if difspkwst = 99 then difspkwst=.a;
  if difremwst = 99 then difremwst=.a;
  if difconwst = 99 then difconwst=.a;
  if distwst = 99 then distwst=.a;
  if irritwst = 99 then irritwst=.a;
  if disslpwst = 99 then disslpwst=.a;
  if sadwst = 99 then sadwst=.a;
  if fatigwst = 99 then fatigwst=.a;
  if seizwst = 99 then seizwst=.a;
  if numbwst = 99 then numbwst=.a;
  if weakwst = 99 then weakwst=.a;
  if painwst = 99 then painwst=.a;
  if drymwst = 99 then drymwst=.a;
  if drowswst = 99 then drowswst=.a;
  if lacapwst = 99 then lacapwst=.a;
  if chgappwst = 99 then chgappwst=.a;
  if viswst = 99 then viswst=.a;
  if chgbowlwst = 99 then chgbowlwst=.a;
  if shortbrwst = 99 then shortbrwst=.a;
  if nauswst = 99 then nauswst=.a;
  if vomwst = 99 then vomwst=.a;
data traj.cgcr; set traj.cgcr;
aMDASI=difundwst+difspkwst+difremwst+difconwst+distwst+irritwst+disslpwst+
sadwst+ fatigwst+ seizwst+ numbwst+ weakwst+ painwst+ drymwst+
drowswst+ lacapwst+ chgappwst+ viswst+ chgbowlwst+ shortbrwst+ nauswst+
vomwst;
```

```
  run;

/* Create a dataset with all variables (weights, traj gps, cg and cr risk
factors) needed for logistic regression model*/
/* traj.merged has traj gps and weights*/
/* traj.cgcr has full cg and cr merged datasets*/

data traj.CGCRsmall (rename=(id_=id) keep= id_ age sex relat2cr race yrseduc
adate bdate cdate ddate edate fdate  aCRASCHED bCRASCHED cCRASCHED dCRASCHED
eCRASCHED fCRASCHED aCESD bCESD cCESD dCESD eCESD fCESD aPOMS bPOMS cPOMS
dPOMS ePOMS fPOMS time_baseline time_4mos time_8mos time_12mos time_18mos
time_24mos aMASTERY aEMOTSTAB aISEL aMDASI ORI ATT LANCOMP LANREP LANNAME
CONST MEM CALC REASSIM REASJUDG);
set traj.cgcr;run;

/* Merge with traj.merged for trajgp output*/
proc sort data=traj.cgcrsmall;by id; run;
proc sort data=traj.merged; by id; run;
data reg;
merge traj.cgcrsmall traj.merged; by id; run;

/* Merge in bereaved, cra dummy codings*/
proc sort data=reg; by id;run;
proc sort data=traj.cg; by id; run;
data traj.logreg (drop=anpsum tum_g);
merge reg traj.cg; by id; run; /* Use traj.logreg for regression models*/

proc contents data=traj.logreg;run;

/* Run frequencies of demographic vars*/
proc freq data=traj.logreg;
tables SEX female RELAT2CR spouse race ber_yes tum_gbm;
run;

proc means data=traj.logreg maxdec=2;
var age yrseduc AMASTERY AEMOTSTAB AISEL aMDASI ORI ATT LANCOMP LANREP
LANNAME CONST MEM CALC REASSIM REASJUDG;
run;

/* Run poms vs cra stratified by cesd*/
title 'Crosstabs of POMSxCESDxCRA_3gps UNWEIGHTED';
proc freq data=traj.logreg;
table cesdgp*pomsgp*cra_3gp/fisher chisq;
run;

title 'Crosstabs of POMSxCESDxCRA_3gps WEIGHTED';
proc freq data=traj.logreg;
table cesdgp*pomsgp*cra_3gp/fisher chisq;
weight allwt; /* allwt is the avg of the max probabilities*/
run;

/* Logistic and Multinomial regression for each trajectory group*/
/* Dataset: traj.logreg*/
/* Date: 12/7/09 */
```

```
/* Fixed factors: age, gender, relat2cr, edu, emotstab, tumor status */
/* Exploratory factors: mastery, isel, ncse domains, mdasi */

options nodate nonumber nofmterr ls=80 ps=55;
libname traj 'C:\Users\Jean Kuo\Desktop\MS Thesis\Trajectory Analysis\6.19.09
Traj Analysis';
data traj.logreg1; set traj.logreg1;
label female="Caregiver Gender"
            spouse="Relationship to Care Recipient"
            tum_gbm="Care Recipient Tumor Type"
            yrseduc="Caregiver Edu(yrs)";
run;

proc freq;
table cesdgp pomsgp cra_3gp;
run;

*Using format for labels*;
proc format;
value cesdgroup 1="low" 2="high";
value pomsgroup 1="low" 2="high";
value cragp 1="low" 2="mod" 3="high";
value gbm 0="astroI-III" 1="gbm";
value fem 0="male" 1="female";
value spousefmt 0="non-spouse" 1="spouse";
run;
proc format;
format cesdgp cesdgroup. pomsgp pomsgroup. cra_3gp cragp. tum_gbm gbm.;
run;

/* get frequencies*/
proc freq;
table cesdgp pomsgp cra_3gp;
format cesdgp cesdgroup. pomsgp pomsgroup. cra_3gp cragp.;
run;
proc freq;
table female spouse tum_gbm;
format female fem. spouse spousefmt. tum_gbm gbm.;
run;
/* get summary stats*/
proc means;
var age yrseduc amastery aemotstab aisel amdasi ori att lancomp lanrep
lanname const mem calc reassim reasjudg;
run;
PROC UNIVARIATE PLOT;
VAR age yrseduc amastery aemotstab aisel amdasi ori att lancomp lanrep
lanname const mem calc reassim reasjudg;
ID id;
HISTOGRAM;
QQPLOT age yrseduc amastery aemotstab aisel amdasi ori att lancomp lanrep
lanname const mem calc reassim reasjudg / NORMAL(MU=EST SIGMA=EST);
RUN;

/* Center all continuous variables by median*/
data traj.logreg1; set traj.logreg;
```

```
age_c = age-53;
edu_c = yrseduc-14;
mastery_c = amastery-20.5;
emotstab_c = aemotstab-15.00;
isel_c = aisel-37.00;
mdasi_c = amdasi-25.00;
ori_c = ori-12.00;
att_c = att-7;
lancomp_c = lancomp-6.00;
lanrep_c = lanrep-12.00;
lanname_c = lanname-8.00;
const_c = const-5.00;
mem_c = mem-8.00;
calc_c = calc-4.00;
reassim_c = reassim-7;
reasjudg_c = reasjudg-5.00;
run;

/* Create composite mean score by domain*/
data traj.logreg1; set traj.logreg1;
if nmiss(of lanrep lanname lancomp)>2 then lan_avg=.;
else lan_avg=mean(of lanrep lanname lancomp);
if nmiss(of reassim reasjudg)>0 then reas_avg=.;
else reas_avg=mean(of reassim reasjudg);
label lan_avg="Composite mean language score"
            reas_avg="Composite mean reasoning score";
run;
/* examine distribution of composite scores*/
proc univariate plot;
var lan_avg reas_avg;
histogram;
run;
proc freq;
table lan_avg reas_avg;
run;

proc print;
where lan_avg>. OR reas_avg>.;
var id lancomp lanname lanrep lan_avg;
var reassim reasjudg reas_avg;
run;

/* Center by median*/
data traj.logreg1; set traj.logreg1;
lang_c=lan_avg-8.5;
reason_c = reas_avg-6.0;
run;

/* Run Caregiver risk factors model*/
/* Fixed factors: age, gender, relat2cr, edu, emotstab, tumor status */
/* Exploratory factors: mastery, isel, ncse domains, mdasi */

/*************************************************************************
**** CESD */
/* Examine relationship between female and spouse*/
```

```
proc freq;
table female*spouse/chisq exact;
format female fem. spouse spousefmt.;
run;
/* Examine relationship between emotional stability and depression*/
TITLE 'Scatterplot - Emotional Stability vs. CESD at Baseline';
SYMBOL1 V=circle C=blue I=r;
PROC GPLOT;
     PLOT acesd*aemotstab ;
RUN;

/* Caregiver Models */
title1 "Caregiver CESDgp Model";
title2 "Block 0 - fixed";
proc logistic data=traj.logreg1 order=data;
class female (param=ref ref="male") spouse (param=ref ref="non-spouse");
model cesdgp(event="high") = age_c female edu_c emotstab_c /rsq lackfit stb;
format female fem. spouse spousefmt. cesdgp cesdgroup.;
weight maxcesd;
run;

title1 "Caregiver CESDgp Model";
title2 "Block 1 - exploratory";
proc logistic order=data;
class female (param=ref ref="male") spouse (param=ref ref="non-spouse");
model cesdgp(event="high") = age_c female edu_c emotstab_c isel_c mastery_c
/rsq lackfit stb;
format female fem. spouse spousefmt. cesdgp cesdgroup.;
weight maxcesd;
run;
/* Remove exploratory factors, keep fixed*/

/*** Care Recipient Model */
/* Fixed factors: tumor status */
/* Exploratory factors: ncse domains, mdasi */

title1 "Care Recipient CESDgp Model";
title2 "Block 0 - fixed";
proc logistic order=data;
class tum_gbm (param=ref ref="astroI-III");
model cesdgp(event="high") = tum_gbm /rsq lackfit stb;
format tum_gbm gbm. cesdgp cesdgroup.;
weight maxcesd;
run;
/* not significant, keep anyway*/

/* include exploratory factors*/
proc corr alpha;
var ori_c att_c lancomp_c lanrep_c lanname_c const_c mem_c calc_c reassim_c
reasjudg_c;
run;
proc corr alpha;
var ori_c att_c lang_c reason_c const_c mem_c calc_c;run;

title1 "Care Recipient CESDgp Model";
```

```
title2 "Block 1 - exploratory";
proc logistic order=data;
class tum_gbm (param=ref ref="astroI-III");
model cesdgp(event="high") = tum_gbm mdasi_c ori_c att_c lang_c reason_c
const_c mem_c calc_c /rsq lackfit stb;
format tum_gbm gbm. cesdgp cesdgroup.;
weight maxcesd;
run;
/* keep only mdasi and calc*/

title1 "Care Recipient CESDgp Model";
title2 "Block 2 - exploratory";
proc logistic order=data;
class tum_gbm (param=ref ref="astroI-III");
model cesdgp(event="high") = tum_gbm mdasi_c calc_c /rsq lackfit stb;
format tum_gbm gbm. cesdgp cesdgroup.;
weight maxcesd;
run;
/* no significant CR predictors*/

/* Combined Caregiver and CR model */
title1 "Combined CESDgp Model";
title2 "Block 0 - fixed";
proc logistic order=data;
class tum_gbm (param=ref ref="astroI-III");
model cesdgp(event="high") =  age_c female emotstab_c edu_c tum_gbm /rsq
lackfit stb;
format tum_gbm gbm. cesdgp cesdgroup.;
weight maxcesd;
run;

/*check multicollinearity*/
proc reg;
model edu_c=age_c female emotstab_c tum_gbm / tol vif collinoint;
run;
proc corr;
var age_c edu_c female emotstab_c tum_gbm cesdgp;
run;
/* no corr btw predictors except for age and edu (p=0.02, r=-0.25)*/
/* Check assumptions*/

/* Output influence statistics*/
proc logistic data=traj.logreg1;
class tum_gbm (param=ref ref="astroI-III");
model cesdgp(event="high") =  age_c female emotstab_c edu_c tum_gbm /rsq
lackfit stb;
output out=traj.cesdinf p=yhat reschi=chires resdev=devres difchisq=difchisq
difdev=difdev h=hatdiag;
format tum_gbm gbm. cesdgp cesdgroup.;
weight maxcesd;
run;

/*Calculate cook's distance*/
data traj.cesdinf;set traj.cesdinf;
cookd=((chires**2)*hatdiag)/(5*(1-hatdiag)**2); /*cook's distance*/
```

```
run;

/*index plots*/
goptions reset=all;
symbol1 v=circle c=blue;
proc univariate data=traj.cesdinf plot;
var cookd;
id id;
run;
title "Index Plot of Cook's D";
proc gplot;
plot cookd*id;
run;
title "Index Plot of Pearson's Residuals";
proc gplot;
plot chires*id;
run;
title "Cook's D by Fitted";
proc gplot;
plot cookd*yhat;
run;

/* Plot cook's D vs. residual-influece and fit*/
title "Cook's D by Pearson Residuals";
proc gplot;
plot cook*chires;
run;

/* List potential outliers*/
proc print;
where cookd>0.11;
var id cesdgp age female aemotstab yrseduc tum_gbm cookd yhat chires;
run;

/*rerun model without outliers*/
proc logistic data=traj.cesdinf;
where cookd<0.11;
class tum_gbm (param=ref ref="astroI-III");
model cesdgp(event="high") =  age_c female emotstab_c edu_c tum_gbm /rsq
lackfit stb;
format tum_gbm gbm. cesdgp cesdgroup.;
weight maxcesd;
run;
/*no effect, keep observations in the model*/

/* CRA */
/* Caregiver Models */
title "Caregiver CRA Model";
title2 "Block 0 - fixed";
proc logistic data=traj.logreg1 order=data;
class female (param=ref ref="male");
model cra_3gp(ref="low") = age_c female edu_c emotstab_c /link=glogit rsq
stb;
format female fem. cra_3gp cragp.;
weight maxcra_3;
```

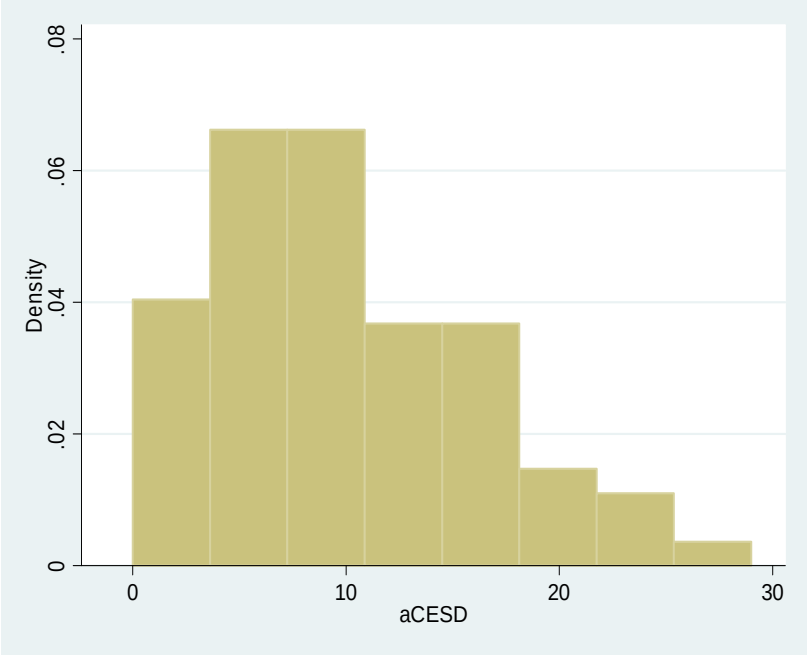
```
run;

proc format data=traj.logreg1;
format female fem.
run;

title1 "Caregiver POMSgp Model";
title2 "Block 1 - exploratory";
proc logistic data=traj.logreg1 order=data;
class female (param=ref ref="male");
model POMSgp(event="high") = age_c female edu_c emotstab_c isel_c mastery_c
/rsq lackfit stb;
format female fem. spouse spousefmt. POMSgp pomsgroup.;
weight maxpoms;
run;

/* Remove exploratory factors, keep fixed*/

/*** Care Recipient Model */
/* Fixed factors: tumor status */
/* Exploratory factors: ncse domains, mdasi */

title1 "Care Recipient POMSgp Model";
title2 "Block 0 - fixed";
proc logistic data=traj.logreg1 order=data;
class tum_gbm (param=ref ref="astroI-III");
model pomsgp(event="high") = tum_gbm /rsq lackfit stb;
format tum_gbm gbm. pomsgp pomsgroup.;
weight maxpoms;
run;

title1 "Care Recipient pomsgp Model";
title2 "Block 1 - exploratory";
proc logistic data=traj.logreg1 order=data;
class tum_gbm (param=ref ref="astroI-III");
model pomsgp(event="high") = tum_gbm mdasi_c ori_c att_c lang_c reason_c
const_c mem_c calc_c /rsq lackfit stb;
format tum_gbm gbm. pomsgp pomsgroup.;
weight maxpoms;
run;
/* keep tum, ori, lang, const, calc, refit*/

title1 "Care Recipient pomsgp Model";
title2 "Block 2 - refit";
proc logistic data=traj.logreg1 order=data;
class tum_gbm (param=ref ref="astroI-III");
model pomsgp(event="high") = tum_gbm ori_c lang_c const_c calc_c /rsq lackfit
stb;
format tum_gbm gbm. pomsgp pomsgroup.;
weight maxpoms;
run;
/* no significant CR predictors*/
proc corr;
var ori_c lang_c const_c calc_c;
run;
```

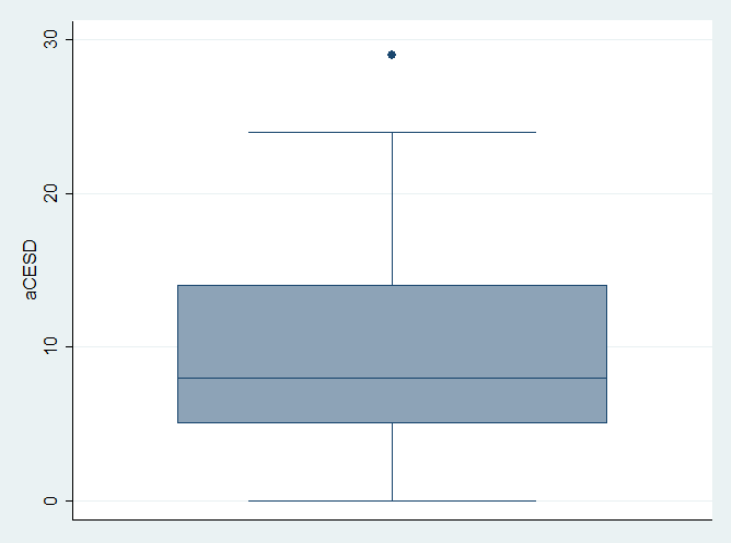
```
/* highly correlated*/
proc reg;
model LANG_C= ORI_c const_c calc_c / tol vif collinoint;
run;
/* Fit lang*/
title1 "Care Recipient pomsgp Model";
title2 "Block 2 - refit";
proc logistic data=traj.logreg1 order=data;
class tum_gbm (param=ref ref="astroI-III");
model pomsgp(event="high") = tum_gbm lang_c /rsq lackfit stb;
format tum_gbm gbm. pomsgp pomsgroup.;
weight maxpoms;
run;

/* Combined Caregiver and CR model */
title1 "Combined POMSgp Model";
title2 "Block 0 - fixed";
proc logistic order=data;
class tum_gbm (param=ref ref="astroI-III") female;
model pomsgp(event="high") =  age_c female emotstab_c edu_c tum_gbm /rsq
lackfit stb;
format tum_gbm gbm. pomsgp pomsgroup.;
weight maxpoms;
run;

/* Output influence statistics*/
proc logistic data=traj.logreg1;
class tum_gbm (param=ref ref="astroI-III") female (param=ref ref="male");
model pomsgp(event="high") =  age_c female emotstab_c edu_c tum_gbm /rsq
lackfit stb;
format tum_gbm gbm. pomsgp pomsgroup. female fem.;
output out=traj.pomsinf p=yhat reschi=chires resdev=devres difchisq=difchisq
difdev=difdev h=hatdiag;
weight maxpoms;
run;

/*Calculate cook's distance*/
data traj.pomsinf;set traj.pomsinf;
cookd=((chires**2)*hatdiag)/(5*(1-hatdiag)**2); /*cook's distance*/
run;

/*index plots*/
goptions reset=all;
symbol1 v=circle c=blue;
proc univariate plot;
var cookd;
id id;
run;
title "Index Plot of Cook's D";
proc gplot;
plot cookd*id;
run;
title "Index Plot of Pearson's Residuals";
proc gplot;
plot chires*id;
```

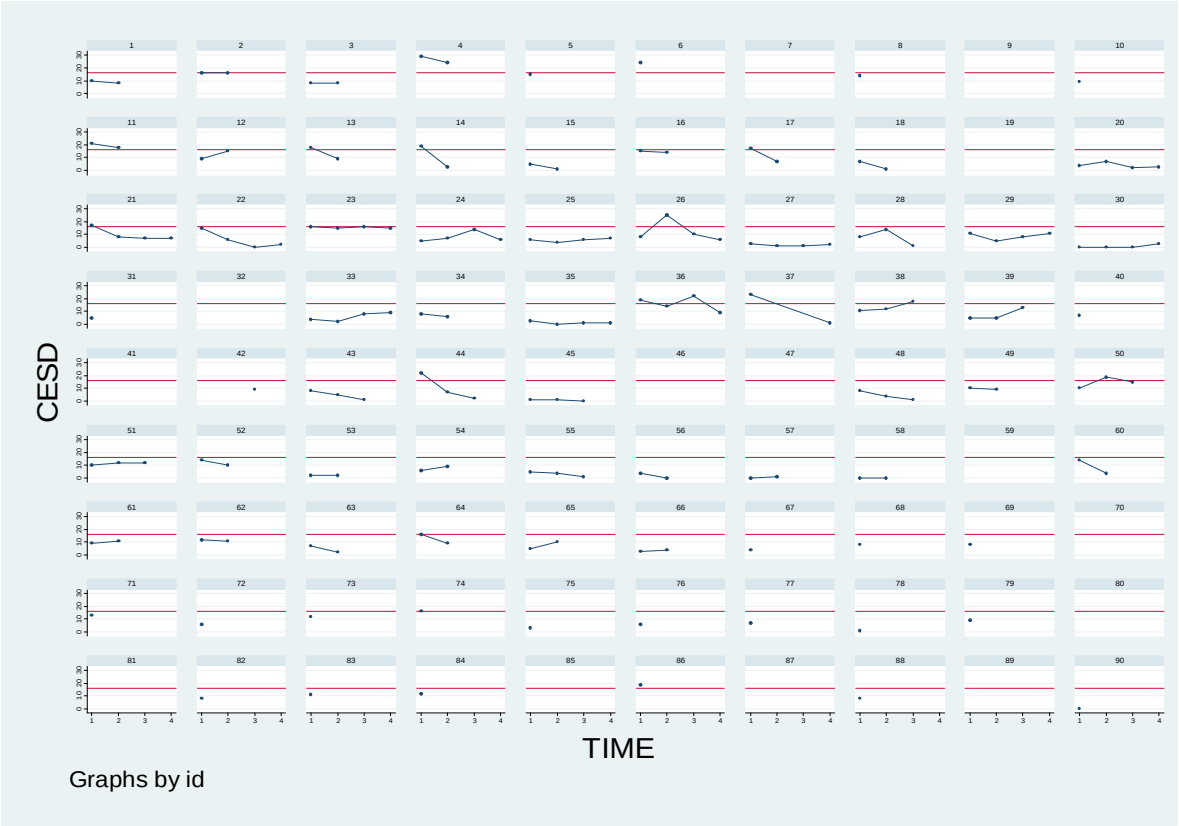
```
run;
title "Cook's D by Fitted";
proc gplot;
plot cookd*yhat;
run;

/* Plot cook's D vs. residual-influece and fit*/
title "Cook's D by Pearson Residuals";
proc gplot;
plot cook*chires;
run;

/* List potential outliers*/
proc print;
where cookd>0.26;
var id pomsgp age female aemotstab yrseduc tum_gbm cookd yhat chires;
run;
/*id 22*/
/*rerun model without outliers*/
proc logistic data=traj.pomsinf;
where cookd<0.26;
class tum_gbm (param=ref ref="astroI-III") female(param=ref ref="male");
model pomsgp(event="high") =  age_c female emotstab_c edu_c tum_gbm /rsq
lackfit stb;
format tum_gbm gbm. pomsgp pomsgroup. female fem.;
weight maxpoms;
run;
/*keep observations in the model*/

/* POMS */
/* Caregiver Models */
title1 "Caregiver POMSgp Model";
title2 "Block 0 - fixed";
proc logistic data=traj.logreg1 order=data;
class female (param=ref ref="male");
model POMSgp(event="high") = age_c female edu_c emotstab_c /rsq lackfit stb;
format female fem. spouse spousefmt. pomsgp pomsgroup.;
weight maxpoms;
run;

title1 "Caregiver POMSgp Model";
title2 "Block 1 - exploratory";
proc logistic data=traj.logreg1 order=data;
class female (param=ref ref="male");
model POMSgp(event="high") = age_c female edu_c emotstab_c isel_c mastery_c
/rsq lackfit stb;
format female fem. spouse spousefmt. POMSgp pomsgroup.;
weight maxpoms;
run;
```

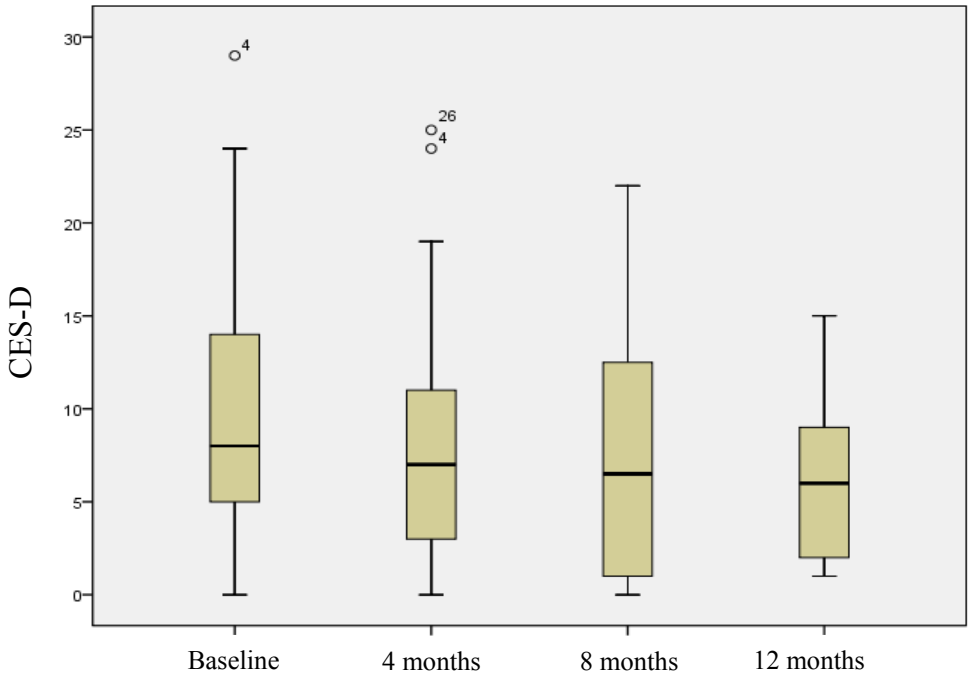
APPENDIX C: EXPLORATORY PLOTS

C.1 DEPRESSIVE SYMPTOMS (CESD)

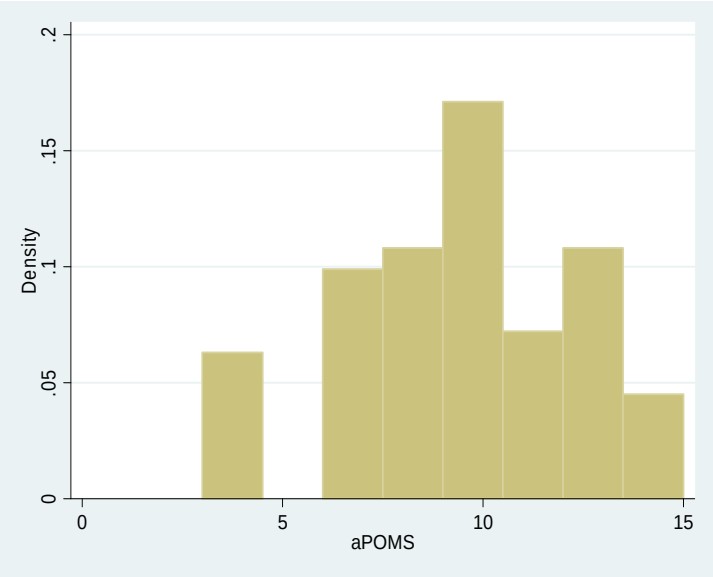


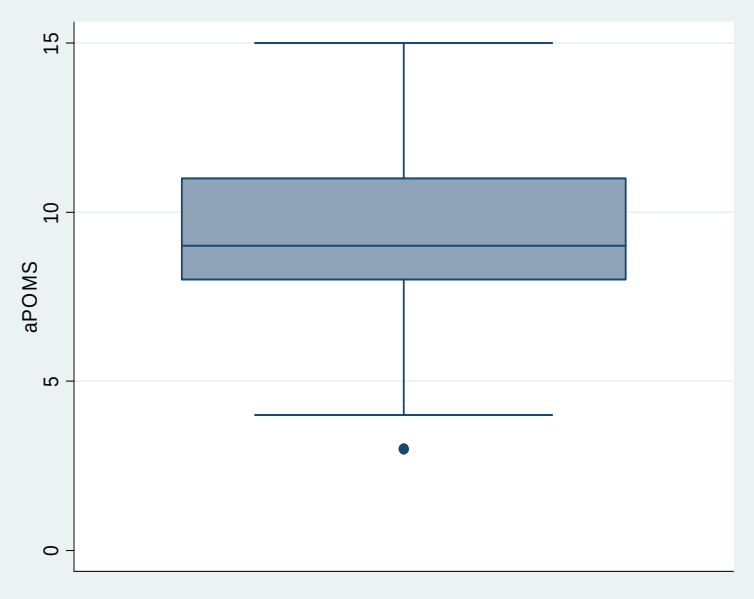

aCESD
0
10
20
30

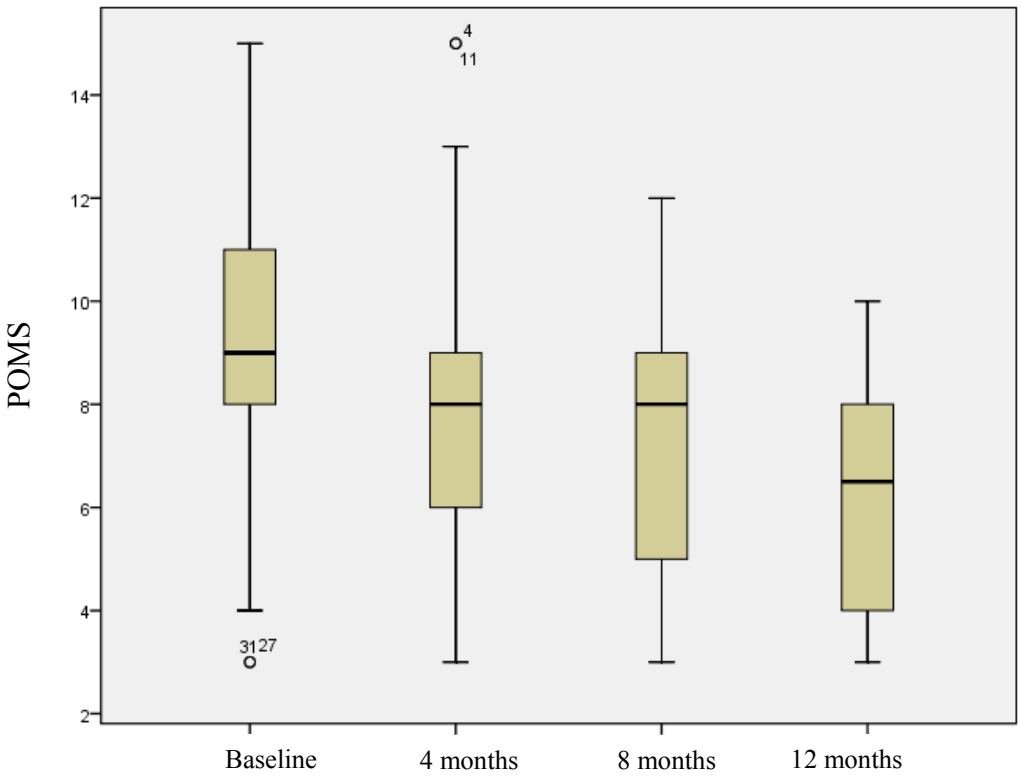

CESD
TIME
Graphs by id


CES-D
30
25
20
15
10
5
0
4
26
4
Baseline
4 months
8 months
12 months
Time from Diagnosis

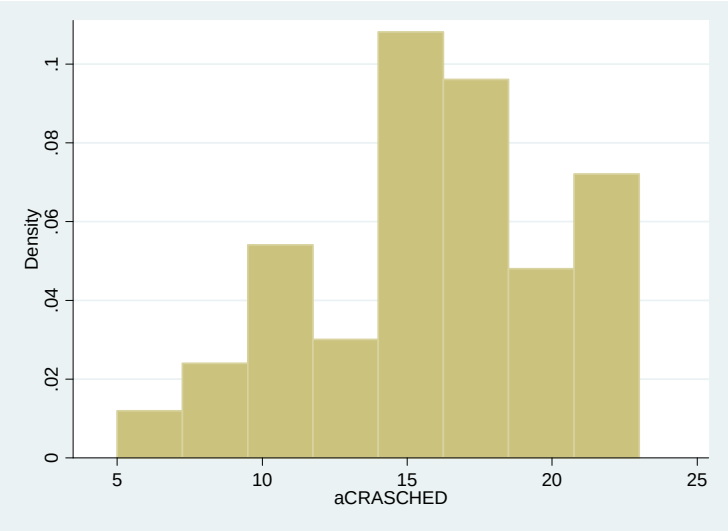
C.2 ANXIETY (POMS)

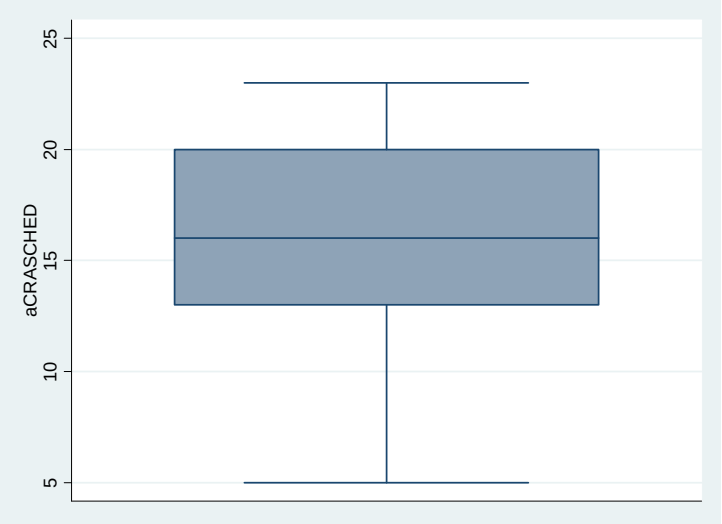


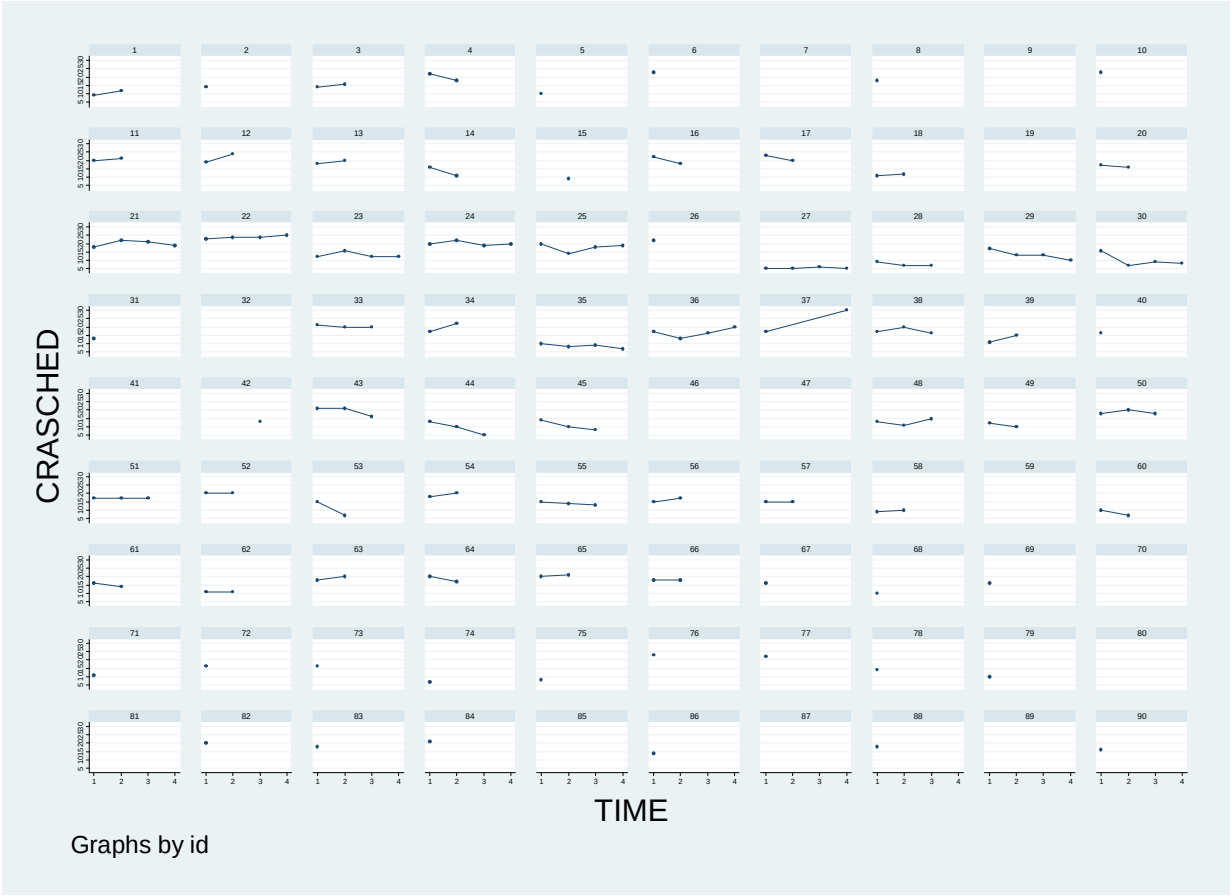


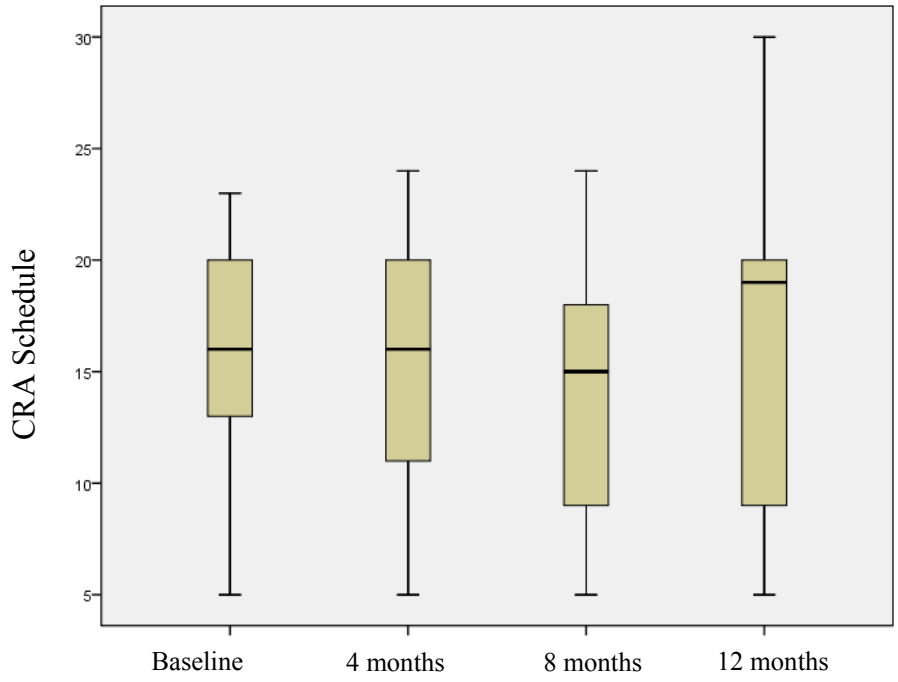

POMS
14
12
10
8
6
4
2
4
11
31
27
Baseline
4 months
8 months
12 months
Time from Diagnosis

C.3 CRA SCHEDULE (CRA)

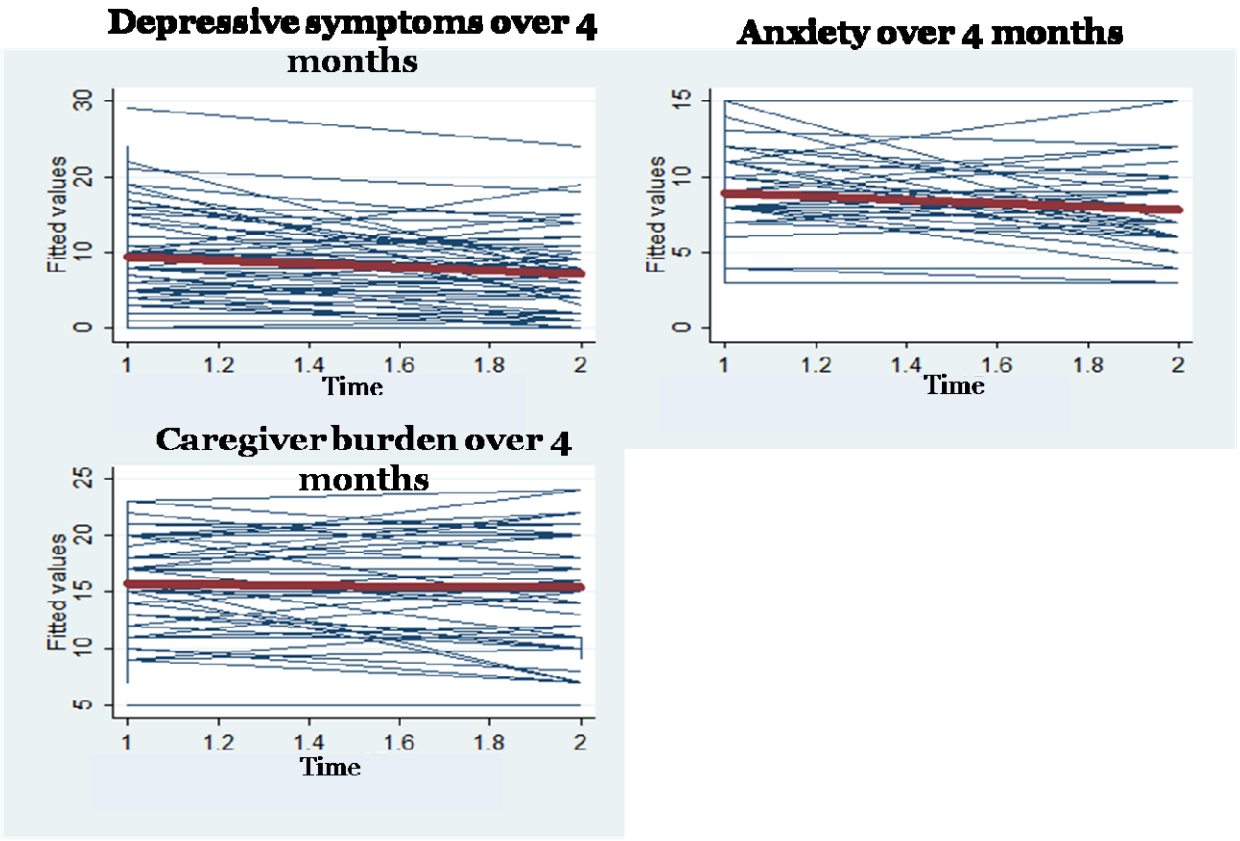





CRASCHED
TIME
Graphs by id


CRA Schedule
30
25
20
15
10
5
Baseline
4 months
8 months
12 months
Time from Diagnosis

C.4 COMBINED PLOTS



APPENDIX D: TRAJECTORY ANALYSIS MODEL OUTPUT

D.1 DEPRESSIVE SYMPTOMS MODEL (1,1)

Maximum Likelihood Estimates
Model: Censored Normal (CNORM)

Group	Parameter	Standard Estimate	Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	5.07324	0.85781	5.914	0.0000
	Linear	-2.39307	1.24004	-1.930	0.0551
2	Intercept	13.86517	0.96613	14.351	0.0000
	Linear	-3.70804	1.43879	-2.577	0.0107
	Sigma	4.65296	0.29227	15.920	0.0000
		Group membership			
1	(%)	54.52460	8.50807	6.409	0.0000
2	(%)	45.47540	8.50807	5.345	0.0000

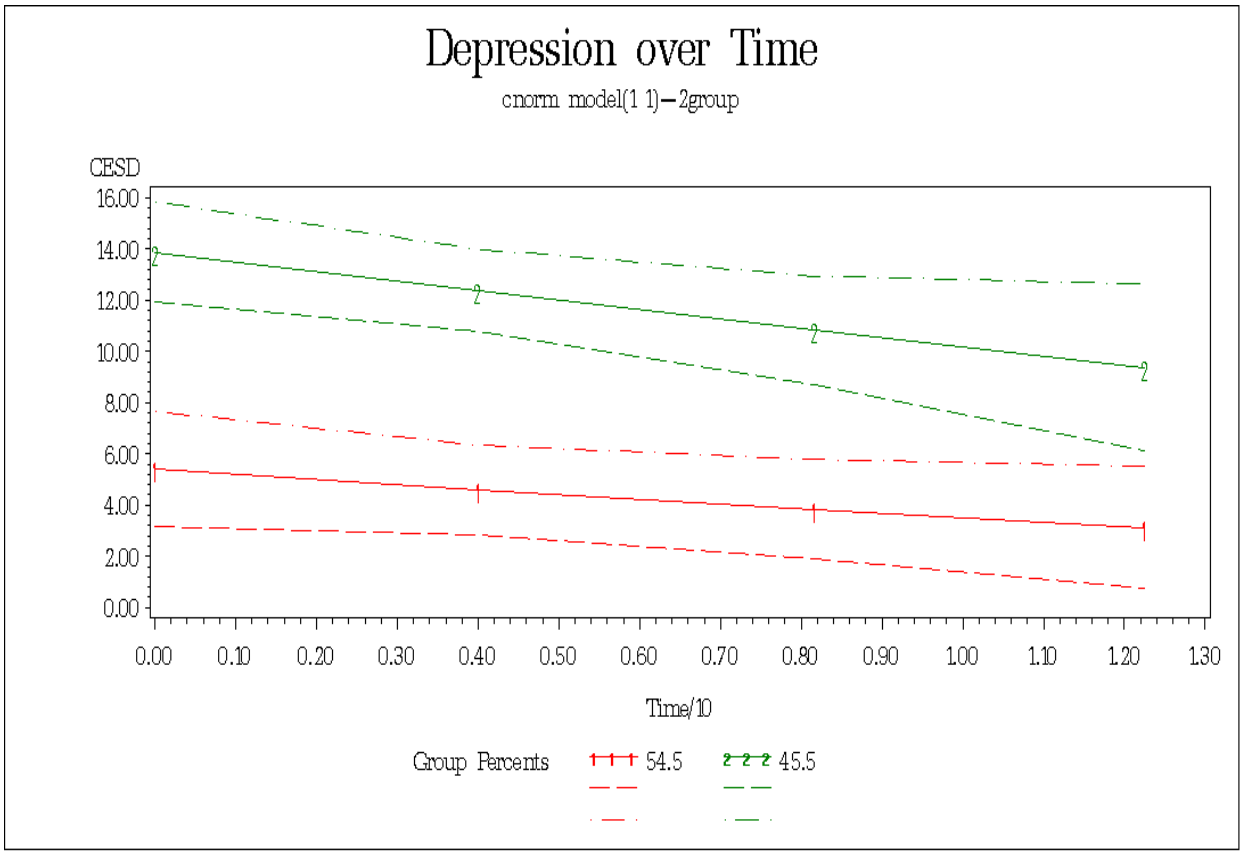
BIC= -581.27 (N=187) BIC= -578.79 (N=82) AIC= -571.57 L= -565.57

Average probability per group

	1	2
1	0.812	0.188
2	0.127	0.873

Mixture Fit Statistics

Entropy	0.533
AIC	1145.140
BIC	1163.235
CAIC	1170.235
ssBIC	1141.130
CLC	1194.572
ICL-BIC	1226.667


Depression over Time
cnorm model(1 1)−2group
CESD
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
Time/10
Group Percents
54.5
45.5

D.2 ANXIETY MODEL (1,1)

Maximum Likelihood Estimates
Model: Censored Normal (CNORM)

Group	Parameter	Standard Estimate	Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	6.33417	0.62658	10.109	0.0000
	Linear	-2.63298	0.83722	-3.145	0.0019
2	Intercept	10.05603	0.32960	30.510	0.0000
	Linear	-1.74192	0.52861	-3.295	0.0012
Sigma		2.26060	0.14424	15.673	0.0000
		Group membership			
1	(%)	28.42256	7.99719	3.554	0.0005
2	(%)	71.57744	7.99719	8.950	0.0000

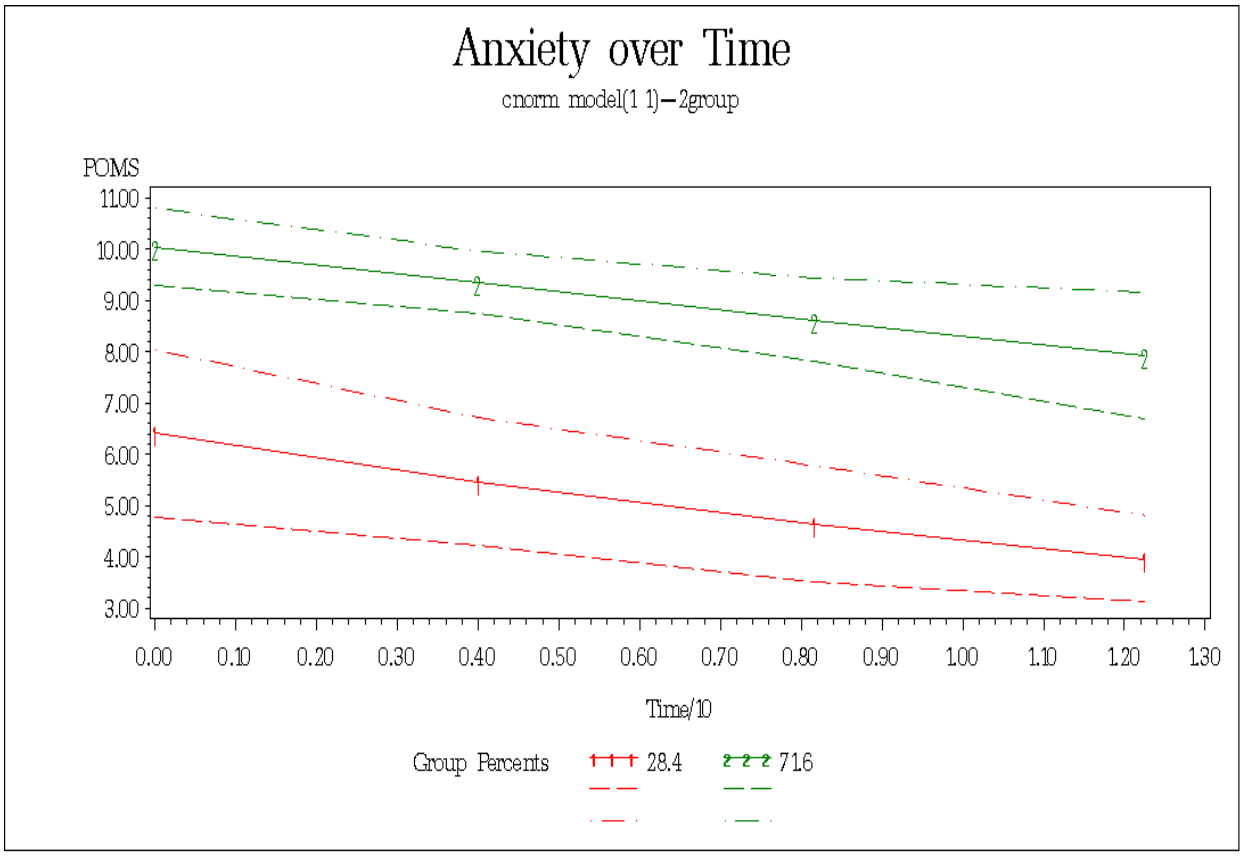
BIC= -438.33 (N=185) BIC= -435.81 (N=80) AIC= -428.67 L= -422.67

Average probability per group

	1	2
1	0.877	0.123
2	0.133	0.867

Mixture Fit Statistics

Entropy	0.573
AIC	859.340
BIC	877.435
CAIC	884.435
ssBIC	855.330
CLC	903.403
ICL-BIC	935.498


Anxiety over Time
cnorm model(1 1)–2group
POMS
11.00
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
Time/10
Group Percents
1 1 1 28.4
2 2 2 71.6

D.3 CAREGIVER BURDEN (1,1,1)

Maximum Likelihood Estimates
Model: Censored Normal (CNORM)

Group	Parameter	Standard Estimate	Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	10.74293	0.68026	15.792	0.0000
	Linear	-4.31827	1.05890	-4.078	0.0001
2	Intercept	14.04227	0.70680	19.867	0.0000
	Linear	-1.00031	1.51593	-0.660	0.5102
3	Intercept	19.31532	0.50969	37.896	0.0000
	Linear	-0.15361	0.81265	-0.189	0.8503
	Sigma	2.57332	0.17017	15.122	0.0000
		Group membership			
1	(%)	24.79885	6.70749	3.697	0.0003
2	(%)	29.53837	7.74050	3.816	0.0002
3	(%)	45.66278	7.01974	6.505	0.0000

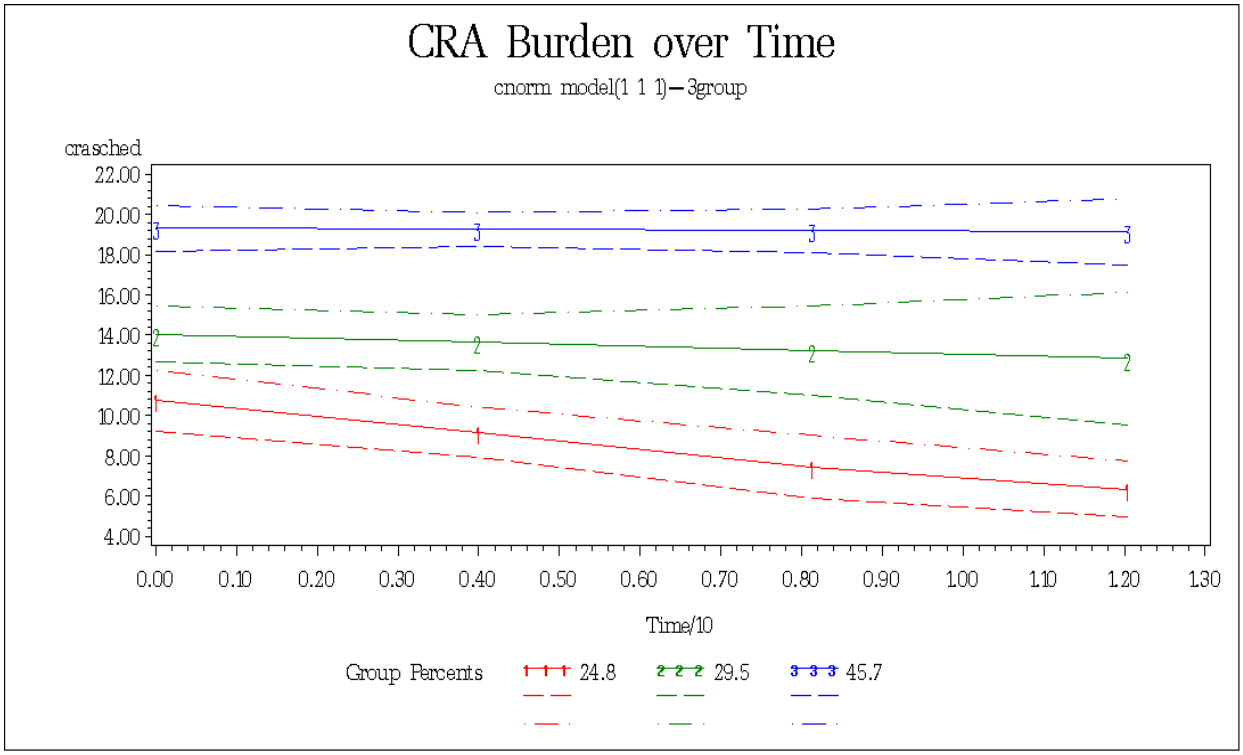
BIC= -489.56 (N=175) BIC= -486.15 (N=82) AIC= -475.32 L= -466.32

Average probability per group

	1	2	3
1	0.848	0.150	0.002
2	0.127	0.744	0.129
3	0.074	0.124	0.802

Mixture Fit Statistics

Entropy	0.601
AIC	952.640
BIC	978.490
CAIC	988.490
ssBIC	946.911
CLC	1018.504
ICL-BIC	1064.353


CRA Burden over Time
cnorm model(1 1 1)−3group
crasched
22.00
20.00
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
Time/10
Group Percents
1 1 1 24.8
2 2 2 29.5
3 3 3 45.7

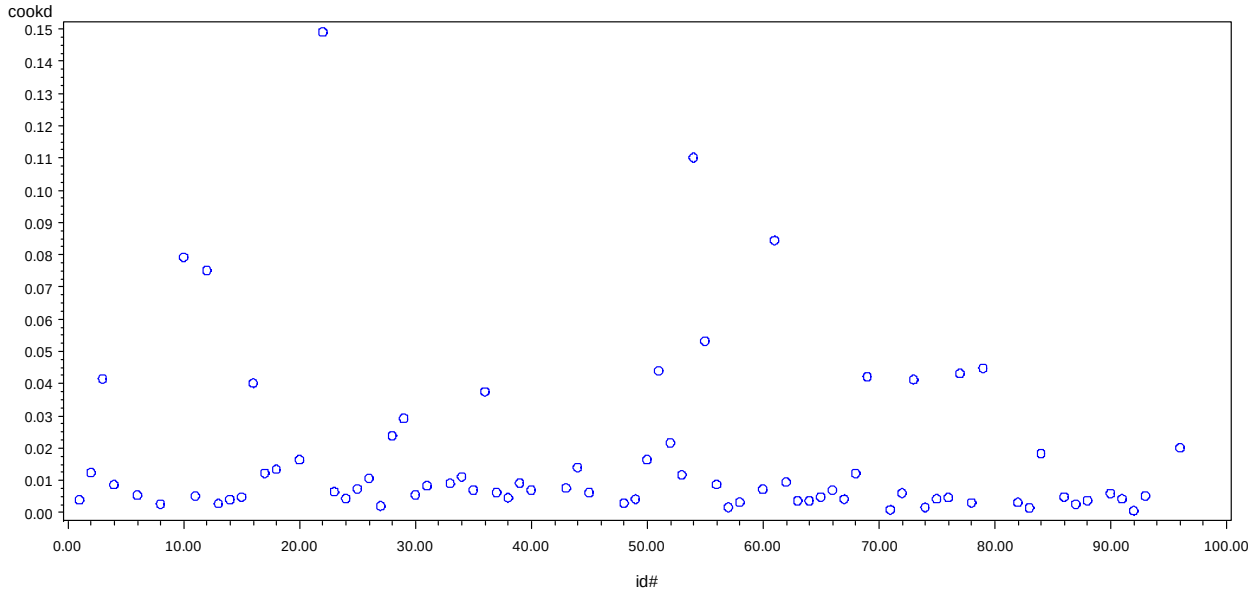
APPENDIX E: LOGISTIC REGRESSION TABLES

E.1 DEPRESSIVE SYMPTOMS TRAJECTORY GROUP RESULTS

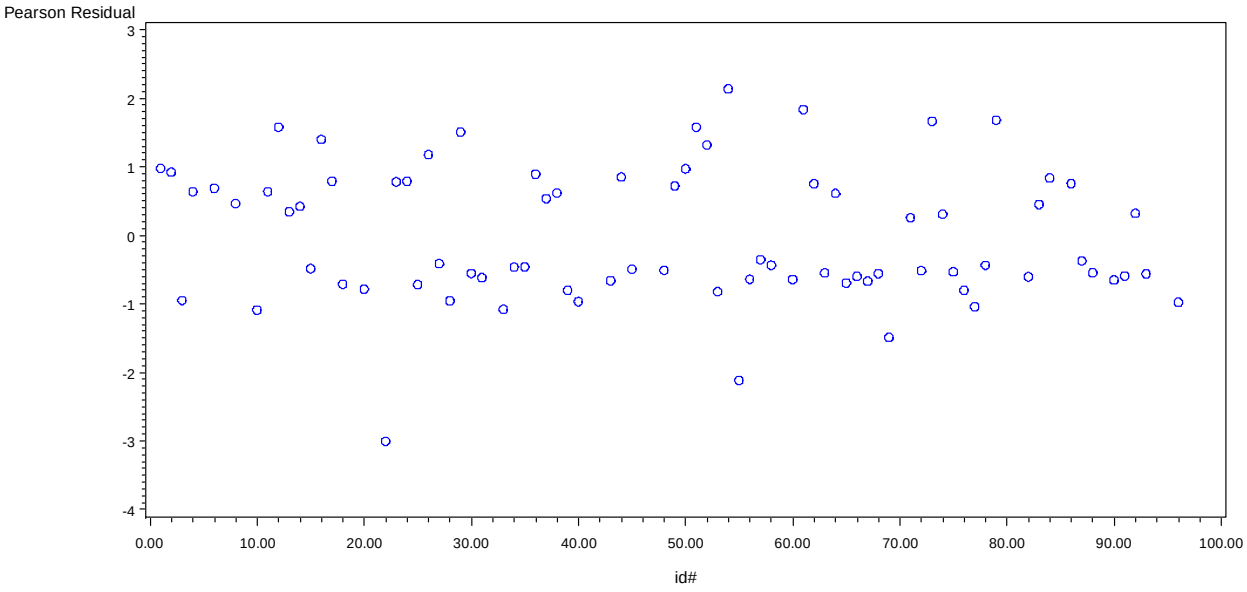
Depressive Symptoms		***Block 0***				***Block I***				***Block II***		
Model Type	***Characteristic***	***B (SE)***	***Std B***	***p***		***B (SE)***	***Std B***	***p***		***B (SE)***	***Std B***	***p***
Caregiver	**Age**	-0.02 (0.03)	-0.1	0.4		-0.03 (0.03)	-0.2	0.3		--	--	--
	Female	0.7 (0.6)	--	0.3		0.8 (0.7)	--	0.2		--	--	--
	Education (yrs)	-0.1 (0.1)	-0.1	0.4		-0.1 (0.1)	-0.1	0.4		--	--	--
	Emotional Stability	-0.3 (0.1)	-0.5	0.003		-0.3 (0.1)	-0.4	0.01		--	--	--
	Social Support	--	--	--		-0.1 (0.1)	-0.2	0.2		--	--	--
	Mastery	--	--	--		-0.1 (0.1)	-0.1	0.7		--	--	--
Global Test*	$\chi2(4)=15.2$, p=0.0043, N=79					$\chi2(6)=17.8$, p=0.007, N=79						
Care Recipient	**Tumor Type**	0.2 (0.5)	--	0.6		-0.5 (0.7)	--	0.5		-0.05 (0.6)	--	0.5
	Symptoms	--	--	--		0.03 (0.02)	0.4	0.09		0.02 (0.01)	0.3	0.1
	Orientation	--	--	--		-0.4 (0.4)	-0.2	0.3		--	--	--
	Attention	--	--	--		-0.2 (0.3)	-0.2	0.4		--	--	--
	Language	--	--	--		-0.4 (0.8)	-0.1	0.6		--	--	--
	Reasoning	--	--	--		-0.2 (0.4)	-0.2	0.5		--	--	--
	Constructional Ability	--	--	--		0.2 (0.2)	0.2	0.4		--	--	--
	Memory	--	--	--		-0.02 (0.1)	-0.03	0.9		--	--	--
	Calculations	--	--	--		1.1 (0.6)	0.6	0.06		0.4 (0.3)	0.2	0.3
Global Test*	$\chi2(1)=0.2$, p=0.62, N=89					$\chi2(9)=8.7$, p=0.47, N=61				$\chi2$ (3)=3.6, p=0.31, N=61		
Combined	**Age**	-0.04 (0.03)	-0.3	0.2		--	--	--				
	Female	1.2 (0.8)	--	0.1		--	--	--				
	Education (yrs)	-0.06 (0.1)	-0.07	0.7		--	--	--				
	Emotional Stability	-0.4 (0.1)	-0.6	0.007		--	--	--				
	Astro III-IV	0.9 (0.6)	--	0.2		--	--	--				
Global Test*	$\chi2(5) = 22.13$, p=0.0005, N=78											

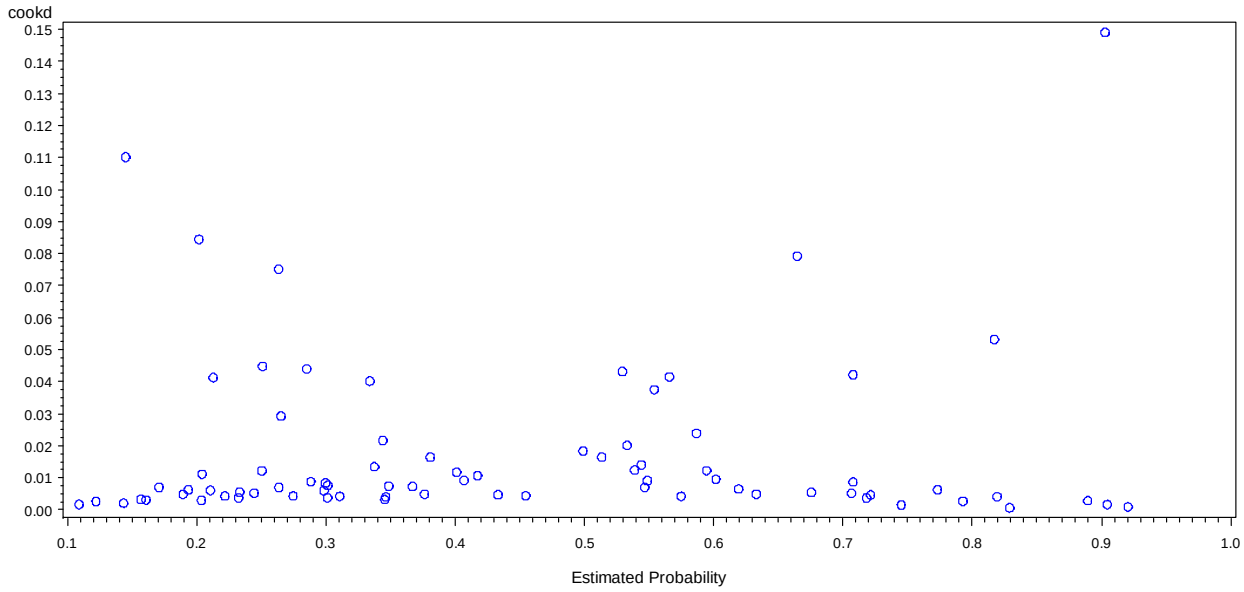
* Likelihood Ratio Test of Global Null Hypothesis; B – beta coefficient, SE – standard error, p – p-value, Std B – standardize beta coefficient

Index Plot of Cook's D



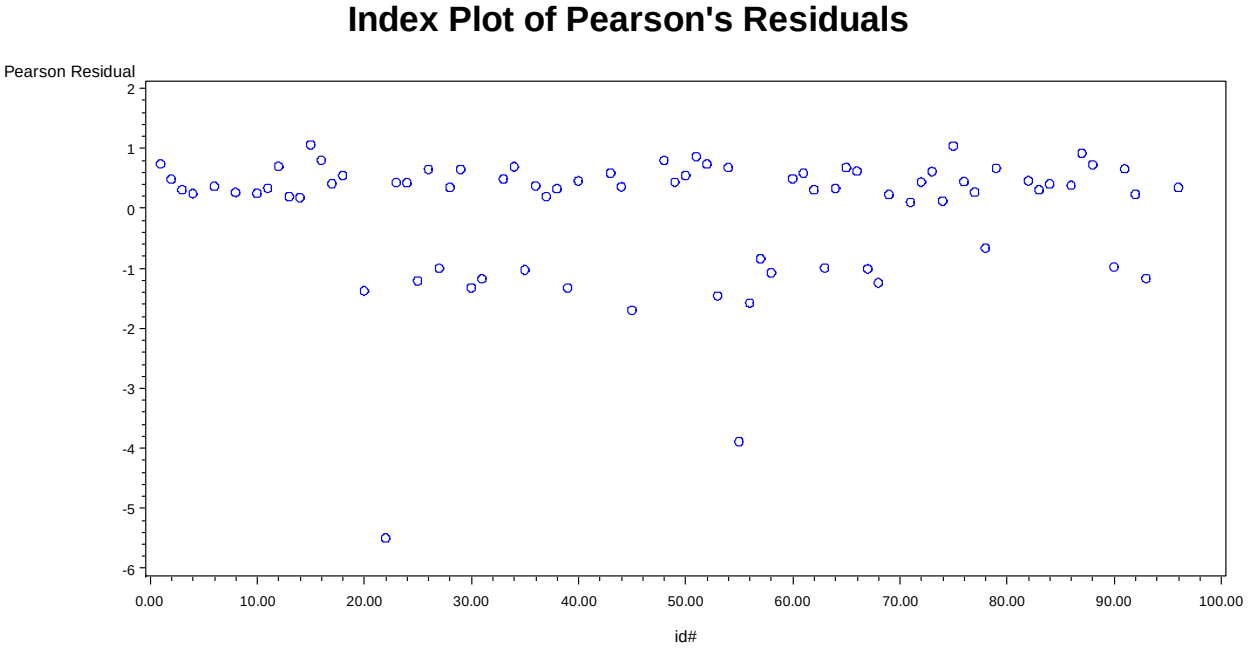
Index Plot of Pearson's Residuals

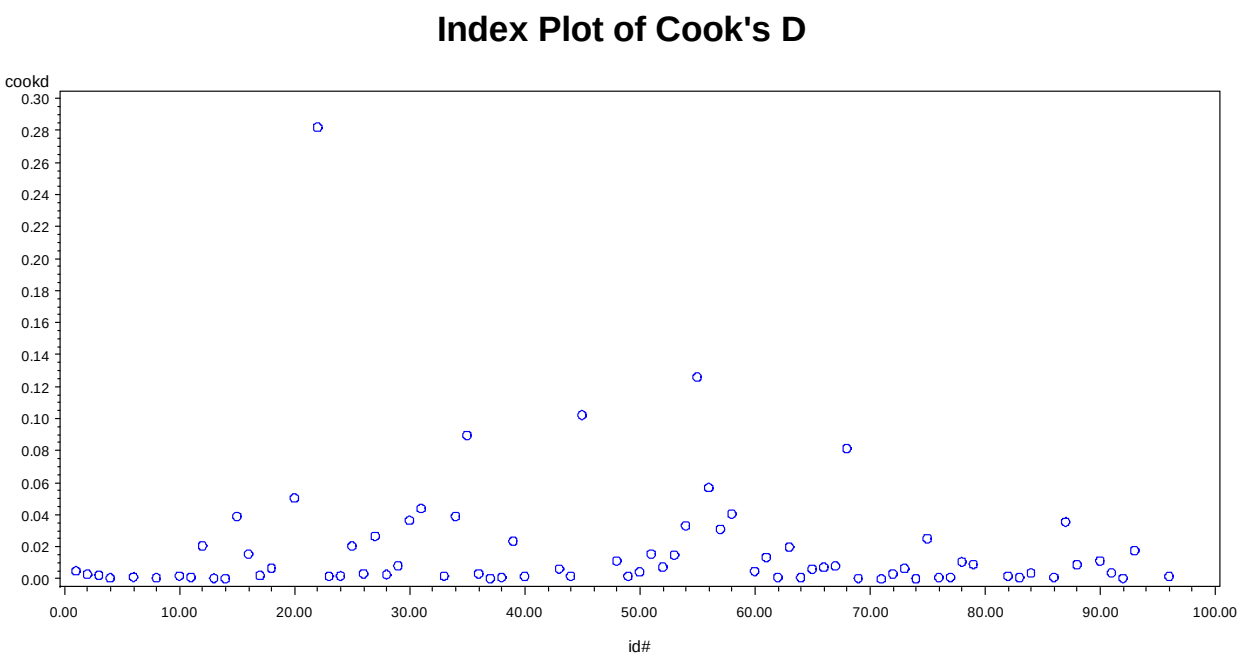


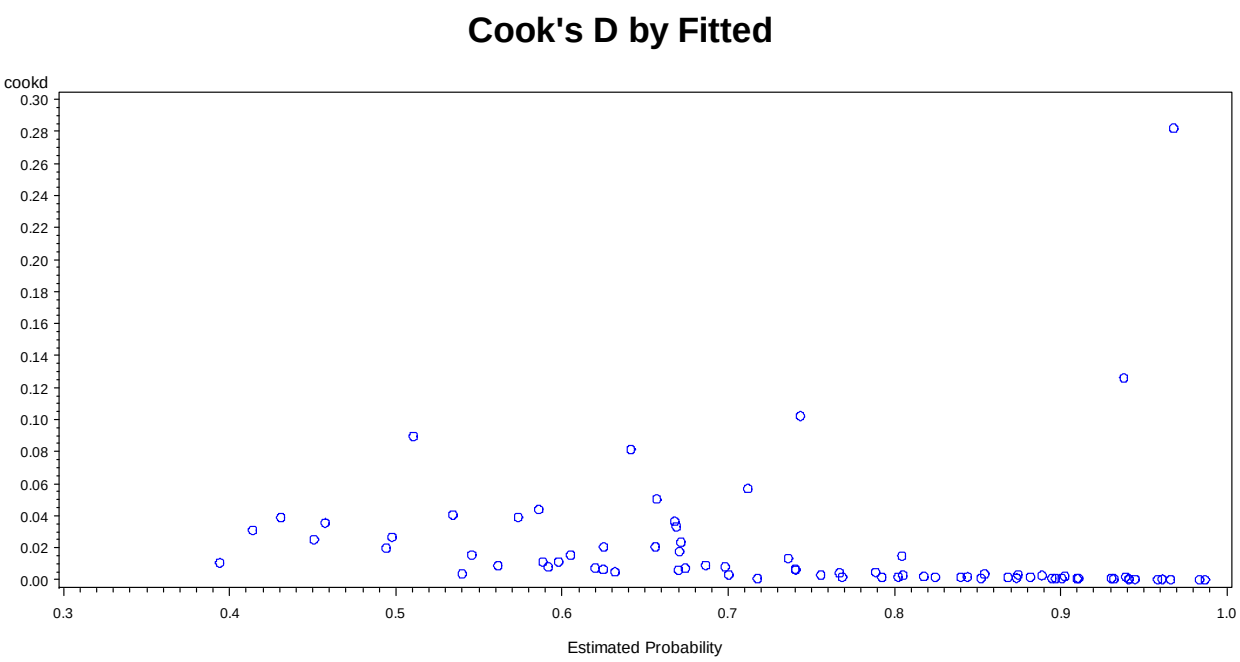

Cook's D by Fitted
cookd
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Estimated Probability

E.2 ANXIETY TRAJECTORY GROUP RESULTS

Anxiety		***Block 0***				***Block I***				***Block II***		
Model Type	***Characteristic***	***B (SE)***	***Std B***	***p***		***B (SE)***	***Std B***	***p***		***B (SE)***	***Std B***	***p***
Caregiver	Age	-0.02 (0.03)	-0.1	0.4		-0.03 (0.03)	-0.2	0.3		--	--	--
	Female	0.01 (0.7)	--	0.9		0.2 (0.8)	--	0.07		--	--	--
	Education (yrs)	-0.1 (0.1)	-0.1	0.4		-0.1 (0.1)	-0.1	0.5		--	--	--
	Emotional Stability	-0.3 (0.1)	-0.5	0.01		-0.3 (0.1)	-0.5	0.03		--	--	--
	Social Support	--	--	--		-0.1 (0.1)	-0.3	0.2		--	--	--
	Mastery	--	--	--		-0.1 (0.1)	-0.1	0.6		--	--	--
Global Test*	$\chi 2(4)=10.9$, p=0.03, N=79					$\chi 2(6)=13.7$, p=0.03, N=81				--		
Care Recipient	Tumor Type	-0.03 (0.6)	0.9	-0.03 (0.6)		-1.0 (0.8)	--	0.2		-0.1 (0.6)	--	0.2
	Symptoms	--	--	--		0.002 (0.01)	0.03	0.9		--	--	--
	Orientation	--	--	--		-1.7 (1.1)	-1.1	0.1		-1.2 (0.9)	-0.7	0.2
	Attention	--	--	--		-0.1 (0.3)	-0.1	0.7		--		
	Language	--	--	--		-2.1 (1.2)	-0.9	0.1		-0.9 (0.8)	-0.4	0.3
	Reasoning	--	--	--		0.1 (0.4)	0.1	0.8		--	--	--
	Constructional Ability	--	--	--		0.3 (0.2)	0.4	0.1		0.2 (0.2)	0.2	0.2
	Memory	--	--	--		0.01 (0.1)	0.02	0.9		--	--	--
	Calculations	--	--	--		0.97 (0.57)	0.48	0.09		0.4 (0.4)	0.2	0.3
Global Test*	$\chi 2(1)=0.003$, p=0.97, N=89					$\chi 2(9)=13.8$, p=0.13, N=61				$\chi 2(5)=7.1$, p=0.21, N=79		
Combined	Age	-0.02 (0.03)	-0.1	0.5		-0.03 (0.03)	-0.2	0.1		--	--	--
	Female	0.1(0.7)	--	0.9		0.3 (0.8)	--	0.7		--	--	--
	Education (yrs)	-0.1 (0.1)	-0.1	0.5		-0.1 (0.1)	-0.1	0.7		--	--	--
	Emotional Stability	-0.3 (0.1)	-0.5	0.01		-0.4 (0.1)	-0.8	0.002		--	--	--
	Tumor Type	-0.2(0.6)	--	0.8		-0.1 (0.7)	--	0.9		--	--	--
Global Test*	$\chi 2(5) = 10.18$, p=0.07, N=78					$\chi 2(5) = 15.80$, p=0.008, N=77						


Index Plot of Pearson's Residuals
Pearson Residual
2
1
0
-1
-2
-3
-4
-5
-6
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
90.00
100.00
id#


Index Plot of Cook's D
cookd
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
90.00
100.00
id#


Cook's D by Fitted
cookd
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Estimated Probability

E.3 CAREGIVER BURDEN TRAJECTORY GROUP RESULTS

CRA												
		Block 0				***Block I***				***Block II***		
CAREGIVER	***Characteristic***	***B (SE)***	***Std B***	***p***		***B (SE)***	***Std B***	***p***		***B (SE)***	***Std B***	***p***
Moderate vs. Low group	Age	0.03 (0.03)	0.2	0.4		0.03 (0.03)	0.2	0.4			--	--
	Female	-1.0 (0.8)	--	0.24		-1.1 (0.9)	--	0.2			--	--
	Education (yrs)	-0.1 (0.2)	-0.1	0.5		-0.1 (0.2)	-0.2	0.5			--	--
	Emotional Stability	0.05 (0.1)	0.08	0.7		0.02 (0.1)	0.03	0.9			--	--
	Social Support	--	--	--		0.05 (0.1)	0.1	0.7			--	--
	Mastery	--	--	--		0.07 (0.2)	0.1	0.7			--	--
Severe vs. Low group	Age	0.04 (0.03)	0.2	0.2		0.03 (0.03)	0.2	0.3				
	Female	-0.4 (0.3)	--	0.6		-0.3 (0.8)	--	0.7				
	Education (yrs)	0.08 (0.1)	0.1	0.5		0.04 (0.1)	0.05	0.8				
	Emotional Stability	-0.1 (0.1)	-0.2	0.2		-0.1 (0.1)	-0.2	0.2				
	Social Support	--	--	--		-0.07 (0.07)	-0.2	0.3				
	Mastery	--	--	--		0.09 (0.1)	0.12	0.5				
Global Test*	$\chi 2(8)=7.9$, p=0.45, N=81					$\chi 2(12)=11.1$, p=0.53, N=81						
CARE RECIPIENT												
Moderate vs. Low group	Tumor Type	1.47 (0.73)	--	0.04		2.7 (1.2)	--	0.03		1.9 (0.9)	--	0.03
	MDASI	--	--	--		0.02 (0.04)	0.27	0.6				
	Orientation	--	--	--		-1.5 (2.3)	-0.9	0.5				
	Attention	--	--	--		-1.1 (0.60)	-1.0	0.08				
	Language	--	--	--		3.9 (1.9)	1.7	0.04		1.3 (1.0)	0.5	0.2
	Reasoning	--	--	--		0.30 (0.5)	0.2	0.6				
	Constructional Ability	--	--	--		-1.3 (0.5)	-1.3	0.009		-1.0 (0.4)	-1.0	0.009
	Memory	--	--	--		-0.22 (0.2)	-0.4	0.2				
	Calculations	--	--	--		0.20 (1.0)	0.1	0.8				
Severe vs. Low group	Tumor Type	2.14 (0.67)	--	0.002		2.8 (1.2)	--	0.02		2.3 (0.8)	--	0.004
	MDASI	--	--	--		0.03 (0.04)	0.41	0.4				
	Orientation	--	--	--		-2.0 (2.3)	-1.3	0.4				

	Attention	--	--	--		-1.0 (0.58)	-1.0	0.07				
	Language	--	--	--		2.0 (1.7)	0.9	0.2		0.4 (0.8)	0.1	0.7
	Reasoning	--	--	--		0.33 (0.6)	0.2	0.6				
	Constructional Ability	--	--	--		-1.1 (0.5)	-1.1	0.03		-0.9 (0.4)	-0.8	0.03
	Memory	--	--	--		-0.12 (0.2)	-0.2	0.5				
	Calculations	--	--	--		0.64 (1.0)	0.3	0.50				
Global Test*	$\chi2(2)=11.4$, p=0.003, N=89					$\chi2(18)=36.6$, p=0.006, N=61				$\chi2(6)=26.1$, p=0.002, N=80		
COMBINED												
Moderate vs. Low group	Age	0.01 (0.04)	0.07	0.8		0.01 (0.04)	0.08	0.7		--	--	--
	Female	0.1 (1.1)		0.9		0.6 (1.1)		0.6		--	--	--
	Education (yrs)	0.02 (0.2)	0.03	0.9		--	--	--		--	--	--
	Emotional Stability	0.02 (0.1)	0.03	0.9		0.03 (0.1)	0.06	0.8		--	--	--
	Tumor Type	1.8 (0.9)		0.04		1.8 (0.9)		0.03		--	--	--
	Constructional Ability	-1.0 (0.5)	-1.0	0.04		-1.0 (0.5)	-0.9	0.03		--	--	--
Severe vs. Low group	Age	0.02 (0.04)	0.12	0.6		0.01 (0.03)	0.06	0.8		--	--	--
	Female	0.7 (1.1)		0.5		0.00 (1.1)	--	1.00		--	--	--
	Education (yrs)	0.2 (0.2)	0.3	0.2		--	--	--		--	--	--
	Emotional Stability	-0.2 (0.1)	-0.3	0.2		-0.1 (0.1)	-0.2	0.3		--	--	--
	Tumor Type	2.4 (0.8)		0.004		2.3 (0.8)	--	0.004		--	--	--
	Constructional Ability	-1.0 (0.5)	-1.0	0.04		-0.9 (0.5)	-0.8	0.05		--	--	--
Global Test*	$\chi2(12)=28.4$, p=0.005, N=75					$\chi2(10)=26.6$, p=0.003, N=76						

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