USING LATENT CLASS GROWTH MODELING TO EXAMINE COGNITIVE PREDICTORS OF SUICIDAL IDEATION IN THE ELDERLY

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ABSTRACT

Late life suicide is a serious public health concern. Suicide rates peak in individuals aged 65 or older. Because individuals 65 or older will comprise 20% of the population by 2039, late life suicide is expected to be a growing public health problem. Recent cross sectional studies suggest that deficits in frontal executive functioning, memory and attention are associated with suicidal ideation in the elderly. Our current study is a secondary analysis of data from a clinical trial entitled "Incomplete Response in Late Life Depression: Getting to Remission". Individuals with major depression received venlafaxine XR monotherapy for depression and were followed repeatedly for up to 16 weeks. We used latent class growth modeling to classify groups of individuals aged $\geq$ 60 based on trajectories of suicidal ideation. We controlled for time dependent variables (depression and antidepressant doses) and baseline demographics. The optimal model classified individuals into three groups with linear or quadratic trajectories of suicidal ideation. We also ran various analyses using different link functions to find the link that was most appropriate for our data (logistic, censored normal or zero inflated Poisson). After trajectory group membership was determined, we examined whether cognitive dysfunction predicted suicidal ideation trajectory membership using multinomial logistic regression. Using the zero inflated Poisson link latent trajectory model, we determined that having a better score on the Trails B frontal lobe measure was statistically significantly associated with individuals

having higher levels of suicidal ideation; however, this association was no longer significant when a multivariable model was used. No statistically significant associations were observed with the other frontal lobe measures, i.e., Trails B/A, Stroop 3 and Stroop 4. In addition, neither individual subscale scores nor total scores from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were associated with individuals with having higher trajectories of suicidal ideation. The present study is the first to our knowledge that examines how cognitive status is associated with long-term trajectories of suicidal symptoms in depressed elderly adults.

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PREFACE

The dataset utilized in this study was provided by Charles Reynolds III and was funded by 5R01-MH083660.

1.0 INTRODUCTION

1.1 SUICIDE IS A CRITICAL PUBLIC HEALTH PROBLEM AMONG INDIVIDUALS WITH SERIOUS MENTAL ILLNESS

The effects of suicidal behavior on family members, friends, and the community are devastating. Individuals at high risk for suicide include those with depressive symptoms, especially those with a primary diagnosis of major depression (Ilgen et al., 2010; Desai et al., 2005). Psychiatric hospitalization is often needed when individuals become suicidal (Godleski et al., 2008). The societal costs associated with suicide are high.

Late life suicide is a serious public health concern (Conwell et al., 2011). Suicide rates peak in individuals age 65 and older worldwide (WHO Mental Health Suicide Prevention [SUPRE] http: //www.who.int/mental health/prevention/suicide/suicideprevent/en.) There is an increased odds of an adult committing suicide when their age is greater than 44 (Beautrais et al., 2002; Waern et al., 2002). It is estimated that by 2030 elderly individuals age 65 or older will comprise 20% of the population (Centers for Disease Control and Prevention, The Merck Company Foundation. Witehouse Station, NJ: 2007. The State of Aging and Health in America. www.cdc.gov/aging.); thus obtaining a better understanding of late life suicide is important in order to prevent and treat this problem.

One approach towards designing interventions to prevent suicide related morbidity and mortality involves determination of risk factors. Preliminary progress has been made in determining pertinent risk factors for suicide in the elderly. Investigators have determined that co-morbid psychiatric illness places one at risk and it has been demonstrated that 71-97% of suicides are associated with a co-morbid psychiatric illness. Affective disorders, particularly major depression are the most common psychiatric illnesses associated with suicide. Other important risk factors for suicide include physical illness, unemployment, marital status, gender, chronic pain, race, and loss of social ties (Juurlink et al., 2004; Sirey et al., 2008; Forkmann et al., 2012; Morrell et al., 1998). A greater proportion of elderly suicides are associated with individuals who live alone suggesting that social isolation and loneliness are important factors to consider (Barraclough, 1971).

1.2 COGNITION, DEPRESSION AND SUICIDE

Cognitive function, in particular executive function and processing speed are often impaired in late life depression, a major risk for suicide in the elderly (Butters et al., 2004a, Bhalla et al., 2006). Furthermore, cognitive dysfunction may be an important predictor of acute and long term antidepressant treatment outcome (Butters et al., 2004; Bogner et al., 2007). Executive dysfunction in depression may reflect underlying structural brain changes, or it may lead to erratic treatment adherence (Magni et al., 1988, Kalayam et al., 1999; Alexopoulos et al., 2000).

There is some evidence from cross sectional studies that certain cognitive deficits in elderly individuals places them at risk for suicidal behavior. One cross sectional study by King et al., (2000) assessed the role of impaired executive functioning in late-life suicide in a small group of

older adults using the Trail Making Test Part B. The Trails Making Test Part B is a neuropsychological test which assesses cognitive flexibility. They found an interaction between age and suicide attempt suggesting that there is an accelerated decline in executive function with age in those who attempt suicide compared to those who do not.

In a cross sectional study, Dombrovski et al., (2008) reported that elderly individuals with depressive symptoms and suicidal ideation perform worse on measures of frontal executive function, memory and attention compared to non-suicidal elderly subjects with depression. The authors noted that the findings of frontal executive dysfunction are important because frontal lobe functioning is known to be essential in the management of stressful circumstances. It was also suggested that these impaired decision making abilities along with the inability to access and use prior experience may be linked to impairments in ventral prefrontal neural circuitry (Arango et al., 1997).

Further studies from the same group examined the relationship of high or low lethality attempters to cognitive control using the Wisconsin Card Sorting task (McGirr et al., 2012). Lethality was determined using the Beck Lethality scale (Beck et al., 1975) and high lethality was defined by a score of 4 or greater and involved either 1) a medical intervention, 2) resulted in a coma, 3) a need for resuscitation, 4) unstable vital signs, 4) third degree burns or 5) major bleeding. The Wisconsin Card Sorting Task is a neuropsychologic test of set shifting. Initially a number of stimulus cards are presented to the subject and the subject is told to match the cards but not how to match. The subject is told if the match is correct or not. The test takes about 15 minutes. It is used as a measure of executive function; specifically, patients with lesions in the dorsolateral frontal lobe make a higher number of perseverative errors.

McGirr et al., (2012) examined Wisconsin Card Sorting score performance in those with high and low lethality. The authors determined that high lethality attempters had a pattern of deficits involving poor conceptual reasoning, perseverative errors and total errors. Compared to low lethality attempters and healthy controls, high lethality attempters had worse conceptual reasoning and higher rates of perseverative errors and total errors. The authors stated that impairments in cognitive control during rule learning may represent a vulnerability distinct from the impulsive profile typically seen in young low lethality attempters.

Gujral et al., (2013) examined global cognition and executive function impairments as correlates of suicidal ideation and suicidal behavior in depressed older adults. Both suicide attempters and suicide ideators performed worse on the EXIT compared to nonsuicidal depressed or nonpsychiatric control subjects. The EXIT is a 10 minute 25 item neuropsychologic test which assesses executive cognitive function. The authors also compared groups with the Dementia Rating Scale (DRS; Mattis et al., 1976). The DRS comprises 36 tasks which assess attention, initiation/perseveration, construction, conceptualization and memory. It is used to assess the cognitive status of individuals with brain dysfunction. The authors noted that with the total DRS score, as well as on Memory and Attention subscales, suicide attempters and ideators and nonsuicidal depressed subjects performed similarly but were impaired relative to nonpsychiatric control subjects. In that study, there were significantly different Beck Scale for Suicidal Ideation scores between the attempters and the ideators (25.0 +/- 5.6 vs 15.5 +/- 7.5) but no differences in DRS scores.

Thus the preliminary studies so far suggest that frontal lobe dysfunction as well as other cognitive deficits as assessed with the Dementia Rating Scale may play a role in late life suicidal behavior. These studies have been limiting in that they have been cross sectional in design. To

our knowledge, no studies to date have examined how suicidal ideation varies over time in elderly depressed individuals and whether cognitive dysfunction could predict degree of suicidal ideation. We will attempt to fill this gap by assessing suicidal symptoms over time in a cohort of elderly patients and use Latent Class Growth Modelling to ask whether cognitive dysfunction will be associated with individuals' trajectories of higher levels of suicidal ideation.

1.3 LATENT CLASS GROWTH MODELING

Latent Class Growth Modelling is a semi-parametric method which is used to identify subgroups of individuals following a similar pattern of change over time on a given variable(s). Different from Latent Class Analysis, which is a cross-sectional approach, Latent Class Growth Modelling is a longitudinal analysis that explores differences in growth trajectories (Nylun et al., 2007). Each individual has a unique longitudinal course; however, the distribution of individual differences in change within the data is summarized by a finite set of polynomial functions each of which correspond to a unique trajectory (Andruff et al., 2009; Nagin, 2005). The magnitude and direction of change can vary across trajectories; thus a set of model parameters which includes intercept and slope is estimated for each trajectory. Latent Class Growth Modelling fixes the slope and intercept to equality across individuals within each trajectory. A degree of freedom is thus available to estimate quadratic trajectories of a variable measured at 3 time points or cubic trajectories with data at 4 time points (Andruff et al., 2009). Using Latent Class Growth Modelling, researchers need to specify the number of trajectories to be extracted and then select the number of trajectories that best fit the data. If possible, it is best to have *a priori*

knowledge concerning the number and shape of trajectories based on theory and literature pertaining to the area of study.

With latent class growth model analysis, the estimated parameter coefficients provide information about group membership probabilities. Each trajectory should hold a group membership probability of at least 5% (Andruff et al., 2009). Posterior probabilities can be calculated to estimate the probability that each case with its associated profile of change is a member of each modeled trajectory. These posterior probabilities can be used to assign each individual membership to a trajectory that best matches his/her profile of change. A maximum probability assignment rule is also used to assign each individual membership to the trajectory to which the participant holds the highest posterior membership probability.

The Bayesian Information Criteria (BIC) is a common criterion for model selection among a finite series of models. The BIC is an asymptotic result derived under the assumptions that the data distribution is in the exponential family. It is based in part on the likelihood function and is closely related to another common criterion, i.e., the Akaike information criteria (AIC). Both BIC and AIC resolve problems in model 'over-fitting' by introducing a penalty term for the number of parameters in the model. The AIC and BIC share the same goodness of fit term but the penalty term of the BIC is much more stringent than the penalty term of the AIC. Because the BIC tends to choose fitted models that are more parsimonious than those favored by AIC, the BIC is preferred (Schwarz, 1978; Bhat and Kumar, 2012; McQuarrie and Tsai, 1998; Kass and Raftery, 1995; Neath and Cavanaugh, 2012).

The calculation of individual BIC values is as follows: if x = observed data, n = number of data points, k = number of free parameters; $p(\mathrm{x}|\mathrm{M})$= marginal likelihood of the observed data given the model M; $\hat{L}$ = maximized value of the likelihood function of the model M, i.e., $\hat{L} =$

$p(x|\hat{\theta}, M)$where $\hat{\theta}$ are parameter values that maximize the likelihood function. An approximate formula for BIC is:

$$-2 \ln p(x|M) \approx -2 \ln \hat{L} + k \ln (n) \quad (1)$$

Under the assumption of normality:

$$\text{BIC} = \chi^2 + k \ln (n) \quad (2)$$

The BIC is thus proportional to the error variance and number of parameters. Thus unexplained variation in the dependent variable and number of explanatory variables increase the value of BIC and a lower BIC indicates there are fewer explanatory variable and/or a better fit. When comparing models with the BIC, the models do not need to be nested (Schwarz, 1978; Bhat and Kumar, 2012; McQuarrie and Tsai, 1998; Kass and Raftery, 1995; Neath and Cavanaugh, 2012).

Given any two models, the model with the lower BIC is preferred. Also, models can be compared by using an estimate of the log Bayes factor. The log Bayes factor is defined as

$$2 \, ln \, (B) = \, 2(\Delta BIC) \quad (3)$$

where B is the Bayes factor based on Jones, et al., (2001). The difference is determined by subtracting the BIC value of the simpler model with the smaller number of trajectories from the more complex model. In order to ensure model parsimony, a set of guidelines has been established for interpreting the estimate of the log Bayes factor when comparing models. BIC difference values ranging from 0-2 are weak evidence for the more complex model; 6-10 is

interpreted as strong evidence; values greater than 10 are considered very strong evidence (Jones et al., 2001). The process of comparing the fit of each subsequent more complex model to the fit of the previous model continues until there is no evidence for improving the fit.

1.4 MATHEMATICAL THEORY OF LATENT CLASS GROWTH MODELLING

The theory of trajectory analysis used in latent class growth modeling is well outlined by Roder and Nagin (2000) as well as Jones and Nagin (2007). To summarize, let $\boldsymbol{Y}_i = \{y_{i1}, y_{i2}, \ldots . y_{it}\}$ represent a longitudinal sequence of measurements of an individual i over T time periods where $T = 1, 2 \ldots . n$. The group-based trajectory model assumes that the population is composed of a mixture of J trajectory groups such that $P(\boldsymbol{Y}_i) = \sum \pi_j P_j(Y_i)$. In this case, $P_j(\boldsymbol{Y}_i)$ is the probability of $\boldsymbol{Y}_i$ given membership in group j and π_j is the probability of being in group j.

Time independent covariates referred to as risk factors are incorporated into the model and are assumed to influence group membership (see Figure 1). Time dependent covariates also affect the observed trajectories. Conditional on group membership, $\boldsymbol{Y}_i = \{y_{i1}, y_{i2}, \ldots . y_{it}\}$ with $t = 1, 2 \ldots . T$ are independent so that $P_j(\boldsymbol{Y}_i) = \prod p_{jt}(y_{it})$, where $p_{jt}(y_{it})$ is defined as the conditional probability of the outcome for subject i at time t given group membership j. Group membership probabilities are estimated by a multinomial logit function with time-stable predictors. Estimated values of π_j are between 0 and 1. For count data, $p_{jt}(y_{it})$ can follow a Poisson distribution or a zero inflated Poisson (Lambert 1992). For psychometric scale data,

p_{jt} (y_{it}) follows the censored normal distribution. For binary data, p_{jt} (y_{it}) follows the binary logit distribution.

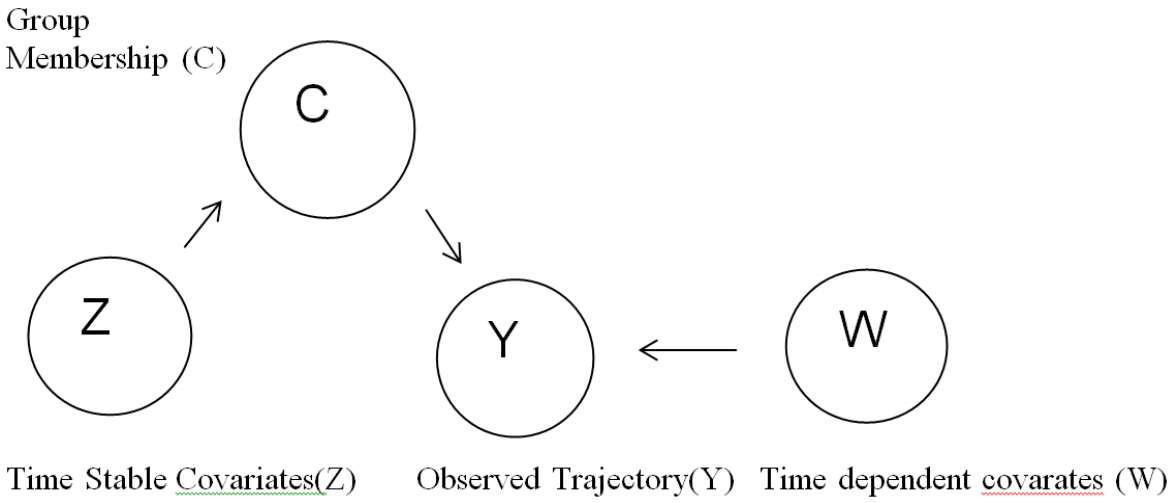


Figure 1. Model of Trajectory Analysis

(Adapted from Jones et al, 2001; Reproduced with permission from Sociologic Methods and Research).

With respect to Figure 1, the marginal density for the data y can be written as

$$f(\boldsymbol{y}) = \sum_{j=1}^{J} \Pr(\boldsymbol{C} = \boldsymbol{j}) \Pr(\boldsymbol{Y} = \boldsymbol{y} | \boldsymbol{C} = \boldsymbol{j}) = \sum_{j=1}^{J} p_j f(\boldsymbol{y}, \lambda_j) \quad (4)$$

where C is group membership and p_j is the probability of group membership in class j with corresponding parameter λ_j. Also the conditional distribution of the observable data for subject *i* given risk factors and a time dependent covariate W is:

$$f(\boldsymbol{y_i} | \boldsymbol{z_i}, \boldsymbol{w_i}) = \sum_{j=1}^{J} \Pr(\boldsymbol{C}_i = \boldsymbol{j} | \boldsymbol{Z}_i = \boldsymbol{z}_i) \Pr(\boldsymbol{Y_i} = \boldsymbol{y_i} | \boldsymbol{C}_i = \boldsymbol{j}, \boldsymbol{W_i} = \boldsymbol{w_i}) \quad (5)$$

A polynomial relationship establishes a link between a time dependent outcome variable and 1 or more time dependent variable(s). For example, with a binary logistic distribution for dichotomized outcomes conditional on group membership in group j, the likelihood of observing a trajectory for participant i given group membership in j is:

$$\Pr(\boldsymbol{Y_i} = \boldsymbol{y}_i | \boldsymbol{C}_i = j, \boldsymbol{W}_i = \boldsymbol{w}_i)$$
$$= \prod_{y_{it} \neq 0} p_{itj} \prod_{y_{it}=0} (1 - p_{itj}) \quad (6)$$

Also, based on the logistic model, the following relationship applies for p_{itj}:

$$p_{itj} = \exp[\beta_{0j} + \beta_{1j}(time)_{it} + \beta_{2j}(time)^2_{it} + \cdots + \omega_{it}\delta_j] /$$
$$[1 + exp\, \beta_{0j} + \beta_{1j}(time)_{it} + \beta_{2j}(time)^2_{it} + \ldots. + \omega_{it}\delta_j] \quad (7)$$

With this relationship, *t* is time and *i* is the i[th] individual; time dependent covariate(s) are represented by the terms "$\omega_{it}\delta_j$".

For the zero inflated Poisson distribution, the probability of observing the data trajectory y given group membership in j is:

$$\Pr(\boldsymbol{Y}_i = \boldsymbol{y}_i | \boldsymbol{C}_i = \boldsymbol{j}, \boldsymbol{W}_i = \boldsymbol{w_i}) \prod_{y_{it}=0} [\, p_{itj}(1\, p_{itj}) e^{-\lambda_{itj}} \prod_{y_{it}>0} (1 p_{itj}) \exp[(-\lambda_{itj}) \lambda^{\,y}_{itj} / y_{ij}\, !] \quad (8)$$

p_{itj} is the extra Poisson probability of a zero. Time dependent covariates are related linearly to ln $\lambda_{itj.}$ For a Poisson regression model, the following polynomial relationship models the link between the time and the model parameters:

$$\ln \lambda_{itj.} = \beta_o + time_{ij}\beta_1 + time_{ij}^2\beta_2 + \cdots + \omega_{it}\delta_j \quad (9)$$

For the censored normal (CNORM) model (Nagin and Tremblay, 1999), the likelihood of observing the data trajectory for subject i, given s/he belongs to group k, is:

$$\Pr(Y_i = y_i |\ C_i = k, W_i = w_i) = \prod_{(yij=\min)} \emptyset([Min\mu_{ijk}]/\sigma)$$
$$\prod_{\min<yij<max}\left(\frac{\varphi}{\sigma}\right)\prod_{yij=\max}(1-\emptyset[(Max-\mu_{ijk})/\sigma]) \quad (10)$$

and

$$\mu_{ijk} = \beta_o + time_{ij}\beta_1 + time_{ij}^2\beta_2 + \cdots + \omega_{it}\delta_j \quad (11)$$

With all link functions, time independent covariates can also be added to the model and their effects on group membership are modeled with a generalized logit function where

$$\Pr(\boldsymbol{C}_i = \boldsymbol{j}|\boldsymbol{Z}_i = \boldsymbol{z}_i) = \frac{\exp(\theta_j + \lambda_j z_i)}{\sum_{l=1}^{J}\exp(\theta_l + \lambda_l z_i)} \quad (12)$$

with i = 1 to j.

1.5 STUDIES WHICH HAVE USED LONGITUDINAL MODELS TO EXAMINE MENTAL ILLNESS IN OLDER ADULTS

Dew et al., (1997) examined depression symptom levels for 18 weeks in individuals 60 and older during an episode of recurrent depression while being treated with nortriptyline and interpersonal psychotherapy. The authors used cluster analysis to identify depression recovery patterns. Furthermore, multivariate analysis considered whether recovery patterns were predicted by pretreatment psychosocial, clinical or electroencephalographic sleep characteristics. Four subgroups of participants were identified. One group showed rapid sustained improvement, a second group showed delayed but sustained improvement; a third group showed partial or mixed response and a fourth group had no response. The following factors predicted group membership: higher levels of stressors, worse social support, younger age at first depressive episode, higher current anxiety levels, older age and worse subjective and objective sleep profile.

Another study by Dew et al., (2001) examined individuals aged 60 and older with recurrent depression maintenance treatment. The authors classified participants into four groups: 1) rapid sustained responders, 2) delayed sustained responders, 3) mixed responders without sustained improvement and 4) prolonged nonresponders. Groups were compared in terms of recovery rates and on time to depression recurrence after randomization to three years of combined maintenance therapy (monthly interpersonal therapy with nortriptyline), monotherapy with either, or medication clinic with placebo. Initial response profile predicted recovery rates. Rapid responders had lower recurrence risk with either combined treatment or monotherapy relative to placebo. In the group classified as initially mixed responders, only combined therapy was superior to placebo. For delayed responders combined therapy was also superior to placebo. Prolonged nonresponders did not improve from maintenance treatment. The authors concluded

that the ability to match patients to maintenance therapies can be enhanced by considering the temporal profile of initial reponse to acute treatment.

Cui et al., (2008) derived depression trajectories in elderly individuals age 65 and older by applying longitudinal cluster analysis to weekly depression data obtained from the 'Longitudinal Follow up Evaluation.' This study followed an older cohort of primary care patients. The authors identified six separate trajectories. Predictors of trajectories included baseline depression severity, medical burden and psychiatric functional status. For some clusters previous history of depression and social support were also predictive factors. The authors stated that determining various trajectories could help identify clusters of individuals who were at higher risk of poorer outcomes; this, in turn could help health care providers determine which individuals need to be prioritized in terms of treatment.

Sun et al., (2012) examined the effects of religiosity on trajectories of depressive symptoms in a sample of community dwelling older adults. A hierarchical linear modeling approach determined that the trajectories of depressive symptoms were curvilinear over time. Participants who attended religious services reported fewer depressive symptoms and those with the most intrinsic religiosity experienced a steady decline in depressive symptoms. Tang et al., (2013) examined trajectories of depressive symptoms among caregivers providing end of life care to cancer patients. Using longitudinal latent class analysis, four trajectories were identified as 1) endurance, 2) resilience, 3) moderately symptomatic, and 4) chronically distressed. The group in the resilient trajectory perceived less subjective caregiving burden than those with moderate or chronic depressive symptoms.

Gildengers et al., (2005) examined the effect of psychosocial and clinical variables on treatment response trajectories in elderly patients with major depressive disorder. A mixture

modeling approach was applied to identify subpopulations of response and to determine whether baseline Hamilton score, depressive illness course, current episode duration, interpersonal self evaluation list-self esteem factor, age at study entry and medical burden risk were risk factor covariates associated with response trajectory. Trajectories were classified as 'rapid response' and 'slower response.' Baseline Hamilton score was a significant predictor of response trajectory.

There are no studies which we are aware of which have examined cognitive predictors of trajectories of depression and suicide in elderly individuals over time. Obtaining such information is important because it could help to identify those who are at higher risk of suicide. From a public health perspective, this could be helpful for screening individuals at risk for suicide.

1.6 GOALS AND HYPOTHESIS

Our first goal is to use latent class growth modelling to classify depressed participants with varying degrees of suicidal ideation into groups according to similar trajectories of suicidal ideation. Here the amount of suicidality will vary within groups but the trajectories of suicidal ideation will be similar. Some of the individuals in a trajectory group may have no suicidal ideation. The overall magnitude of suicidal ideation will be greater in the groups with higher trajectories of suicidal ideation relative to the groups with lower trajectories of suicidal ideation.

We will explore various models using different link functions such as the logistic, zero inflated Poisson (ZIP) and censored normal distribution. For each link function we will use both maximum likelihood analysis and Bayesian Information Criteria values to determine the optimal

model, i.e., how many groups of trajectories will be in each model and the optimal polynomial degree for each group. Furthermore, because the Beck Scale for Suicidal Ideation (SIS) scores are skewed to the right, for models using the censored normal distribution, we will attempt to transform our SIS scores with various approaches which include natural logarithm and square root transformation.

Our second goal is to examine whether cognitive function at baseline is associated with suicidal ideation trajectory group membership. Previous cross sectional studies have suggested that frontal lobe dysfunction is associated with worse suicidal behavior. In this study, our 1st hypothesis is that cognitive dysfunction involving the frontal lobes will be worse in elderly individuals with trajectories of higher levels of suicidal ideation relative to those with trajectories of lower levels of suicidal ideation. Cognitive predictors will include measures from the Delis-Kaplan Executive Function Scale, i.e., the Trails A, Trails B/A, Stroop 3 and Stroop 4 tests.

Our second hypothesis is that worse scores from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will be associated with individuals with higher trajectories of suicidal ideation relative to those individuals with lower trajectories. This will include testing measures of global cognition, immediate and delayed memory, language, attention, and visuospatial/constructional ability.

2.0 METHODS

2.1 DESCRIPTION OF THE MAIN STUDY

All participants were involved in an ongoing clinical trial entitled “Incomplete Response in Late Life Depression: Getting to Remission” (5R01-MH083660). This is a three site trial which involves the University of Pittsburgh as the lead site. Secondary sites include the University of Toronto and Washington University. The current study is a secondary analysis of data from this clinical trial which were obtained between 7/20/2009 and 3/14/2013. Patients were referred with depression from specialty mental health clinics, outpatient general medical clinics, inpatient services or from patients as self referrals.

The parent study aims to study incomplete response in the treatment of late-life depression. The study hypothesis of the parent trial states that aripiprazole augmentation will be superior to placebo for bringing about and sustaining remission in elderly patients who respond incompletely to venlafaxine XR. The study enrolls patients aged 60 and older with major depressive disorder and treats them openly for up to 16 weeks with venlafaxine XR (phase 1). Participants meeting criteria for incomplete response (N=200) are then randomly assigned to receive either aripiprazole (2.5-15 mg/d; target dose: 10 mg/d) or placebo augmentation of venlafaxine for 12 weeks (phase 2), with the goal of achieving remission. Those who remit in phase 2 (N=80) will receive continuation treatment, with the same double-blinded intervention to

which they were randomly assigned (phase 3), for 12 weeks to determine the stability of remission.

For the current work in this thesis, participants are those who have completed phase 1, i.e., the open phase venlafaxine treatment. In phase 1, patients are assessed at baseline, and additional multiple time points - weeks one, two, four, six, eight, 10 and then in a final time period between weeks 12 and 16 for the final visit; patients are assessed with scales focusing on suicidal ideation and depression. In addition, neuropsychological assessments were obtained on patients at baseline.

Drug titration with venlafaxine ER in phase I starts patients with a dose of 37.5 mg/d with increases of 37.5 mg every three days, up to 150 mg/d. In those with a MADRS > 10, venlafaxine ER is again increased by 37.5 mg increments every three days up to 300 mg/d to achieve a final dose until the end of the 12-week Phase one. Subjects who demonstrate intolerable side effects were able to have temporary dose reductions or a slower titration.

2.2 PRIMARY MEASURES

Our primary measure is the Beck Scale for Suicidal Ideation (SIS). This is a 21-item scale which has been shown to predict completed suicide (Beck, 1979; 1999; Brown, 2000). To reduce participant burden, five screening items are initially administered; the participant then completes items 6-19 (each rated on a scale of 0-2) if the following scores are obtained: > 0 on item 1 (which indicates a weak or no wish to live); and/or > 1 on item 2 (which indicates a moderate to strong wish to die); and/or > 1 on item 3 (which indicates reasons for dying outweigh reasons for living); and/or > 0 on item 4 (which indicates active suicidal ideation); and/ or > 0 on item 5

(which indicates passive suicidal ideation). If items 6-19 are not administered each of the item scores are zero. The final SIS score is the sum of items 1-19. The time dependent depressive symptoms were measured with the Montgomery Asberg rating Scale (MADRS). This scale was designed to assess treatment sensitive change in major depression. It includes a 10 item checklist with items rated on a scale of 0-6. A second time dependent variable will be venlafaxine ER dose.

2.3 COGNITIVE MEASURES

To assess executive function, four tests from the Delis-Kaplan Executive Function Scale (D-KEFS; Dean et al., 2001) will be used: 1) The Stroop condition 3 and 2) condition 4 measures behavioral inhibition as well as the ability of individuals to focus their attention and 3) the Trails B/A comparison score measures cognitive flexibility while controlling for attention and 4) trails B measures attentional processes. The Stroop is considered a test of executive function because of the inhibitory control it requires. Condition 3 of the Stroop test, which is called "Inhibition," assesses a participants ability to inhibit an automatic task of reading words of colors; instead they must name the colors of the words. For instance participants may be presented with a word which states "green" but the color of the word is "red". The correct response would be "red". With condition 4 of the Stroop (called inhibition/switching) the participant must switch back and forth between naming the dissonant ink colors and reading the words. This measures both inhibition and cognitive flexibility. The scoring of this test has been modified so that the final scores take into account both speed and accuracy. If a person is slow but accurate, they earn a low score. If they have average speed but make many errors, they also earn a low score. If they

are both slow and make errors they earn a very low score. Permission to alter the score has been obtained from Pearson. The Stroop 3 and 4 scores represent standardized scores with a mean of 10 and standard deviation of 3. Higher scores on the Stroop 3 and 4 test reflect better performance.

The Trails test is considered an assessment of scanning and visuomotor tracking, attention and cognitive flexibility. Part A focuses more on attention while part B depends more on working memory and is sensitive to cognitive inflexibility. A comparison score is obtained by dividing the trails B score by the trails A score; this removes the 'speed' element from the test evaluation so that cognitive flexibility can be ascertained independently of speed (Lezak et al., 2012). The Trials B and Trails B/A scores are calculated from the raw scores as follows. The Trails B score was the time taken to complete the Trails B task divided by the number of connections made. The Trails A score was similarly calculated by dividing the ratio of the time needed to complete the task/number of connections for the Trails A task. Higher scores of the Trails B and Trails B/A reflect worse performance.

As a global cognitive measure, we will use the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The RBANS assesses several domains: immediate and delayed memory, language, attention, and visuospatial/constructional ability. It was developed to assess neurocognitive status in older patients (Randolph et al., 1998). The RBANS total score can also be used as a global measure in older individuals (Duff et al., 2006). The RBANS total score and subscale scores were standardized scores with a mean of 100 and standard deviation of 15. Higher scores reflect better performance. All of the cognitive measures required a total of 1 hour for administration for each individual.

2.4 SCREENING EVALUATION

For the parent study, subjects were screened with the Structured Clinical Interview for DSM-IV Axis 1 disorders (SCID; American Psychiatric Association, 2000), the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and the IQCODE if the MMSE was 21-26 in order to determine eligibility for phase 1. The IQCODE is the 'Informant Questionnaire on Cognitive Decline in the Elderly' and is a tool used to assess cognitive impairment in older people (Jorm, 1994). Potential subjects signed an informed consent form approved by the Institutional Review Board at the respective institutions. At time of enrollment and prior to receiving any study medication, all subjects had a medical history and physical examination to assess physical health and to determine whether they could safely take study medication. Also medical illnesses that could be causing depression were ruled out. All ineffective psychotropic medications were tapered and discontinued.

Inclusion/Exclusion Criteria were as follows:

Inclusion criteria

1. Age $\geq$ 60 years.
2. Major depressive disorder (MDD), single or recurrent, as diagnosed by the SCID-IV.
3. Montgomery Asberg Depression Rating Scale (MADRS) score $\geq$ 15.

Exclusion criteria

1. Inability to provide informed consent.

2. Dementia, as defined by MMSE < 24 and clinical evidence of dementia.

3. Lifetime diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms, as diagnosed by the SCID.

4. Abuse of or dependence on alcohol or other substances within the past 3 months.

5. High risk for suicide (e.g., active SI and/or current/recent intent or plan) AND unable to be managed safely in the clinical trial (e.g., unwilling to be hospitalized).

6. Contraindication to venlafaxine XR or aripiprazole.

7. Failure to respond to at least 6 weeks of venlafaxine (≥225 mg/d) plus aripiprazole (≥10 mg/d).

8. Inability to communicate in English.

9. Non-correctable clinically significant sensory impairment (i.e., cannot hear well enough to cooperate with interview)

10. Unstable medical illness.

2.5 DATA ANALYSIS

2.5.1 Analysis of Baseline and Time Dependent Variables

Descriptive statistics for baseline demographic and clinical characteristics were computed. Because one of the approaches for analysis will involve dichotomizing our main outcome

variable – Beck Scale for Suicidal Ideation (SIS) scores, we will also include values of Beck Suicidal Ideation scores dichotomized to "SIS score 0 = 0" and "SIS score > 0 = 1." This approach divides the groups into those without any suicidal ideation and at least mild levels of thoughts of harm to self. Furthermore, dichotomizing the scores in this manner is performed given that there were many zero's resulting in a right skewed distribution. In addition, there were often multiple SIS and MADRS scores at each time point. The reason for this was that very high scores of suicidality may have led to excluding individuals from participating; thus it was necessary to wait for those individual's scores to improve and then retest them. Because of these repeated measures, the first score obtained for that individual was chosen to be representative of that time point.

Age, years of education, gender, marital status, living status (living alone or not), gender, employment status and race were initially chosen as time independent covariates because they are known to be risk factors for depression and/or suicide (Juurlink et al., 2004; Sirey et al., 2008; Forkmann et al., 2012, Morrell et al., 1998). The MADRS scores, venlafaxine ER doses, the two demographic variables - age and years of education and other baseline cognitive covariates were treated as continuous outcomes. Race, gender, marital status, living status were dichotomized as follows: race 0 = white; other = 1; gender: male = 0 and female = 1; marital status: 0 = not married; 1 = married; employment: full time, part time or in a sheltered workshop = 1; no employment = 0; living alone = 0, not living alone = 1. SAS 9.3 statistical software was used to generate the results with the exception of the Little's test (Little, 1988) which was used to assess whether data were missing completely at random. This was performed with SPSS 21 software.

2.5.2 Latent Class Growth Modelling

We used latent class growth models to produce trajectories of suicidal ideation. These models use a semi-parametric mixture model of normal probability distributions to model heterogeneity in a sample where unobserved subpopulations might exist (Nagin, 1999). The procedure develops models of latent groups that are not predefined. We used various link functions; these included a logistic model which dichotomized SIS scores to "SIS score 0 = 0" and "SIS score > 0 = 1", a zero inflated Poisson model and a censored normal distribution with various transformations, i.e., natural logarithm and square root. With each of these approaches, subject-specific probabilities of trajectory group membership were computed. Within each model, group membership was based on the largest probability obtained. In all cases, SAS Proc Trajectory software was used for the trajectory analyses.

When using the various link functions, we first examined models with two to four trajectory groups and with linear, quadratic, cubic or quartic polynomial terms. These models included time independent covariates (i.e., demographics). The Bayesian Information Criteria in the SAS TRAJ procedure was used to identify the optimal number of trajectory groups and polynomial degree. The optimal model chosen was the model with the most positive BIC scores. This included comparing models with 2, 3 or 4 groups. We initially compared the 3 groups with all linear, all quadratic, all cubic or all quartic terms based on Nagin (1999). We then compared groups with various iterations of polynomial degree. These iterations of group and polynomial degree were again compared with respect to BIC values. The PROC TRAJ program estimated parameters with maximum likelihood using a general quasi-Newton maximization procedure. Because the data were used from a multi-site trial, clinical site was also incorporated as a time independent covariate in the analyses.

2.5.3 Multinomial logistic regression analysis

Once we determined which model was optimal for each link function, an initial univariate regression model followed by a multivariable multinomial logistic regression was used to assess the association between the cognitive measures and the probability of trajectory group membership. For hypothesis 1, we tested whether cognitive dysfunction involving the frontal lobes will be worse in elderly individuals with trajectories of higher levels of suicidal ideation relative to those with trajectories of lower levels of suicidal ideation. Predictor variables initially included Stroop 3, Stroop 4, Trails B and Trails B/A. For hypothesis 2, worse scores from the Repeatable Battery for the Assessment of Neuropsychological Status will be associated with individuals with higher trajectories of suicidal ideation relative to those individuals with lower trajectories. The multivariable model included all five subscales of the RBANS, i.e., immediate memory, delayed memory, visuospatial skills/construction, language and attention. Since the total RBANS score was a composite score of the individual subscales, we only tested this variable with a univariate approach.

We then tested for multicollinearity among the predictor variables. We first determined whether there was any appreciable correlation between any of the cognitive measures within each model. A correlation of 0.6 or greater between variables in each of the models was used as a 'cut-off' value of concern based on Allison (1999, 2012). If present, we then calculated the variance inflation factors within each of the two multivariable multinomial logistic regression models. With this approach, a variance inflation factor of 10 or greater was an indication of multicollinearity based on Kleinbaum et al., (2008).

With our multinomial regression models, each data point consists of 1 variable which can take on one of *K* possible values (in this case K refers to group number). For *K* possible

outcomes, there are *K*-1 independent regression models, in which the lowest risk suicidal ideation trajectory is chosen as a pivot. Mathematically, the model is:

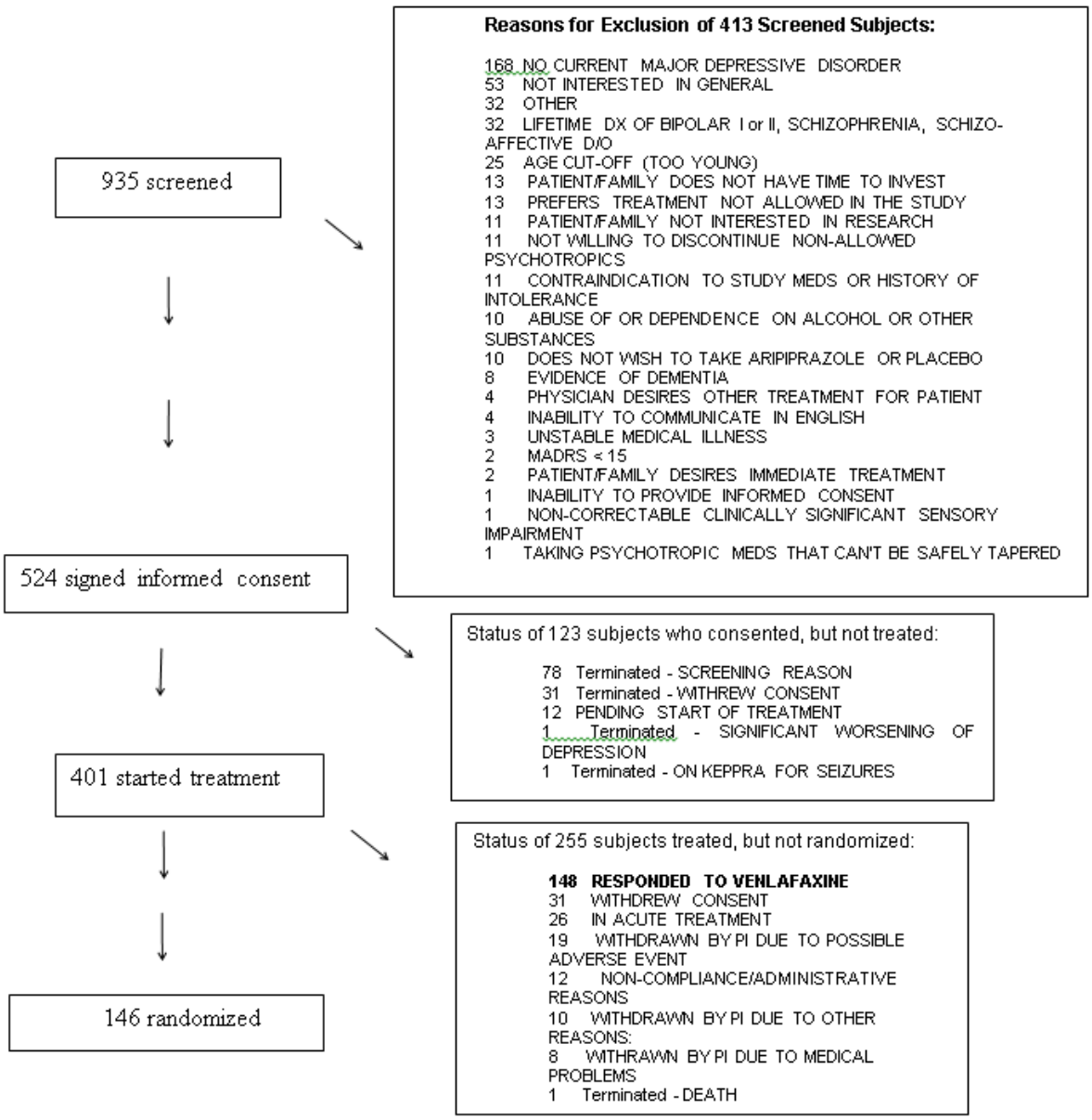
$$ln\, Pr(\boldsymbol{Y}_i = \boldsymbol{k})/Pr(\boldsymbol{Y}_i = \boldsymbol{1}) = \beta_0 + \beta_j x_j \quad (13)$$

with j representing each predictor variable. When this expression is exponentiated, it is interpreted as an odds ratio (Agresti, 2007). Also, the multinomial logit model assumed independence of irrelevant alternatives, i.e., the odds of preferring one class over another do not depend on the presence or absence of other "irrelevant" alternatives.

3.0 RESULTS

The parent study is currently ongoing. At the time of dataset creation for this secondary analysis, there were 935 individuals screened, from which 524 individuals signed consent. From those that signed consent, 401 started treatment with venlafaxine ER. As depicted in figure 2, there were 148 individuals who responded to venlafaxine treatment and an additional 146 who completed phase 1 and did not respond. Of these 294 individuals, there were 291 who also had baseline cognitive data available for the current secondary analysis.

In order to assess internal consistency reliability, Cronbach's alpha score were determined for the main outcome variable, i.e., SIS scores. The Cronbach's alpha scores were determined at each time point using all 19 items based on the procedures of Beck et al., (1997) who assessed the scale's psychometrics in outpatients. A score of 0.7 or greater is indicative of acceptable levels of internal consistency (Tavachol and Dennick, 2011) and this was achieved for all time points. The scores ranged from 0.93 to 0.97.



This recruitment flow chart indicates that there were 148 individuals who responded to venlafaxine treatment (in bold, lower right box) and an additional 146 who did not respond and who were randomized. Of these 294 individuals there were 291 who also had baseline cognitive data, making them eligible for the current secondary analysis.

Figure 2. Recruitment Flow Chart

3.1 MISSING VALUES

Patterns of data for missingness were examined based on Felding et al., (2009). Shown in Table 1 are the numbers of missing values at each time point for the main outcome variable – Scale for Suicidal Ideation (SIS) and the time dependent covariate – Montgomery Asberg Depression Rating Scale (MADRS) scores. Also shown in Tables 2 and 3 are the number of missing values for the baseline cognitive measures, i.e., respectively the frontal lobe measures and the RBANS measures. There were 41 missing values for SIS scores at baseline and from weeks, 1-16, the number of missing values varied from 2 to 11. For MADRS scores, there were 29 data points missing at baseline and from weeks 1- 16, the number of missing data points ranged from 1-9. For the cognitive measures the percent of missing data varied from 1.0 to 3.8% of the total. For the venlafaxine ER doses at each time point, there were no missing data. There were no missing values for the following baseline demographics: race, age, living status, employment status, gender and marital status.

Table 1. Missing Values – SIS and MADRS Scores

Outcomes	**Week (Wk) 0**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12-16**
SIS Scores	41 (14.1%)	7(2.4%)	2(.7%)	8(2.7%)	7 (2.4%)	8 (2.77%)	1 (3.8%)	8(.2.7%)
MADRS Scores	29 (10.0%)	(3.1%)	1 (2.4%)	2 (.3%)	5(.017%)	6 (2.1%)	9 (3.1%)	3(.010%)

Values reflect numbers and percentages (in parentheses) of missing values.

Table 2. Missing Values – Frontal Lobe Scores

Frontal Lobes Tests	**DEKS Stroop Test 3**	**Stroop Test 4**	**Trail Making Tests Trails B/A**	**Trails A**
n (percentage)	11 (3.8%)	10 (3.4%)	10 (3.8%)	10 (3.8%)

This table depicts the number and percentages (in parentheses) of missing values

Table 3. Missing Values – RBANS scores

Frontal Lobes Tests	DEKS Stroop Test 3	Stroop Test 4	Trail Making Tests Trails B/A	Trails A
n (percentage)	11 (3.8%)	10 (3.4%)	10 (3.8%)	10 (3.8%)

This table depicts the number and percentages (in parentheses) of missing values.

Tables 4 and 5 display the patterns of missingness for the main time dependent variables of interest. With SIS scores, there were six cases in which the pattern of missingness fit the monotone pattern; there were 62 cases which fit the intermittent pattern. In addition, there were two cases in which the pattern was mixed, i.e., exhibiting both intermittent and monotone patterns. With the MADRS data, there were three cases in which the patterns of missing data fit the monotone pattern and 47 cases with intermittent missingness.

We then tested whether the missing SIS data and MADRS data were missing completely at random. This was assessed using Little's test with SPSS 21 software (Little et al., 1988). For the SIS scores, we obtained $\chi^2 = 107.14$; df = 108; p = .51; for the MADRS scores, we obtained $\chi^2 = 75.26$; df = 71; p = .37. Both tests support the hypothesis that the missing data of both SIS and MADRS datasets were missing completely at random. As explained below, with the SIS scores, we initially tested our hypotheses with all participants included and also re-tested them after excluding individuals (n = 41) who had missing baseline data.

Table 4. Patterns of Missing Scores: SIS Scores each week

Week 0	1	2	4	6	8	10	12-16	Frequency(%)	Pattern
0	0	0	0	0	0	0	0	221 (76.97%)	None
0	0	0	0	0	0	0	1	4 (1.37%)	Monotone
0	0	0	0	0	0	1	1	1 (.34%)	Monotone
1	1	1	1	1	1	1	1	1 (.34%)	Monotone
0	0	0	1	0	0	0	1	1 (.34%)	Mixed
1	0	0	0	0	0	0	1	1 (.34%)	Mixed
1	0	0	1	0	0	0	0	1(.34%)	Intermittent
0	0	0	0	1	1	0	0	1 (.34%)	Intermittent
0	0	1	0	0	0	0	0	1 (.34%)	Intermittent
0	0	0	0	1	0	0	0	3 (1.0%)	Intermittent
0	0	0	1	0	0	0	0	5 (1.72%)	Intermittent
0	1	0	0	0	0	1	0	5 (1.72%)	Intermittent
1	0	0	0	0	0	0	0	32 (11.00%)	Intermittent
0	0	0	0	0	1	0	0	4 (1.37%)	Intermittent
1	0	0	0	0	1	1	0	1 (.34%)	Intermittent
0	0	0	0	1	1	1	0	1 (.34%)	Intermittent
1	1	0	0	0	0	0	0	1 (.34%)	Intermittent
0	0	0	0	0	0	1	0	3(1.0%)	Intermittent
1	0	0	0	0	0	1	0	4 (1.37%)	Intermittent

Table 5. Patterns of Missing MADRS scores each week

Week (Wk) 0	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12-16	Frequency	Pattern
0	0	0	0	0	0	0	0	241(82.82%)	None
0	0	0	0	0	0	0	1	2(.67%)	Monotone
1	1	1	1	1	1	1	1	1(.34%)	Monotone
0	0	0	0	0	0	1	0	2(.67%)	Intermittent
0	0	0	0	0	1	0	0	3(1.03%)	Intermittent
0	0	0	0	1	0	0	0	2(.67%)	Intermittent
0	0	0	0	1	1	1	0	1(.34%)	Intermittent
0	0	0	1	0	0	0	0	2(.67%)	Intermittent
0	0	0	0	1	1	0	0	1(.34%)	Intermittent
0	1	0	0	0	0	0	1	8(2.74%)	Intermittent
1	0	0	0	0	0	0	0	23(7.90%)	Intermittent
1	0	0	0	0	0	1	0	4(1.37%)	Intermittent
1	0	0	0	0	1	1	0	1(.34%)	Intermittent

3.2 DESCRIPTIVE STATISTICS

Summary statistics are shown in Table 6 which includes at each time point overall medians (range) for raw SIS scores or percentage of participants with dichotomized SIS scores = 1, as well as means (standard deviations) of the time dependent variables – MADRS scores and venlafaxine ER doses. Table 7 depicts the baseline values of the baseline demographics and cognitive measures. As depicted in Table 6, note that average dichotomized SIS scores as well as the range of non-dichotomized SIS scores steadily decreased from baseline until week 10; at the final time point, there was a slight increase in dichotomized SIS scores. MADRS scores consistently decreased with time and venlafaxine ER doses increased over time.

Table 6. Mean SIS, MADRS scores and doses

Week	Median Scale for Suicidal Ideation Scores (Range)	Percentage of Participants with Dichotomized Scale for Suicidal Ideation Scores = 1	Montgomery Asberg Depression Rating Scale Scores (MADRS)	Venlafaxine ER Dose
0	0 (0-26)	0.316	26.71 (5.64)	36.86 (42.86)
1	0 (0-19)	0.232	22.48 (7.65)	105.42 (39.05)
2	0 (0-17)	0.194	19.93 (8.33)	145.23 (29.89)
4	0 (0-20)	0.184	18.38 (9.06)	150.90 (27.75)
6	0 (0-24)	0.154	17.10 (9.82)	163.02 (41.43)
8	0 (0-23)	0.145	14.68 (9.39)	214.69 (64.50)
10	0 (0-18)	0.136	13.86 (9.69)	235.31 (69.43)
12-16	0 (0-18)	0.155	13.75(10.60)	239.69 (71.60)

Venlafaxine ER Doses are in milligrams. MADRS scores and Venlafaxine ER doses are means (standard deviations).

The study cohort was mostly Caucasian, the average age was 68.56 and only 4% were living in the community with supervision while the remaining 96% were living in the community without supervision. In addition, 20% were employed, 65% were female, 47% were married and the average years of education was 13.31. The mean standardized RBANS cognitive measures ranged from 91.50 to 99.46. The RBANS scores had been standardized to a mean of 100 with a standard deviation of 15. Except for the language scores which had a standard deviation of 13.28 all other scaled cognitive measures had standard deviations greater than the standardized value of 15. For the frontal lobe tests, the scores were standardized to a mean of 10 and a standard deviation of 3. The mean scores ranged from 8.37 to 9.93. Each of the standard deviations for the frontal lobe tests exceeded the standardized score of 3. For the Trails B and Trails B/A tests, inspection of the histograms revealed that there was sufficient variability for hypothesis testing. Visual inspection of histograms of cognitive predictor variables and the other predictors determined that there were no apparent outliers (see Appendix A).

Table 7. Distribution of baseline variables

Demographic Variables	**Mean (Standard Deviation) or Percent**
Race (% non white)	11.3%
Age	68.56 (7.09)
Living status (% with supervision)	4%
Employment status (% employed)	20%
Gender (% female)	65%
Marital Status (% married)	47%
Years of education	14.31 (2.88)
Frontal Lobe Cognitive Measures	
DEKS Stroop Tests	
Stroop condition 4	9.93 (3.66)
Stroop condition 3	9.93 (3.10)
Trail Making Tests	
*Trails B	*3.75(1-19.97)
*Trails B/A	*3.15 (1-19.48)
Repeatable Battery for the Assessment of Neuropsychologic Status (RBANS)	
Visuospatial/Construction Score Index	91.50 (18.44)
Delayed Memory Index Score	95.51 (16.62)
Attention Index Score	99.46 (17.72)
Immediate Memory Index Score	96.56 (18.14)
Language Index Score	98.01 (13.28)
Total Index Score	94.93(17.20)

lobe Trails B and Trails B/A scores are reported as medians (ranges) of non-standardized raw scores given that the data were right skewed (see appendix A histograms of cognitive measures). RBANS scores are standardized scores with a mean of 100 and standard deviation of 15; For all standardized scores, higher scores reflect better performance. For Trails B and trails B/A higher scores reflect worse performance.

3.3 LATENT CLASS GROWTH MODELING

We then explored various models using SAS PROC TRAJ with various link functions. For each link function utilized, we describe below the approach taken along with the associated results. Race and living status were dropped as covariates because there were instances in which groups had only white individuals and/or only individuals who were living alone.

3.3.1 Logistic link function model

Based on dichotomized SIS scores, our optimal model with a logit link function was a set of trajectories with three groups (see Figure 3); group 1 had a quadratic trajectory and groups 2 and 3 were linear. The BIC value obtained was -729.59. Figure 3 depicts the trajectories obtained. The trajectory with the highest levels of suicidal ideation was defined as the "declining high ideation" group; the trajectory with intermediate levels was defined as the "declining medium ideation" group and the trajectory with the lowest levels was defined as the "declining low ideation" group. The percentages of group membership for the 'declining low ideation' (group 1), 'declining medium ideation' (group 2) and 'declining high ideation' (group 3) groups were respectively 58.3%, 22.3% and 19.4% of the sample.

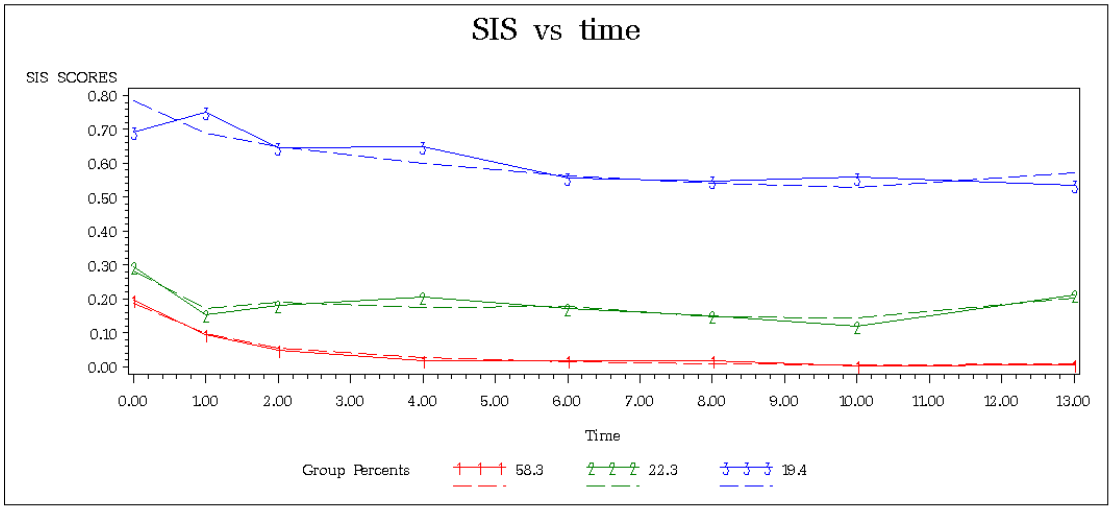


Figure 3. Logistic link function model for the best fitting model. Week 13 represents endpoint measures on weeks 12-16.

3.3.2 Zero inflated poisson link function model

Based on the Zero Inflated Poisson link function our optimal model was a set of trajectories with four groups; all four groups had linear trajectories. The BIC value was -1830.82. However, with this four group model, two of the groups included less than 5% of the participants. This was also the case when all other iterations of four groups were examined. Based on Andruff et al., (2009), group membership should be greater than or equal to 5% for each group. Thus we decided to use a three group trajectory model (see Figure 4). The lowest BIC value with three groups was obtained when the polynomial profile was quadratic in the first trajectory and linear in the other two group trajectories. The BIC value for this model was -1887.82. Group membership was 69.5% for the 'stable low suicide ideator' group (group 1), 24.3% for the 'declining medium suicide ideator' group (group 2) and 6.2% for the 'declining high suicide ideator' group (group 3).

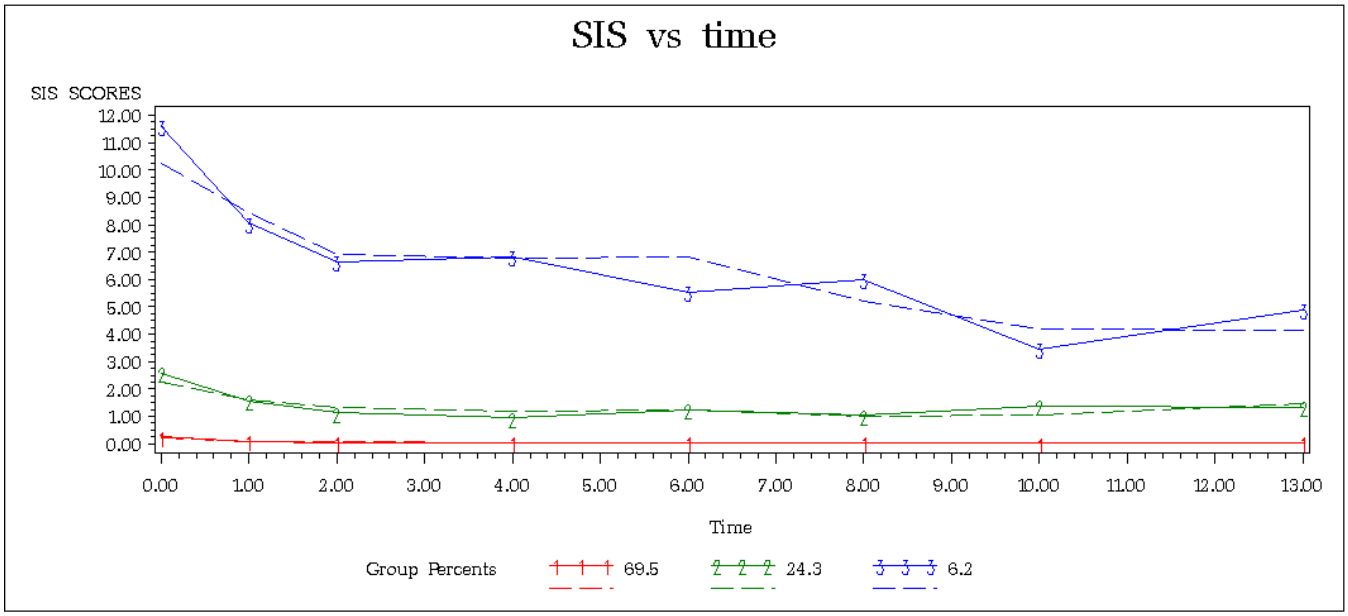


Figure 4. Zero inflated poisson link function model for the best fitting model. Week 13 represents endpoint measures on weeks 12-16.

3.3.3 Censored normal distribution link function model with a log transformation

When using the censored normal distribution as a link function, we tried two transformation strategies. First, we added the value of '1' to each of our SIS scores since there were many zero's and then performed a natural logarithm transformation. This was based on methods of McDonald (2009). We then used a censored normal distribution as the link function. Based on BIC values, our optimal model was a set of trajectories with three groups. The first group 'declining low suicide ideation' had a quadratic term while the other two were linear. The BIC value associated with this model was -1178.87. The percentage of individuals in each group was as follows:

'declining low suicidal ideation' (group 1): 59.7%; 'declining medium suicidal ideation' (group 2): 31.5%; 'declining high suicidal ideation' (group 3): 8.8%. Figure 5 shows the trajectories obtained.

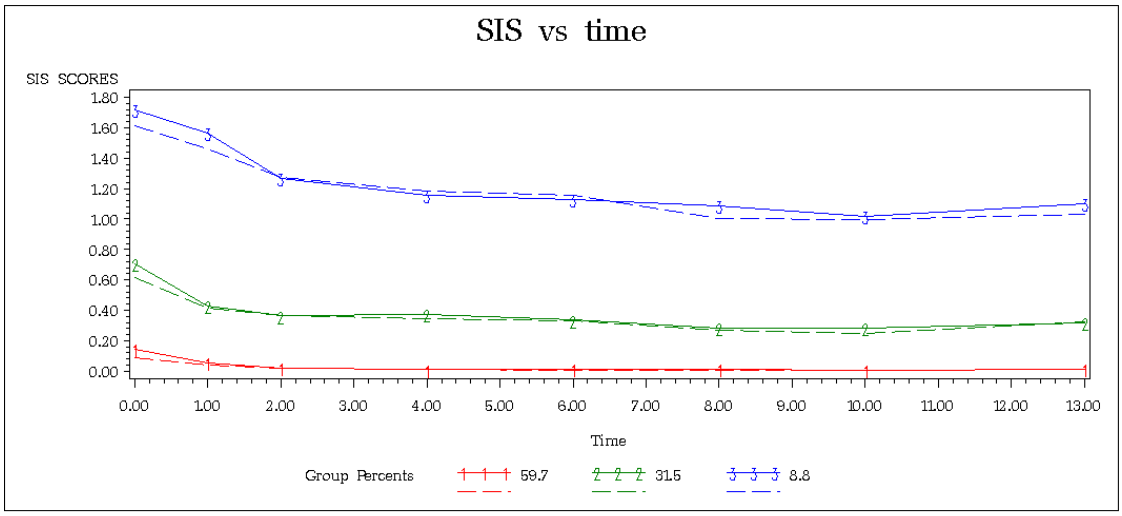


Figure 5. Censored normal distribution link function model with a log transformation for the best fitting model. Week 13 represents endpoint measures on weeks 12-16.

3.3.4 Censored normal distribution link function model with a square root transformation

As another attempt to normalize the data, we then transformed our original data of SIS scores with a square root transformation and then used a censored normal distribution as the link function. Based on BIC values, our optimal model was a set of trajectories with three groups. The first group, i.e., 'declining low suicidal ideation' had a quadratic trajectory while groups two and three had linear trajectories. The BIC value associated with this model was -1306.97. The

percentage of individuals in each group was as follows: 'stable low suicidal ideation' (group 1): 59.3%; 'declining medium suicidal ideation' (group 2): 31.5%; 'declining high suicidal ideation' (group 3): 9.2%. Figure 6 shows the trajectories obtained.

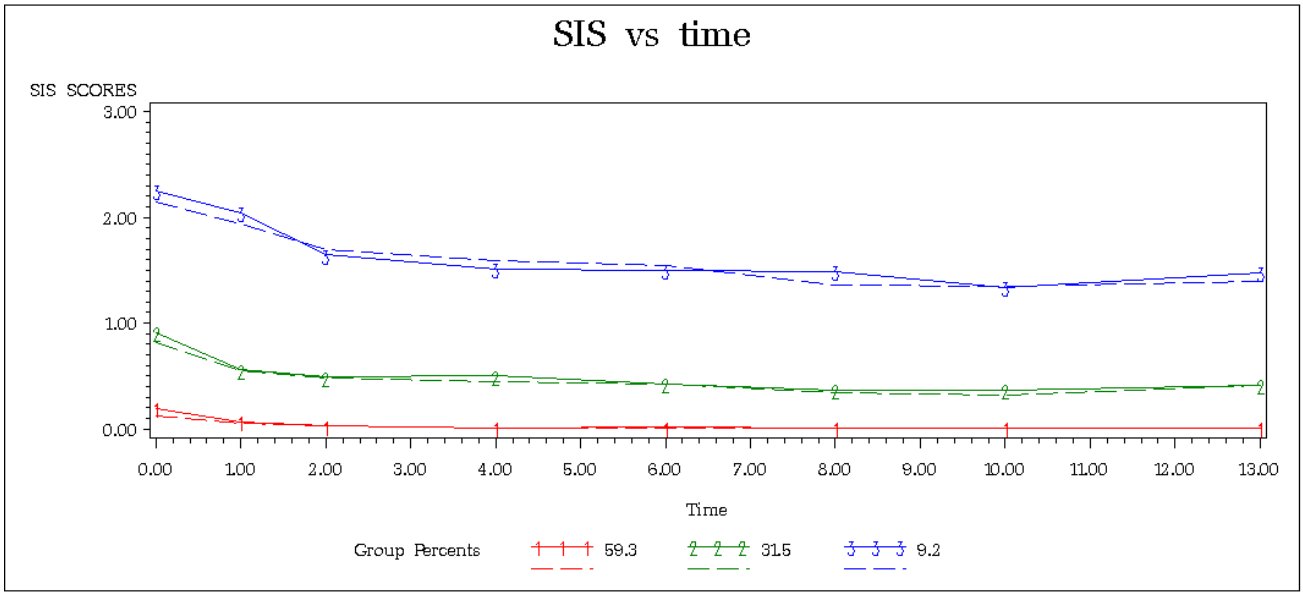


Figure 6. Censored normal distribution link function model with a square root transformation for the best fitting model. Week 13 represents endpoint measures on weeks 12-16.

Table 8 summarizes the optimal models obtained as defined by numbers of groups and type of trajectory. It was not possible to compare each of our models based on BIC values given that only one model utilized the raw data and each of the other models transformed the data in a different manner. However, from a clinical perspective, the model obtained from the Zero inflated Poisson is the most optimal. The zero inflated Poisson model utilized the original data and thus there was no loss of information. Data transformation altered the data set in all other models which makes the interpretation of the findings more difficult. With the logistic regression

model, much of the original information was lost following transformation into two scores, i.e., "0" or "> 0". With past studies, the Scale for Suicidal Ideation has been dichotomized in this manner (e.g., Bruce et al., 2004); however, there have been no studies performed to determine whether this is the most valid approach.

Table 8. Models examined

Link function	**Binary Logistic**	**Zero Inflated Poisson**	**Censored Normal Distribution: log transformation**	**Censored Normal Distribution: square root transformation**
Optimal Model	3 groups; polynomial terms 2 1 1	3 groups; polynomial terms 2 1 1	3 groups; polynomial terms 2 1 1	3 groups; polynomial terms: 2,1,1

For each model, the optimal number of groups was three. The first group was always a quadratic trajectory and the second and third groups were linear trajectories; 1 = linear; 2 = quadratic. Note that the first term for the polynomial degree indicated in the boxes starts with group one, i.e., the group with the lowest SIS scores.

As noted earlier, there were missing SIS data at baseline. We then explored whether this affected our analysis. We re-ran our Zero inflated Poisson model without these individuals. As before, the four group model with all linear polynomial terms was most optimal in terms of BIC values (-1635.067). However, group membership for all groups in this model nor in any other four group model did not exceed 5% so that a three group model was examined. The optimal three group model had a BIC = -1696.59 with a quadratic trajectory with group one and a linear trajectory with groups two and three. However, with this model, membership in group three was 4.8% (i.e.,

< 5%). As a result, we then examined the model with the next 'most positive' BIC value; this was a three group model. Groups one and three had quadratic trajectories and group two had a linear trajectory. The BIC value was -1698.10 and the three groups each had at least 5% of the participants in each group. Figure 7 below displays the trajectories obtained. The three groups include 'stable low suicidal ideation' (group 1): 69.1%; 'declining medium suicidal ideation' (group 2): 25.0%; 'declining high suicidal ideation'(group 3): 5.8%.

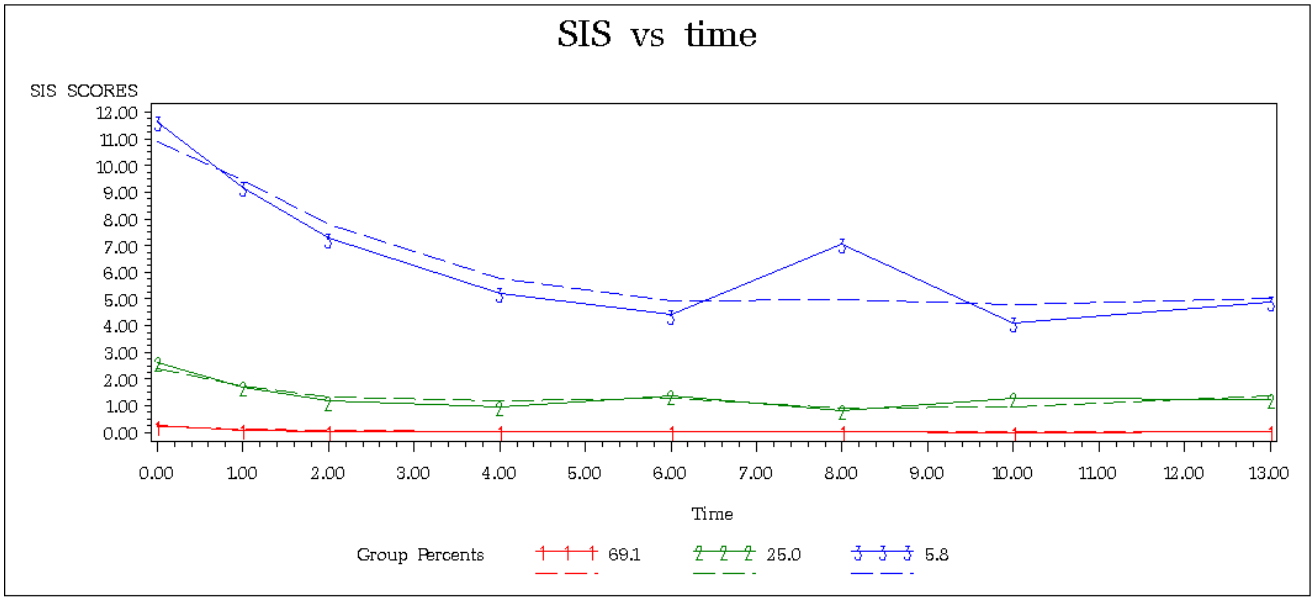


Figure 7. Zero inflated Poisson link function model: 41 participants with missing baseline SIS scores excluded. Week 13 represents endpoint measures on weeks 12-16.

3.4 MULTINOMIAL LOGISTIC REGRESSION ANALYSIS

Using multinomial logistic regression, we then asked whether cognitive dysfunction was associated with individuals with higher levels of suicidal ideation. This was performed with the zero inflated Poisson model. As with all models this one had already incorporated five time stable covariates: age, years of education, marital status, employment status and gender, as well as site. In addition, it had also already incorporated two time dependent covariates: MADRS scores and effexor XR dose. We initially tested our hypotheses with each predictor in a univariate multinomial logistic regression model. The results for this are displayed in Table 9. Lower scores of the trails B test were significantly associated with the 'declining high suicide group', i.e., group three. The results from all other univariate analyses were not significant.

Table 9 . Multiple logistic regression: Zero inflated poisson link function. Univariate Analysis

Outcome	Group	Odds Ratio	95% Confidence Interval		P value
Hypothesis 1: Frontal Lobe Tests: Trails B	2	.98	.91	1.07	.70
	3	**.72**	**.52**	**.99**	**.045**
Trails B/A	2	.93	.80	1.07	.28
	3	.77	.54	1.08	.13
Stroop condition 3	2	1.03	.94	1.13	.57
	3	1.17	.98	1.38	.083
Stroop condition 4	2	1.05	.97	1.14	.21
	3	1.04	.90	1.20	.60
Hypothesis 2: Repeatable Battery of Neuropsychologic Assessment					
Immediate Memory Score	2	.99	.98	1.01	.63
	3	1.01	.98	1.04	.63
Language Score	2	.98	.96	1.01	.14
	3	1.00	0.96	1.01	.94
Attention Score	2	1.00	.99	1.02	.97
	3	.99	.97	1.03	.91
Delayed Memory	2	.99	.98	1.01	.50
	3	.99	.97	1.03	.88
Visuospatial/Construction Index Score	2	1.00	.99	1.02	.59
	3	1.00	.97	1.03	.96
Total RBANS scores	2	1.00	.98	1.02	.93
	3	1.00	.98	1.03	.78

This table displays odds ratios, 95% confidence intervals and associated p values for each cognitive measure examined in a separate univariate multinomial logistic model. This table shows whether each test predicted group placement. A significant odds ratio greater than 1 would indicate that higher test scores are associated with individuals with higher levels of suicidal ideation. In all cases the reference group (group 1) is the group with the lowest level of suicidal ideation. For hypothesis 1, the model included: Trails B/A, Trails B, Stroop 3 and Stroop 4 as predictor variables; for hypothesis 2, the predictors included immediate memory, delayed memory, attention,

visuospatial/construction, language and total scores. Except for Trails B and Trails B/A scores, higher test scores indicate better test performance.

Prior to pursuing a multivariable model to examine our 2 hypotheses, we first determined univariate correlations between predictor variables. The more conservative spearman's rho test was used rather than Pearsons because the normality of some of the predictor variables was questionable (see Appendix A). The correlations are displayed in Table 10 and 11. The correlations suggest potential problems with multicollinearity based on Allison (1999, 2012) given that the magnitude of some of the correlations exceeded 0.6.

For testing each hypothesis, we then determined the variance inflation factor for each set of predictor variables in order to determine whether the predictors should be used in the multivariable modelling. For hypothesis 1, our model included the 4 predictors: Trails B, Trails B/A, Stroop 3 and Stroop 4 with respective variance inflation factor scores at baseline of 4.04, 3.76, 1.64, 1.68. Similar values were obtained at the other time points. Because none of the scores were 10 or greater, all 4 variables were retained in the model. When calculating variance inflation factor scores for our second hypothesis, we included the following subscale scores of the RBANS: immediate memory, language, attention, delayed memory, visuospatial. The total RBANS score was not included in this analysis because it was a composite of those subscale scores. The variance inflation factor scores for the subscale scores at baseline were as follows: immediate memory: 2.00, language: 1.33, attention: 1.46, delayed memory: 2.06, visuospatial: 1.36. With all other time points, a similar pattern was observed with variance inflation factors <10. Thus, we used all predictors when testing the 2 hypotheses using multivariable models. When testing total RBANS scores as a predictor of suicidal ideation, we used a separate univariate multinomial logistic regression model.

Table 10. Correlations among predictor variables for hypothesis 1

Predictor variable	Trails B/A	Trails B	Stroop 3	Stroop 4
Trails B/A		*.688	-.199	-.231
Trails B			-.347	-.400
Stroop 3				**.592

This table displays correlations based on Spearman's rho. All correlations were significant based on $p < 0.001$; n = 276 except for * where n = 280 and ** when n = 279.

Table 11. Correlations among predictor variables for hypothesis 2

RBANS Predictor Variable	Immediate Memory Score	Language Score	Attention Score	Delayed Memory	Visuospatial/ Construction Index Score
Immediate Memory Score		*.438	.472	.704	**.394
Language Score			.474	.405	**.307
Attention Score				.406	**.321
Delayed Memory					**.496
Visuospatial/Construction Index Score					

This table displays correlations based on Spearman's rho. All correlations were significant based on $p < 0.001$; n = 287 except for * with n = 288 and ** with n = 284.

Tables 12 displays the odds ratios, 95% confidence intervals and associated p values for each cognitive measure examined in a multivariable multinomial logistic model for testing hypotheses 1 and 2. With hypothesis 1, none of the variables were significantly associated with individuals with medium or higher levels of suicidal ideation. With hypothesis 2, the same was true.

Table 12. Multiple logistic regression: Zero inflated poisson link function: Multivariable Model

Outcome	Group	Odds Ratio	95% Confidence Interval		P value
Hypothesis 1: Frontal Lobe Tests					
Trails B	2	1.06	.93	1.21	.36
	3	.69	.44	1.09	.11
Trails B/A	2	.88	.71	1.09	.23
	3	1.09	.67	1.75	.74
Stroop condition 3	2	.98	.86	1.11	.75
	3	1.17	.95	1.43	.13
Stroop condition 4	2	1.08	.97	1.20	.17
	3	.90	.76	1.08	.26
Hypothesis 2: Repeatable Battery of Neuropsychologic Assessment					
Immediate Memory Score	2	1.01	0.98	1.03	.69
	3	1.02	.98	1.06	.41
Language Score	2	.99	.96	1.01	.93
	3	1.00	0.96	1.05	.93
Attention Score	2	1.01	.99	1.03	.62
	3	.99	0.96	1.03	.72
Delayed Memory	2	.99	.97	1.02	.56
	3	.99	0.95	1.03	.57
Visuospatial/Construction Index Score	2	1.01	.99	1.03	.37
	3	1.00	.97	1.03	.99

This table displays odds ratios, 95% confidence intervals and associated p values for each cognitive measure examined in a multivariable multinomial logistic model for each hypothesis. This table shows whether each test predicted group placement. A significant odds ratio greater than 1 would indicate that higher test scores are associated with individuals with higher levels of suicidal ideation. In all cases the reference group (group 1) is the group with the lowest level of suicidal ideation. For hypothesis 1, the model included: Trails B/A, Trails B, Stroop 3 and Stroop 4 as predictor variables; for hypothesis 2, the predictors included immediate memory, delayed memory, attention, visuospatial/construction, language. Except for Trails B and Trails B/A scores, higher test scores indicate better test performance.

We had determined previously that 41 of our participants were missing baseline SIS data. To explore whether the missingness of this baseline data affected our results, we ran the zero inflated Poisson model without those participants who were missing baseline SIS scores. As noted above (see also Figures 4 and 7), this altered the model. In testing hypothesis 1 with this altered model with a univariate analysis, better Trails B scores were no longer associated with individuals with higher levels of suicidal ideation. As demonstrated with previous models, the rest of the cognitive measures for hypothesis 1 or hypothesis 2 did not exhibit significant associations. However, the magnitude of the odds ratios and 95% confidence intervals were numerically slightly different (see Table 13).

Table 13. Zero inflated Poisson link function deleting 41 participants with missing baseline SIS scores - univariate analysis

Outcome	Group	Odds Ratio	95% Confidence Interval		P value
Hypothesis 1: Frontal Lobe Tests					
Trails B	2	.99	.91	1.07	.77
	3	.79	.58	1.06	.11
Trails B/A	2	.95	.82	1.09	.47
	3	.89	.66	1.21	.46
Stroop condition 3	2	1.03	.93	1.13	.58
	3	1.20	.99	1.44	.056
Stroop condition 4	2	1.06	.98	1.16	.14
	3	1.08	.93	1.26	.32
Hypothesis 2: Repeatable Battery of Neuropsychologic Assessment					
Immediate Memory Score	2	.99	.98	1.01	.80
	3	1.02	.99	1.05	.21
Language Score	2	.99	0.97	1.01	.19
	3	1.03	.99	1.07	.20
Attention Score	2	1.00	.99	1.02	.77
	3	1.01	.99	1.05	.38
Delayed Memory	2	.99	.98	1.05	.38
	3	1.01	.98	1.05	.52
Visuospatial/Construction Index Score	2	1.00	.99	1.02	.52
	3	1.02	.99	1.05	.29
Total RBANS	2	1.00	.99	1.02	.81
	3	1.03	.99	1.06	.14

This table displays odds ratios, 95% confidence intervals and associated p values for each cognitive measure examined in a separate univariate multinomial logistic model. This table shows whether each test predicted group placement. A significant odds ratio greater than 1 would indicate that higher test scores are associated with individuals with higher levels of suicidal ideation. In all cases the reference group (group 1) is the group with the lowest level of suicidal ideation. For hypothesis 1, the model included: Trails B/A, Trails B, Stroop 3 and Stroop 4 as predictor variables; for hypothesis 2, the predictors included immediate memory, delayed memory, attention, visuospatial/construction, language. Except for Trails B and Trails B/A scores, higher test scores indicate better test performance.

When we tested our hypotheses with the multivariable approach, none of the Frontal Lobe nor RBANS scores were significantly associated with individuals with higher levels of suicidal ideation (see Table 14).

Table 14. Zero inflated Poisson link function deleting participants with missing baseline SIS scores – multivariable model

Outcome	Group	Odds Ratio	95% Confidence Interval		P value
Hypothesis 1: Frontal Lobe Tests					
Trails B	2	1.06	.93	1.21	.35
	3	.71	.46	1.12	.14
Trails B/A	2	.90	.72	1.11	.32
	3	1.25	.81	1.92	.32
Stroop condition 3	2	.98	.86	1.11	.75
	3	1.18	.95	1.47	.14
Stroop condition 4	2	1.08	.97	1.21	.15
	3	.94	.78	1.14	.52
Hypothesis 2: Repeatable Battery of Neuropsychologic Assessment					
Immediate Memory Score	2	1.01	.99	1.03	.44
	3	1.02	.98	1.07	.37
Language Score	2	.98	.96	1.01	.18
	3	1.02	.97	1.08	.40
Attention Score	2	1.01	.99	1.03	.50
	3	1.00	.96	1.04	.96
Delayed Memory	2	.99	.96	1.01	.40
	3	.98	.94	1.04	.33
Visuospatial/Construction Index Score	2	1.01	.99	1.03	.44
	3	1.01	.98	1.05	.49

This table displays odds ratios, 95% confidence intervals and associated p values for each cognitive measure examined in a multivariable multinomial logistic model for each hypothesis. This table shows whether each test predicted group placement. A significant odds ratio greater than 1 would indicate that higher test scores are associated with individuals with higher levels of suicidal ideation. In all cases the reference group (group 1) is the group with the lowest level of

suicidal ideation. For hypothesis 1, the model included: Trails B/A, Trails B, Stroop 3 and Stroop 4 as predictor variables; for hypothesis 2, the predictors included immediate memory, delayed memory, attention, visuospatial/construction, language. Except for Trails B and Trails B/A scores, higher test scores indicate better test performance.

4.0 SUMMARY AND CONCLUSIONS

This thesis illustrates the use of latent class growth modeling to examine patterns of suicidal ideation over time in a sample of older depressed individuals receiving treatment with venlafaxine ER. The present study is the first of which we are aware that documents how cognitive status is associated with trajectories of suicidal ideation over time in a sample of elderly adults. With each link function , i.e., logistic, censored normal or zero inflated Poisson, the optimal models classified individuals into three groups with linear or quadratic trajectories; each group included individuals with varying degrees of suicidal ideation ranging from 'low' to 'high' levels which were constant over time. With our three group models, the 'low suicide' group had a quadratic trajectory and the 'medium suicide' and 'high suicide' groups had a linear trajectory. The optimal model chosen was the one with the zero inflated Poisson as the link function. Our model incorporated two time dependent covariates: MADRS score and antidepressant dose. In addition, it incorporated five demographic factors as time stable covariates: age, years of education, gender, marital status and employment status as well as site. When these time independent covariates were not included in the model, the shapes of the trajectories did not differ; however, there were slight differences with regards to the proportion of individuals in each of the three groups.

There are few reports which have investigated how frontal lobe functioning affects suicidal behavior in older individuals. Of the studies available, none have assessed this using

longitudinal data (for instance, see King et al., 2000; Dombrovski et al., 2008). In a cross sectional study, Gujral et al., (2013) compared four groups of older individuals: 1) those who had a suicide attempt, 2) those who had current suicidal ideation, 3) those who were depressed and not having suicidal ideation and 4) those without psychiatric problems. EXIT scores were worse in the first two groups (i.e., those with past suicide attempts or only suicidal ideation) relative to the other two groups (i.e., depressed and non-psychiatric controls). However, the investigators did not compare levels of suicidal ideation between all four groups; thus it is difficult to compare their findings on changes with regards to frontal lobe functioning to our findings.

In an earlier cross sectional study, Dombrovski et al., (2008) compared individuals with suicidal ideation, defined as either having a suicide attempt within three months of the assessment or as current suicidal ideation with a specific plan, serious enough to precipitate an inpatient admission. A comparison group was judged to be non-suicidal if they had never reported suicidal ideation or a feeling that life is empty or not worth living. This was reflected by having a score of 0 on the Hamilton suicide item in 12 weekly assessments before and during depression treatment (Hamilton, 1960). There was worse frontal lobe functioning in the group with suicidal behavior, i.e., they had worse EXIT scores. However, these investigators did not compare groups of patients with higher levels of suicidal ideation vs groups with lower levels of suicidal ideation as was done in our study.

An earlier study by (King et al., 2000) compared frontal lobe functioning in a group of older individuals with suicide attempts to a group without a history of suicidal behavior. This was a cross sectional study and their measure of frontal lobe functioning was the Trails B tests. The investigators showed that attempters exhibited greater performance declines with age. However, none of these studies compared individuals with varying degrees of suicidal ideation.

Furthermore, the studies of King et al., (2000) did not incorporate the Trails B/A contrast measure.

Our data did not support our first hypothesis, i.e., cognitive dysfunction involving the frontal lobes will be worse in elderly individuals with trajectories of higher levels of suicidal ideation. We did demonstrate with our univariate model that lower Trails B scores was associated with individuals with trajectories of worse suicide scores which is the opposite result from what we expected based on the literature. However, the finding was no longer significant with the multivariable model when all frontal lobe measures were included as predictor variables, i.e., the Trails A, Trails B/A, Stroop 3 and Stroop 4 test. Furthermore, the Trails B/A measure is a better assessment of frontal lobe functioning than the Trails B and the Trails B/A measure was not significant in either univariate or multivariable models. It is possible this could be related to performing multiple comparisons; thus, the chance of finding a significant finding becomes elevated.

Our second hypothesis stated that worse scores from the Repeatable Battery for the Assessment of Neuropsychological Status will be associated with individuals with higher trajectories of suicidal ideation relative to those individuals with lower trajectories. We used the RBANS total score as well as the individual components of the RBANS to test this hypothesis. Based on the zero inflated Poisson link function, we found that none of the RBANS measures were associated with individuals with higher levels of suicidal ideation. In the Gujral et al., (2013) report, the authors noted that those who made a recent suicide attempt or who only had suicidal ideation performed similarly with the total Dementia Rating Scale score and also with the Memory and Attention subscales; all three groups were impaired relative to nonpsychiatric control subjects. The Gujral et al., (2013) study did report significantly different Beck Scale for

Suicidal Ideation scores between the attempters and the ideators (25.0 +/- 5.6 vs 15.5 +/- 7.5). Thus, their study indicated that there were no cognitive differences between the groups with different levels of suicidal ideation. Unlike our study, the investigators did not control for depressive symptoms or antidepressant dose.

Limitations of the current study include missing data at baseline for scores from the Scale for Suicidal Ideation for baseline scores of MADRS scores. For instance there were 41/291 (15% of individuals) missing SIS values and 30/291 (10% of individuals) missing MADRS values. We then re-ran our model without data from these 41 individuals using the Zero inflated Poisson distribution as our link function. Deleting the 41 participants yielded a slightly different optimal model, i.e., the 3rd group had a quadratic trajectory instead of a linear trajectory. However, deleting the 41 participants did not alter the overall results. Another potential concern is whether there was sufficient variability in the cognitive measures to test our hypotheses. With the exception of the language scores (standard deviation 13.28), all of the RBANS measures had standard deviations which were greater than the standardized standard deviation of 15. Thus for the language subscale, there may not have been enough variability to sufficiently test hypothesis 2. For the standardized frontal lobe tests, each of the standard deviations exceeded the standard deviation of 3. For the Trails B and Trails B/A tests, inspection of the histograms revealed that there was sufficient variability for hypothesis testing.

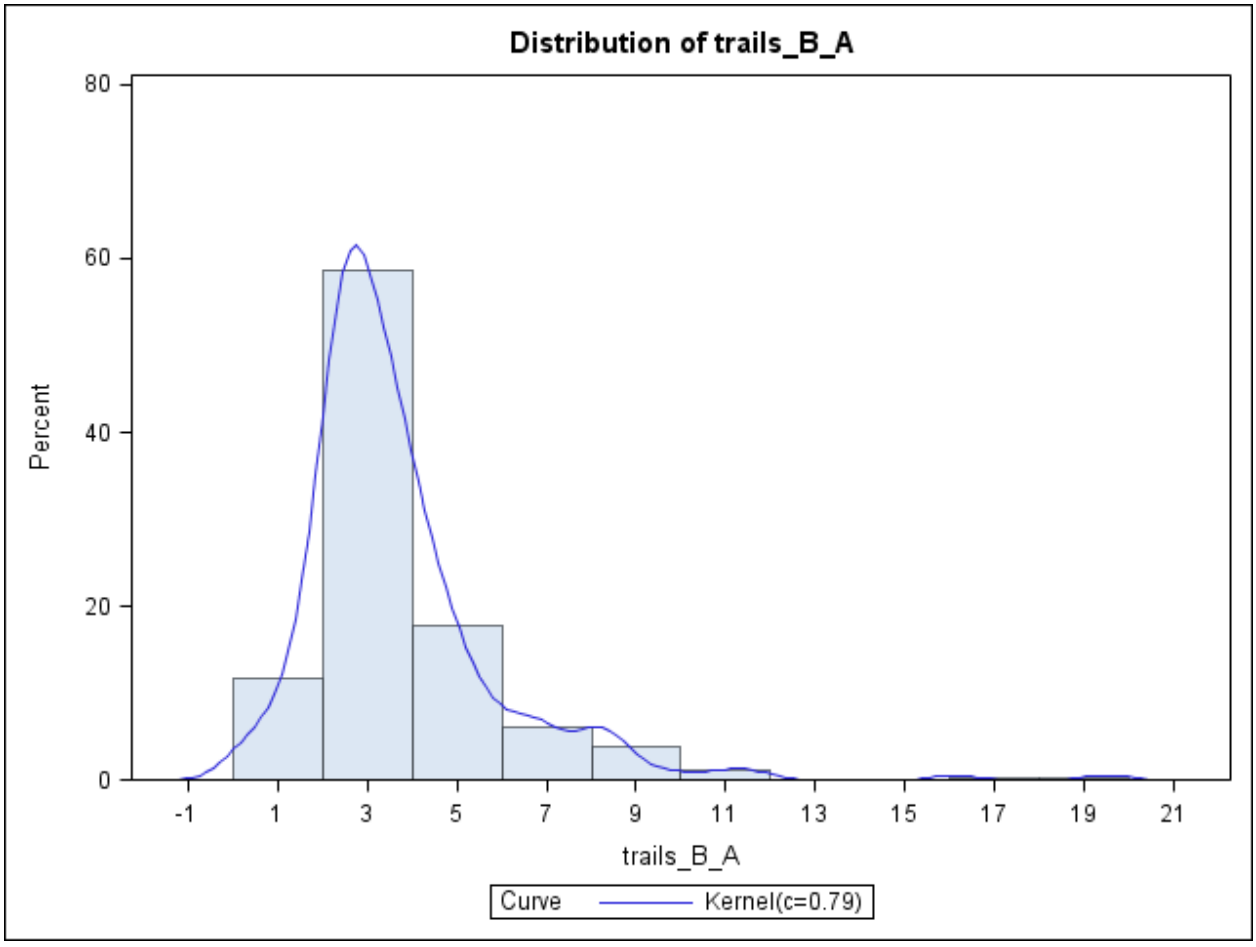
It is possible that lack of statistical power may have accounted for the lack of statistically significant findings. Latent class growth modelling is a relatively new technique and little is known with regards to the requirements for sample size and the number of time points needed for good estimation and power. Preliminary studies on power estimation for growth models have been performed using Monte Carlo simulation studies with MPLUS software (Muthen, 2002

2004; Muthen and Muthen, 2002). With this approach, Muthen and Muthen (2002) determined that sample size estimates appear to be directly proportional to the number of covariates and to the amount of missing data. With respect to the first point, we ran our analyses without any of the time independent covariates. However, this did not affect the overall findings when testing our hypotheses except for slight changes in the magnitude of the odds ratios. With respect to the second point, we ran our analysis without the 41 individuals who were missing SIS baseline data. While this did slightly affect the trajectories obtained (see Figure 7 and last paragraph of section 3.3.4), this did not affect the findings when testing our hypotheses, except for slight changes in the magnitude of the odds ratios (see Tables 13 and 14). This suggests the possibility that there may have been sufficient power; however, without performing simulation studies, we cannot be certain. Another limitation is the fact that we were not able to control for medical comorbidity, another high risk factor for suicide. In addition, because of data sparseness, we were not able to control for race nor whether individuals were living alone with or without supervision.

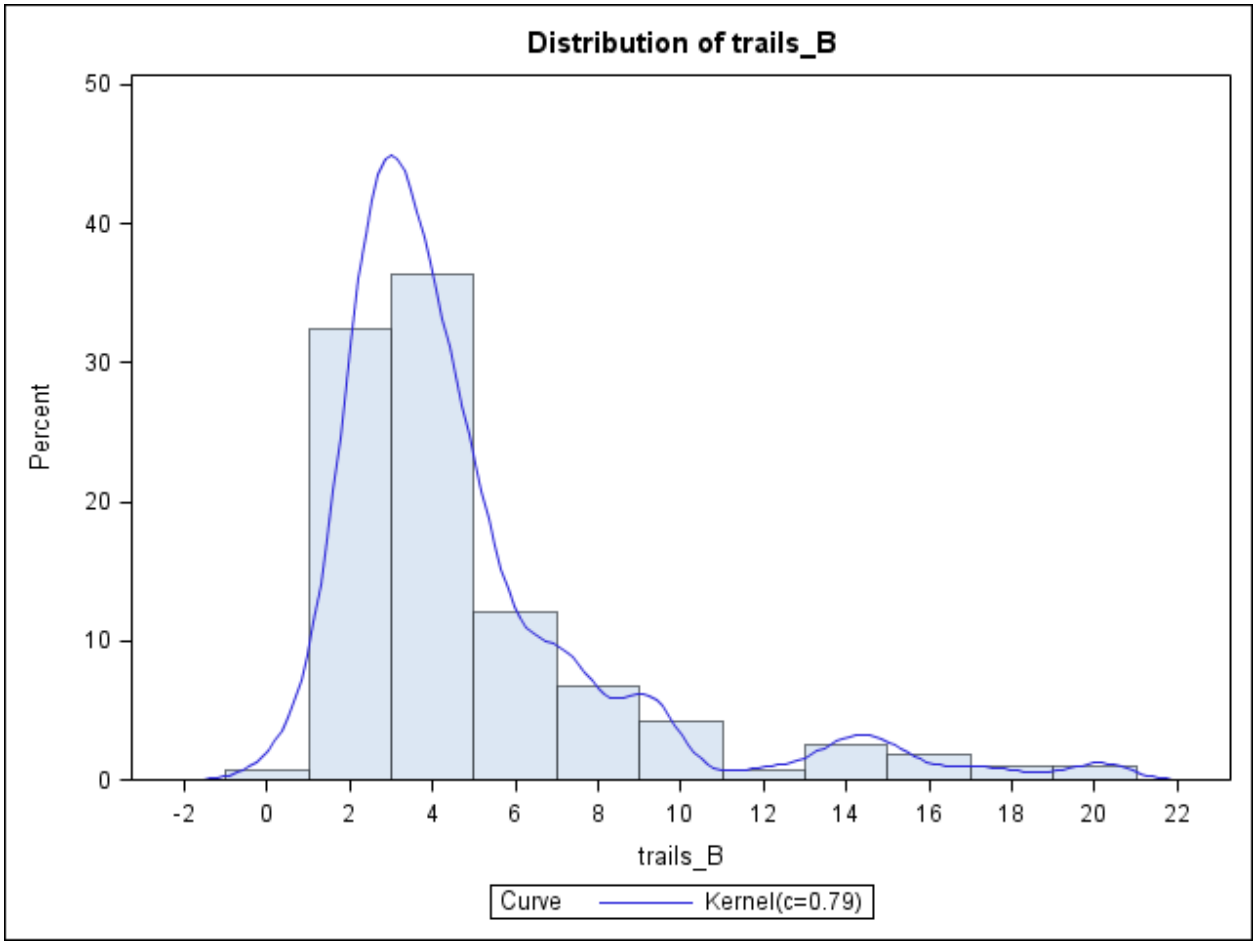
In conclusion, the present study is the first to our knowledge that documents how cognitive dysfunction is associated with trajectories of suicidal ideation in depressed elderly adults over time. It does not consistently support the premise that clinicians should screen older individuals for cognitive status as a way to detect degree of suicide risk. Our results add to the literature on cognitive factors and suicidal ideation in the elderly. Clearly more studies are needed to determine whether these findings are reproducible. It would be important to determine whether cognitive functioning in these individuals affects the risk of future suicide attempts or of suicide completion.

APPENDIX

DISTRIBUTION OF THE VARIABLES



TRAILS B/A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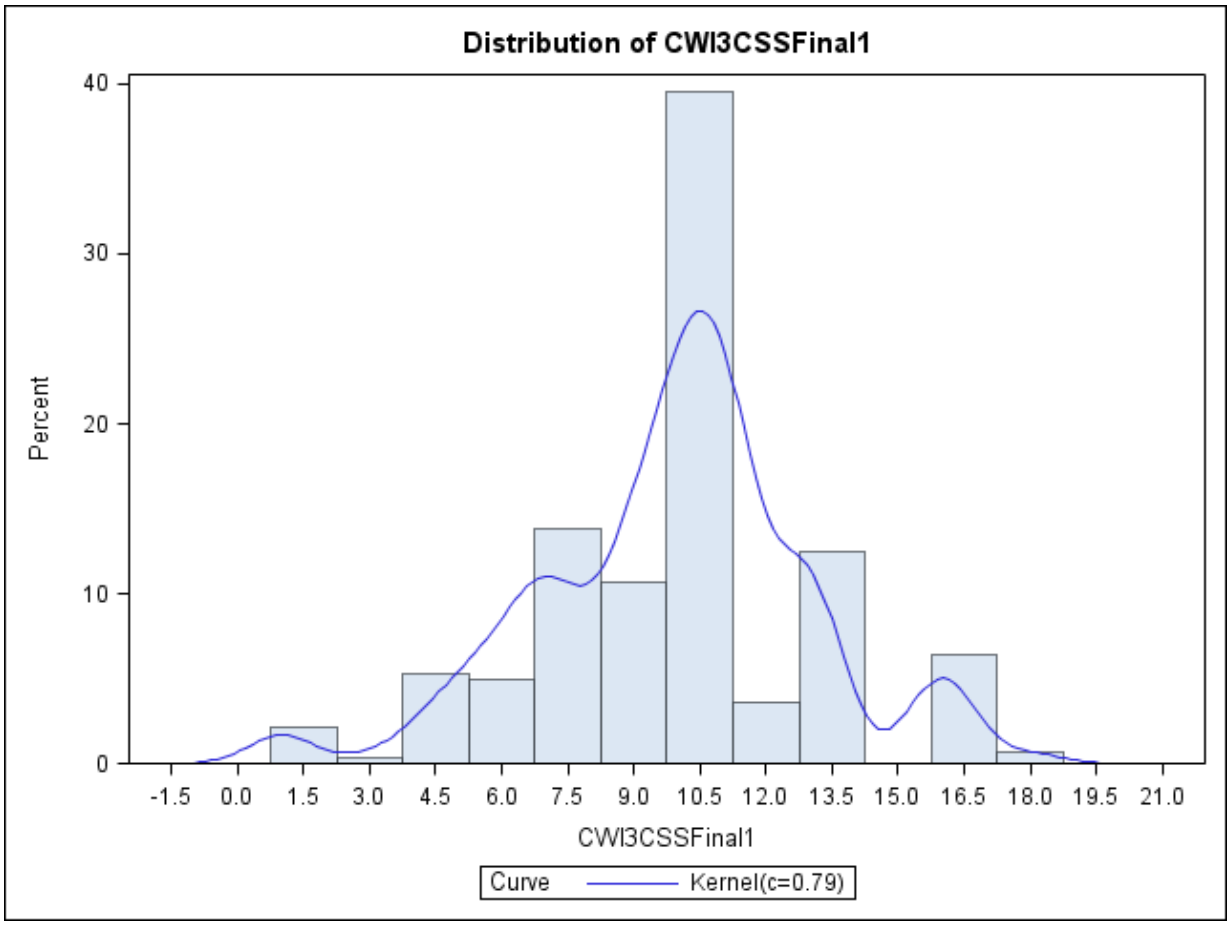
TRAILS B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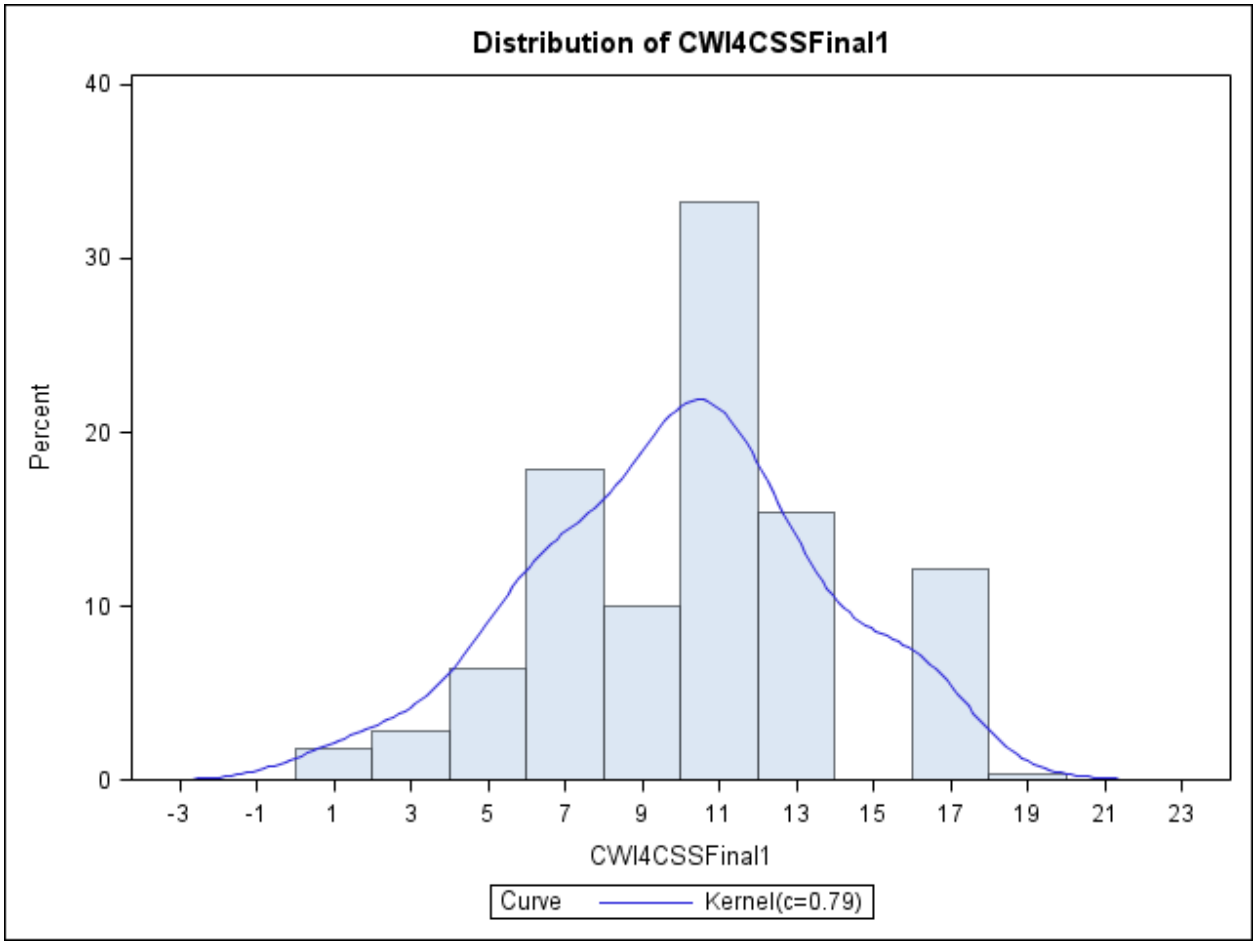
STROOP 3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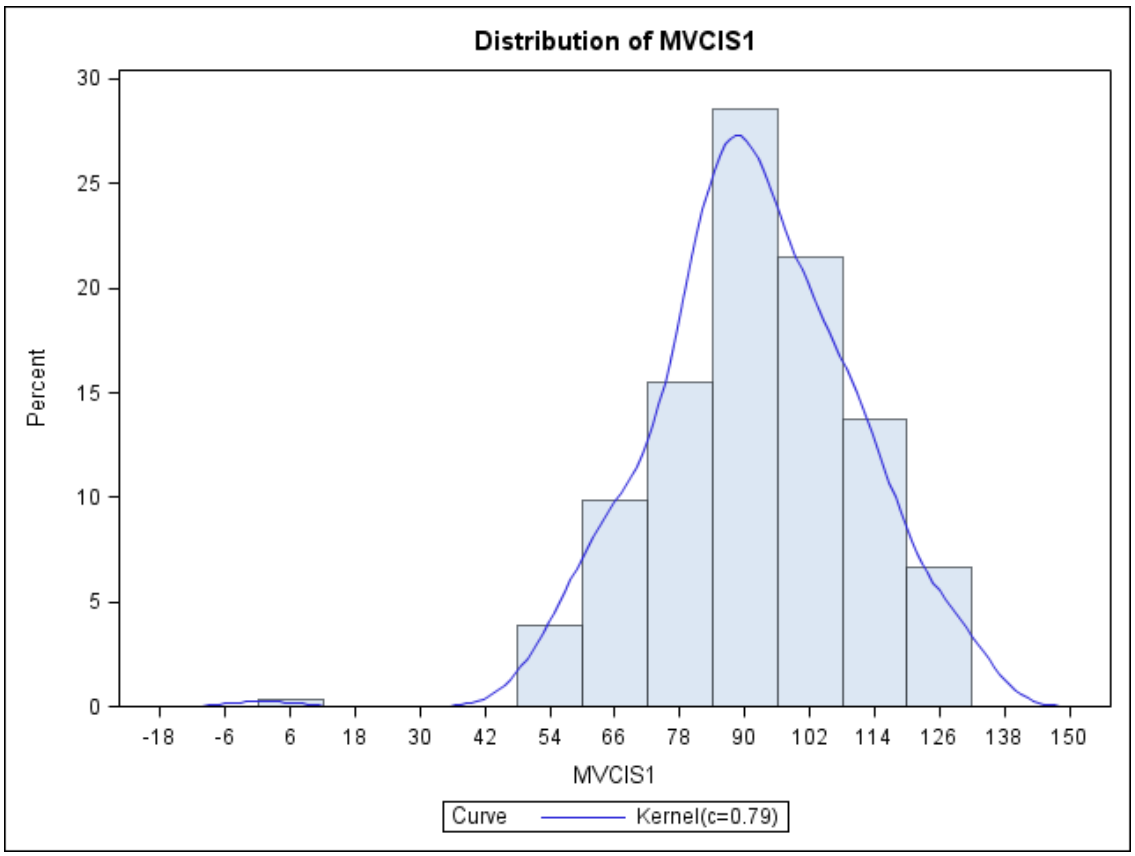
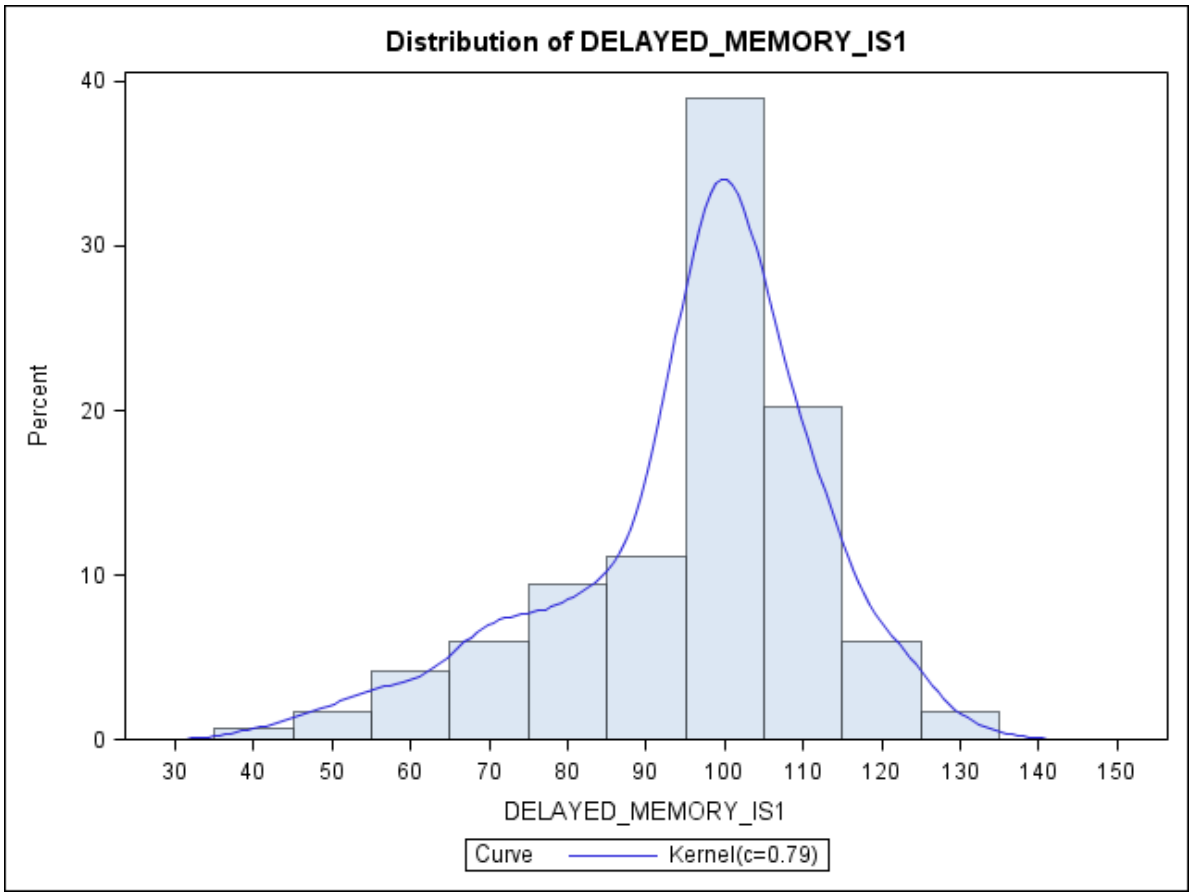
STROOP 4



RBANS VISUOSPATIAL/CONSTRUCTION



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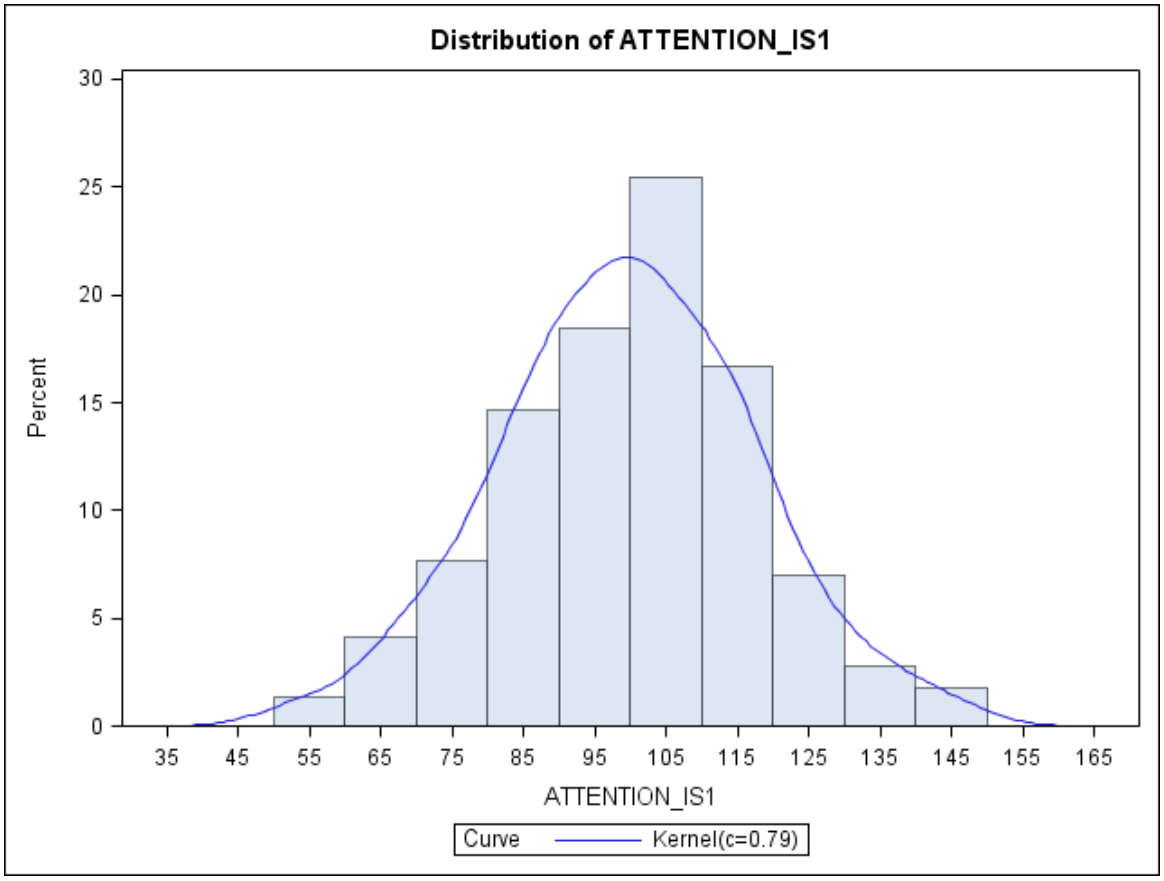

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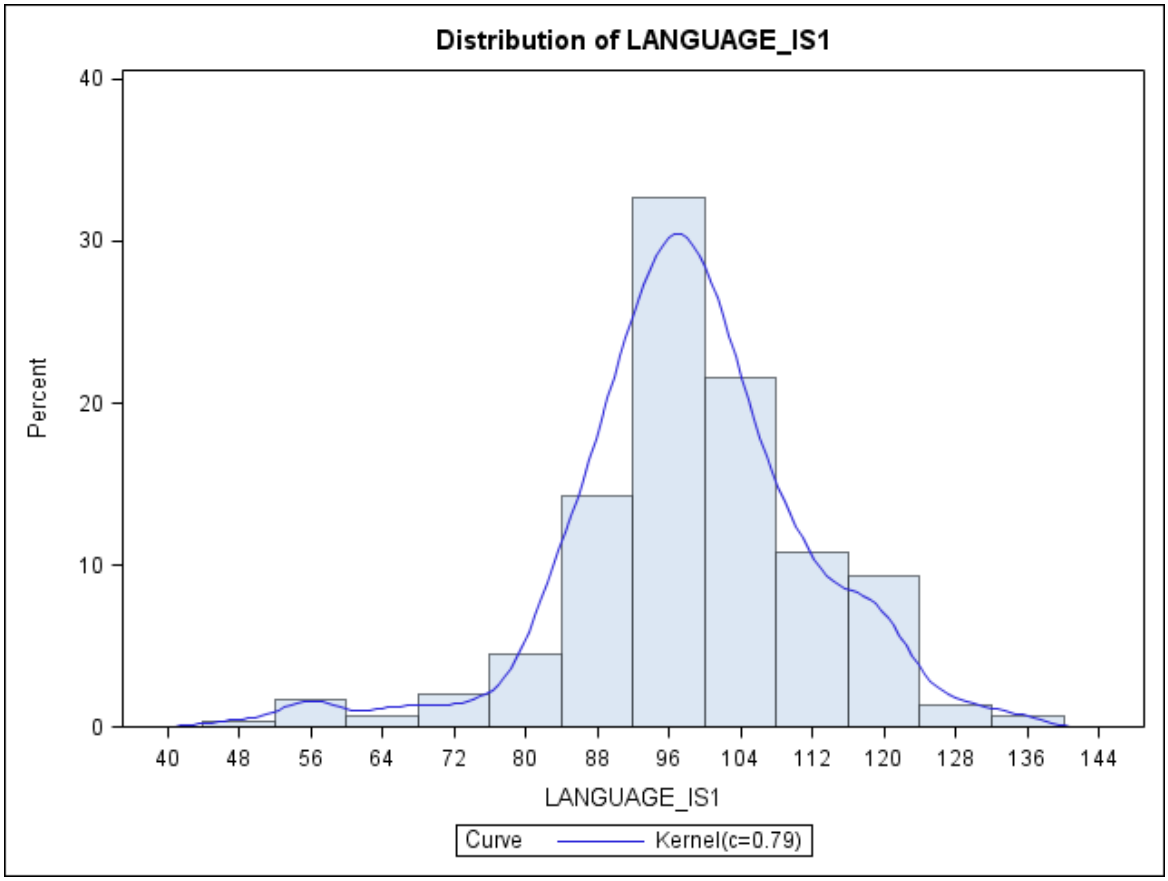
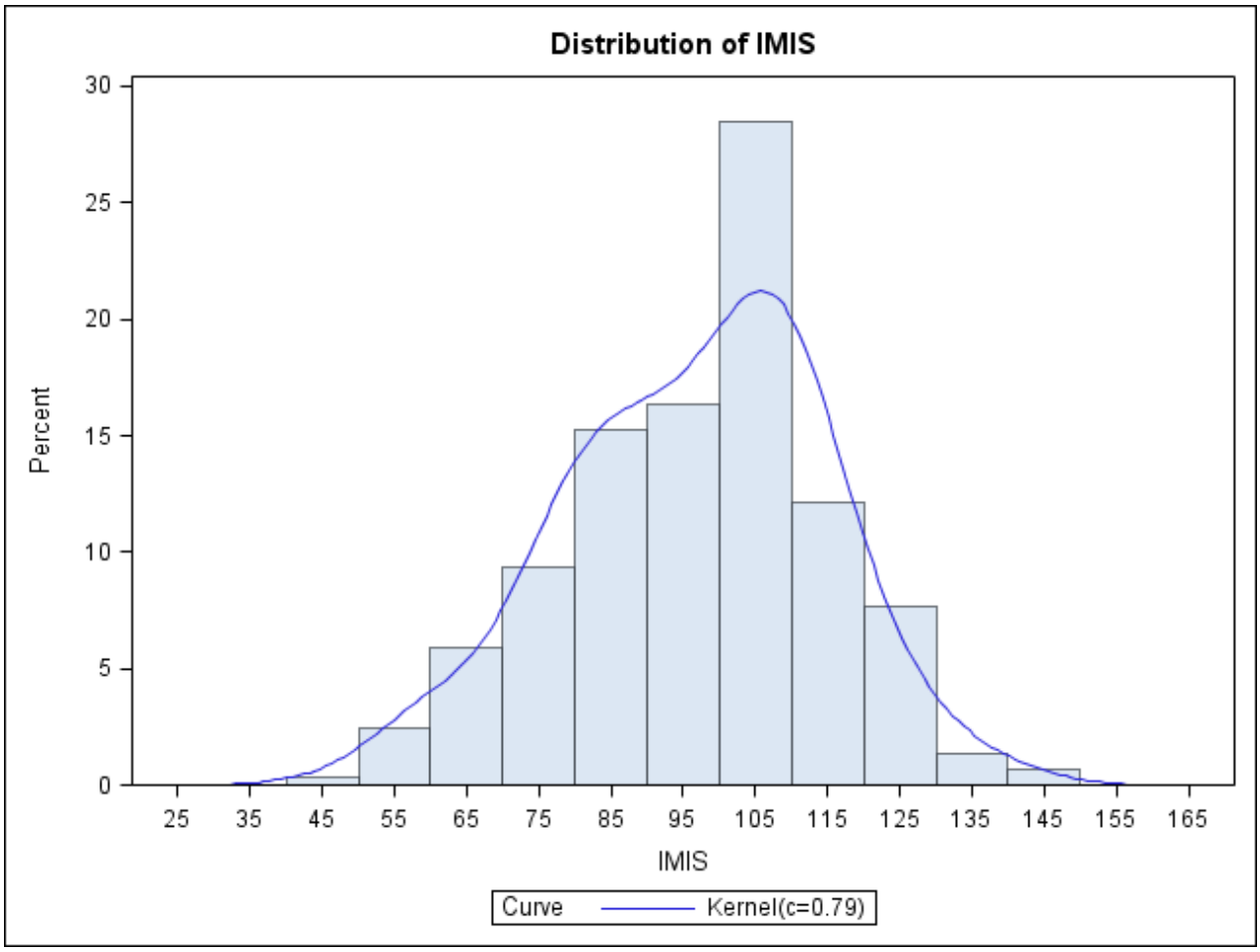
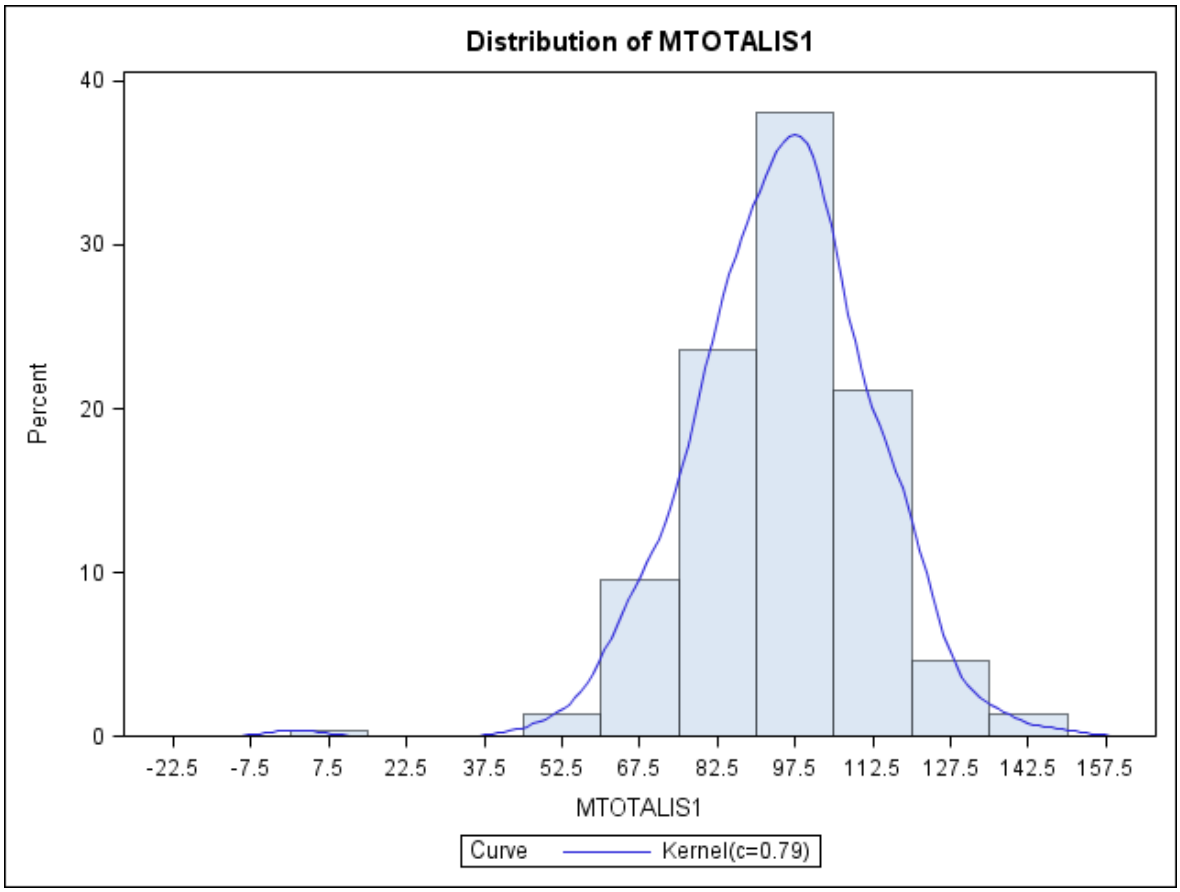


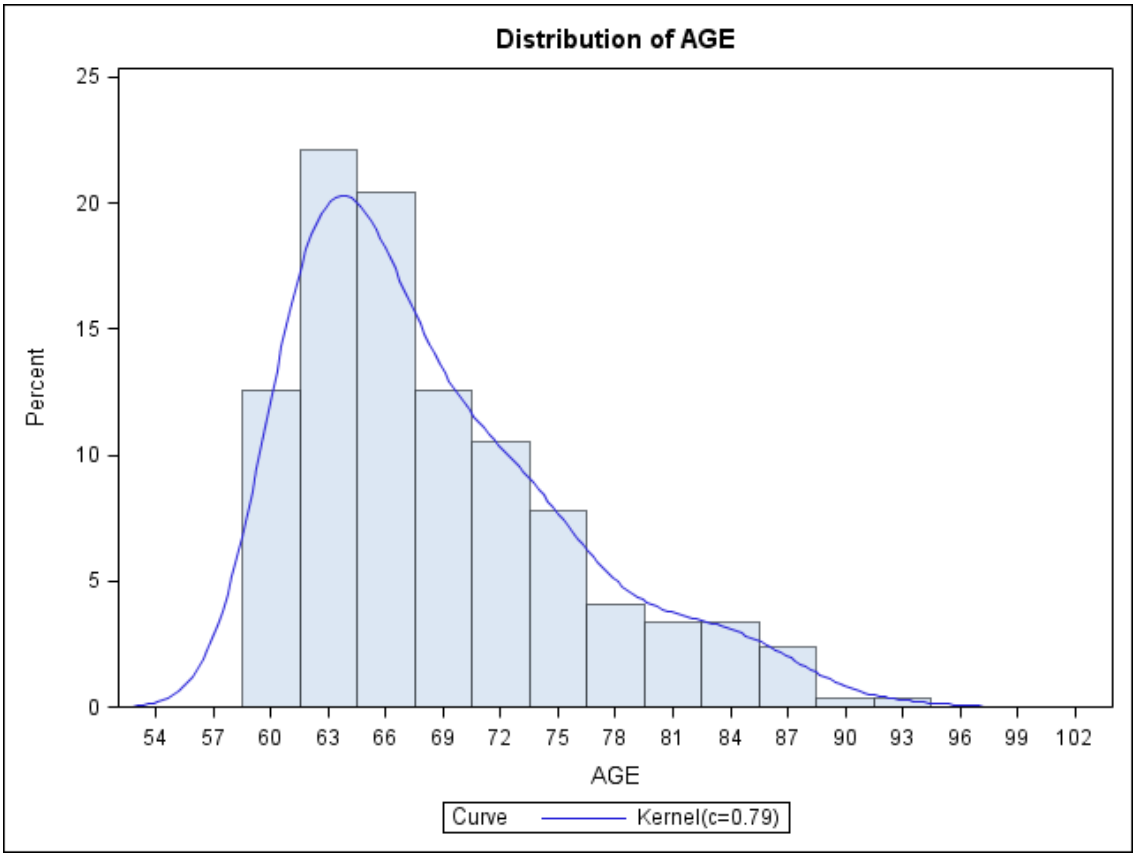
RBANS LANGUAGE



RBANS IMMEDIATE MEMORY INDEX SCORE (IMIS)



RBANS TOTAL INDEX SCORE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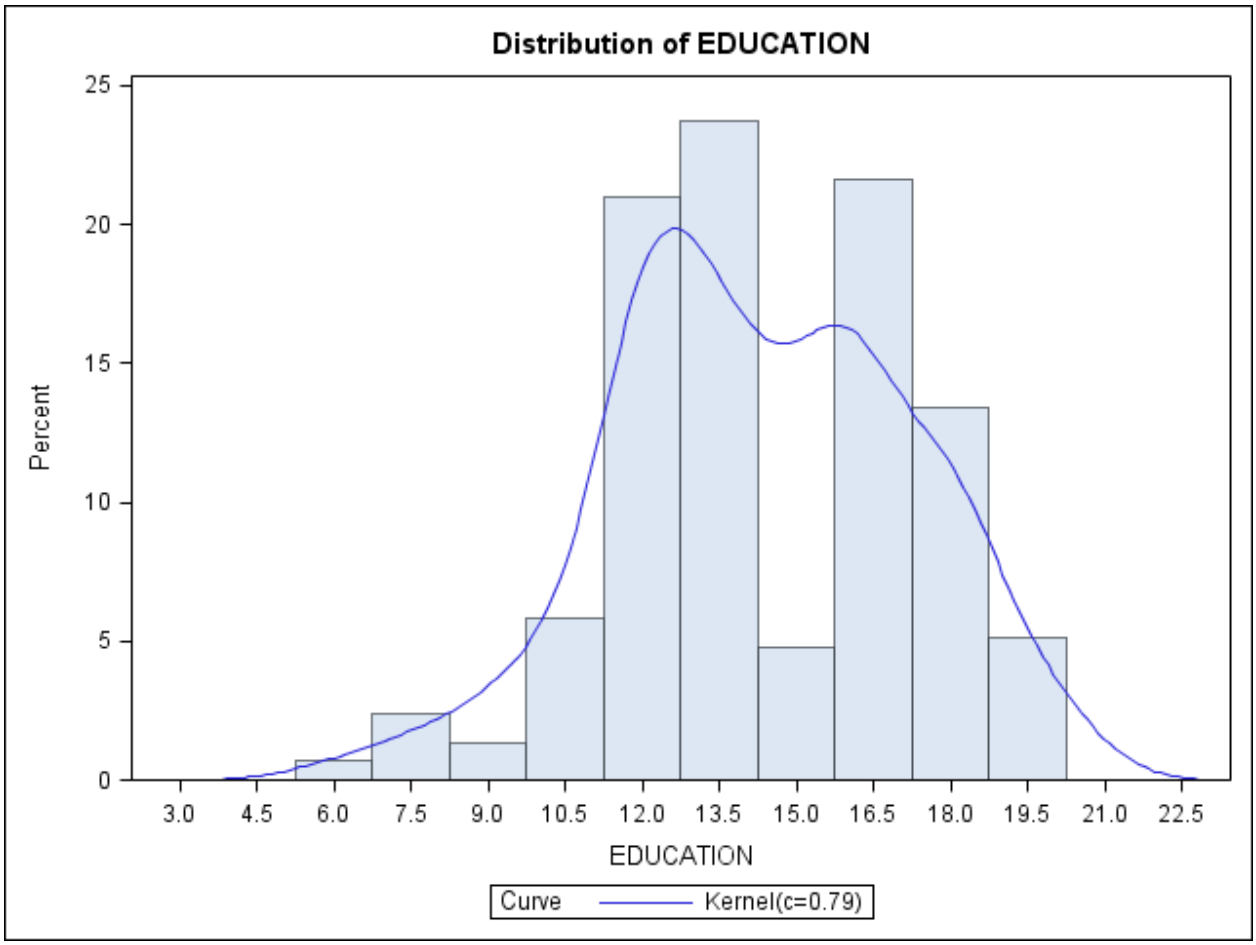
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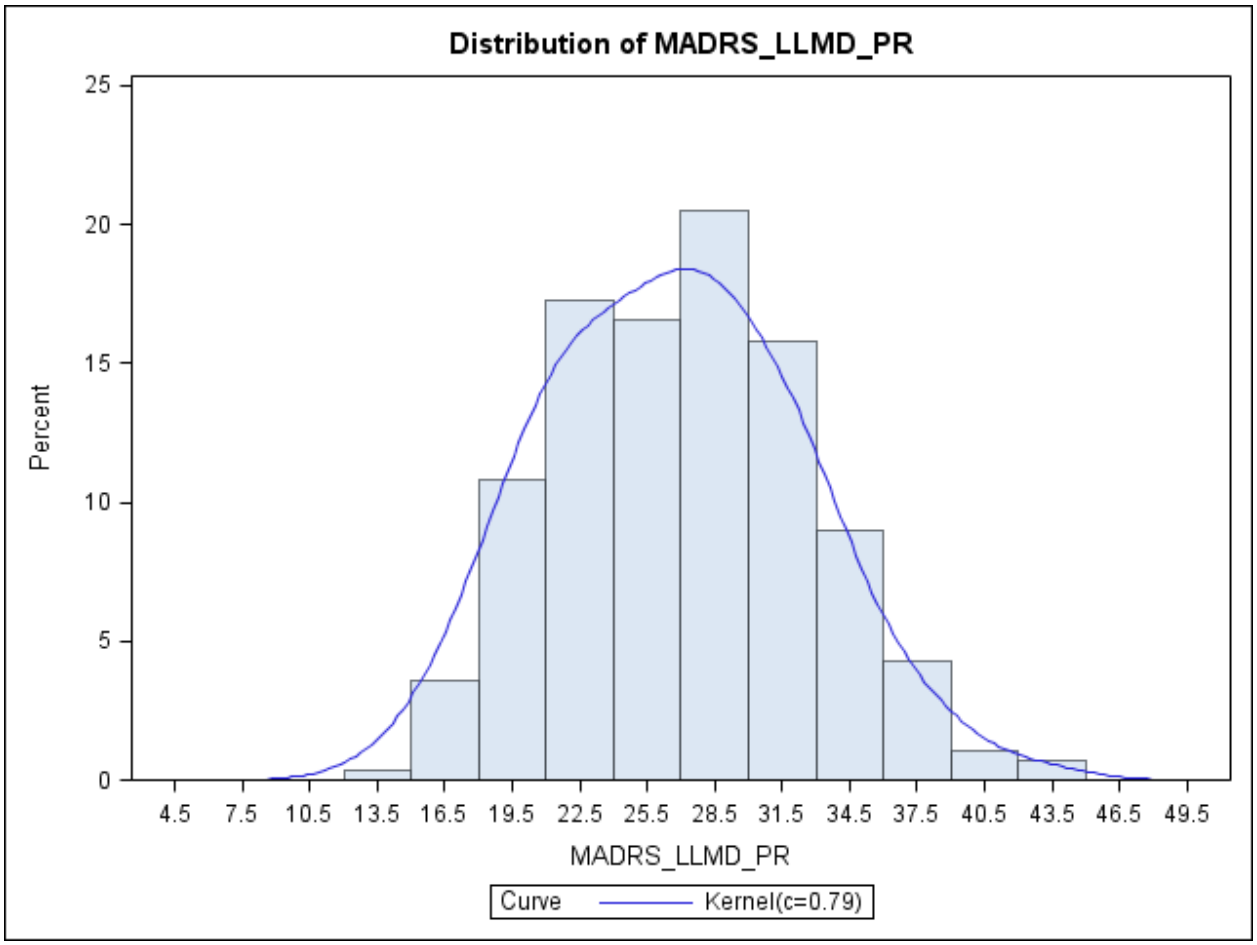
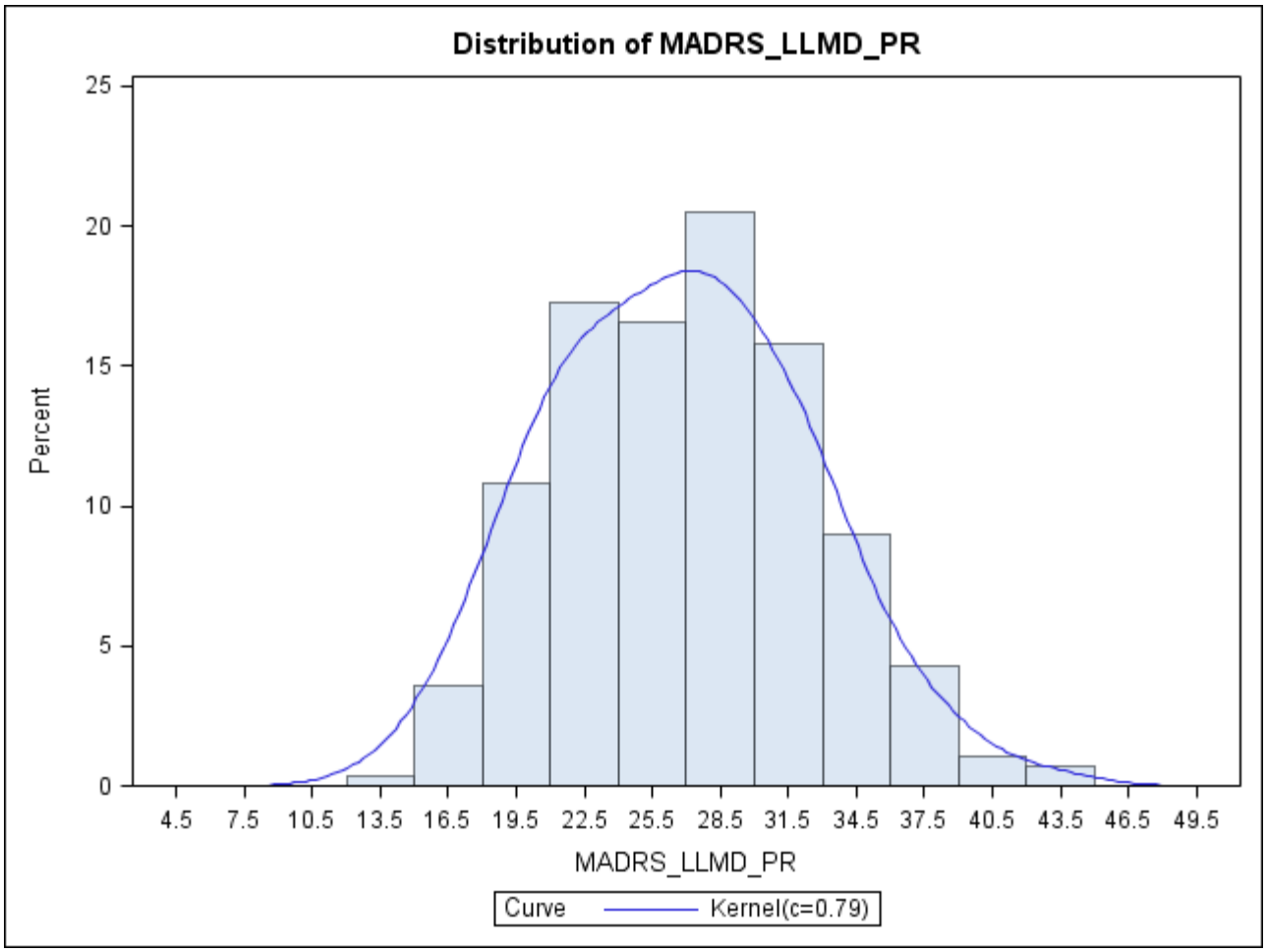
EDUCATION



BASELINE MADRS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22.5
25.5
28.5
31.5
34.5
37.5
40.5
43.5
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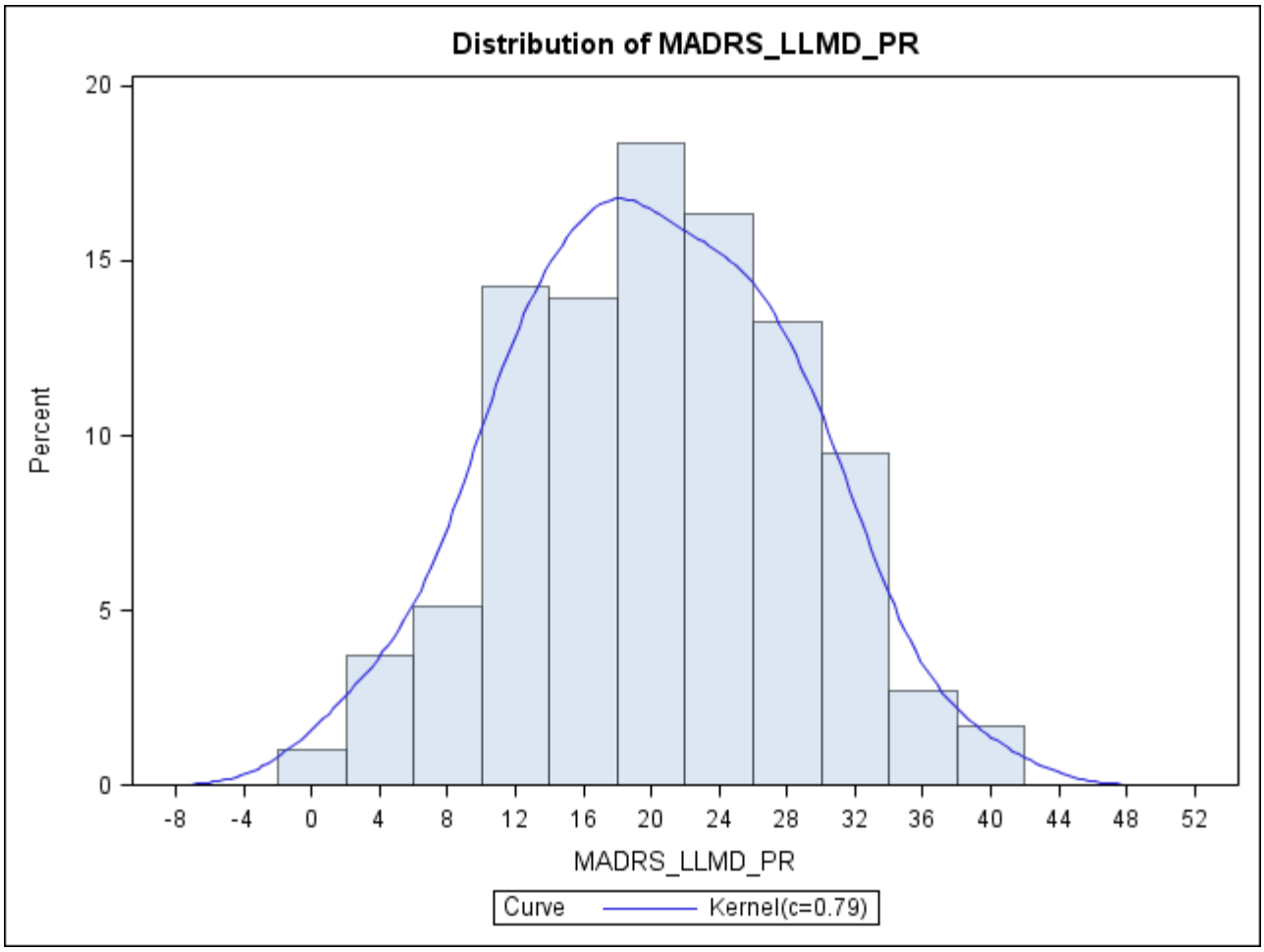
49.5
MADRS_LLMD_PR
Curve
Kernel(c=0.79)

MADRS 1 WEEK



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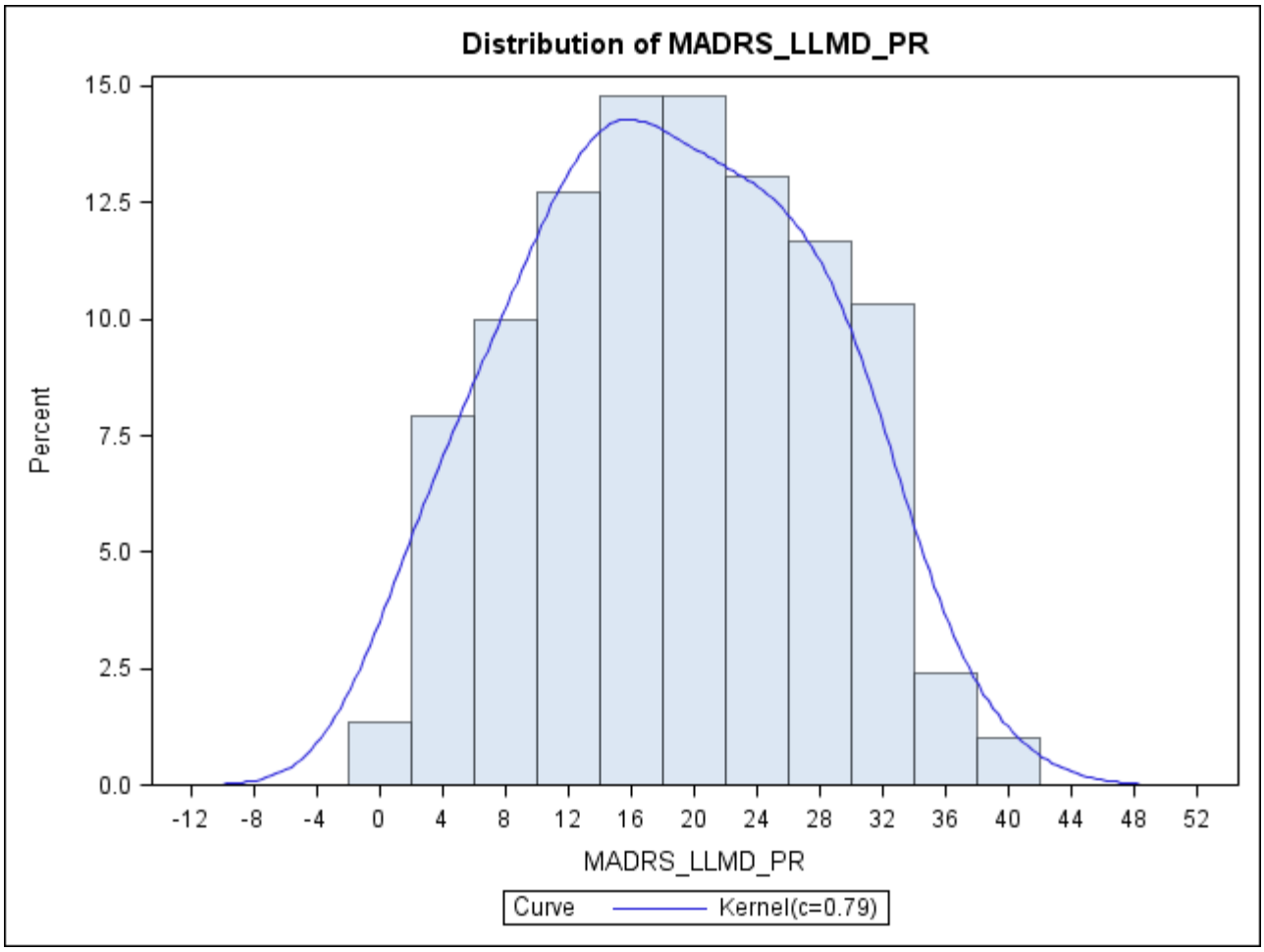
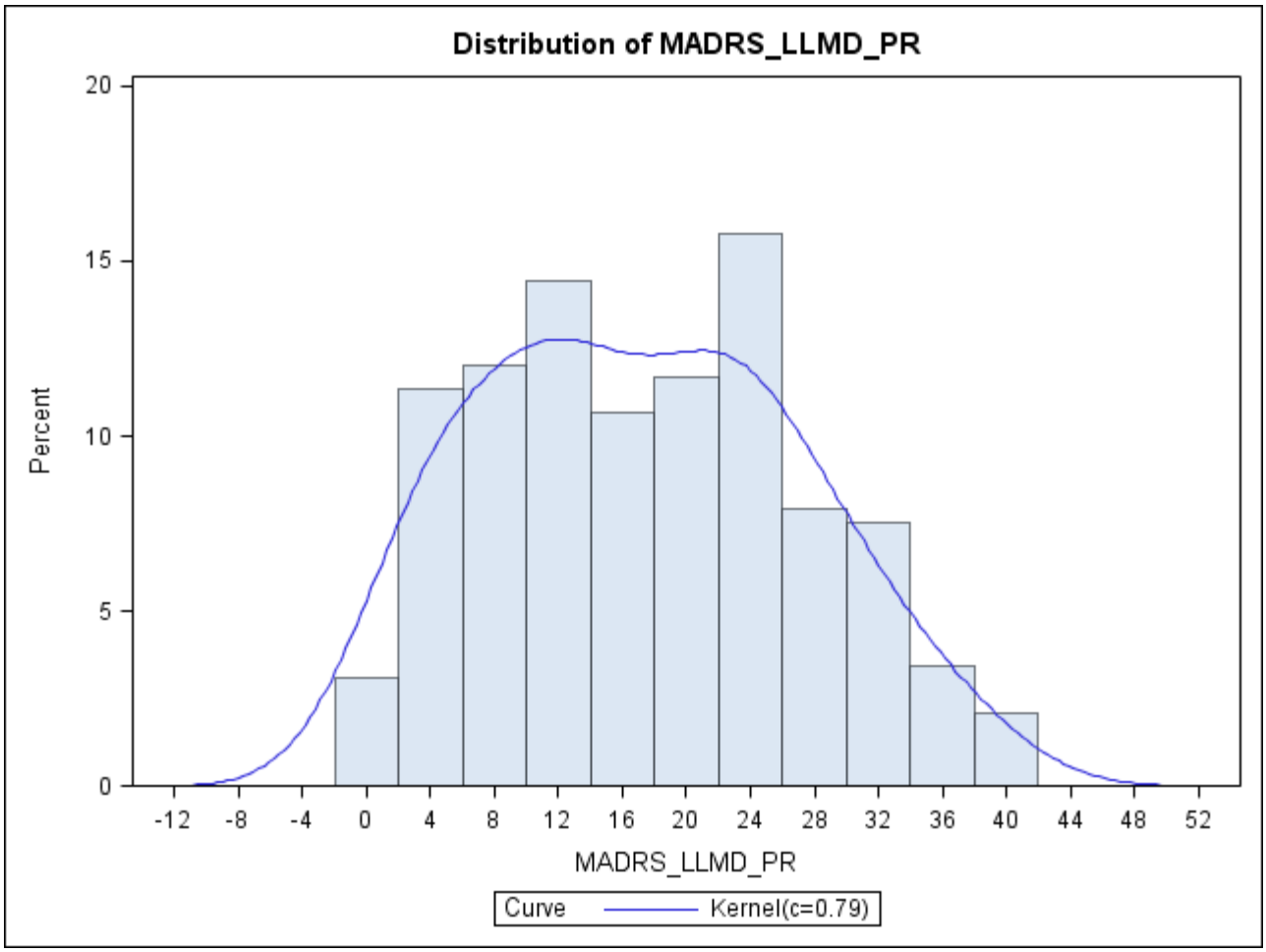
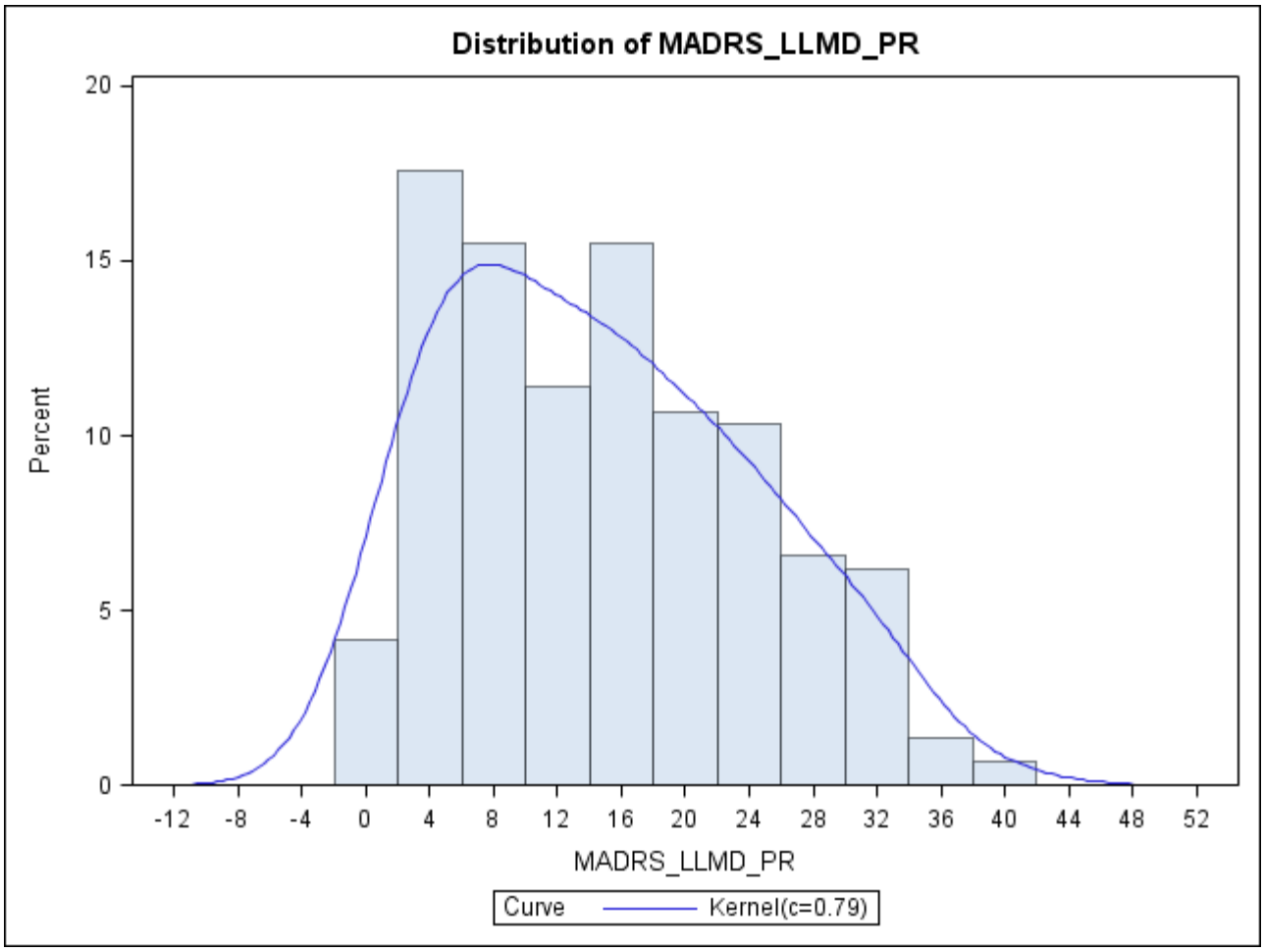


MADRS 4 WEEKS



MADRS 6 WEEKS



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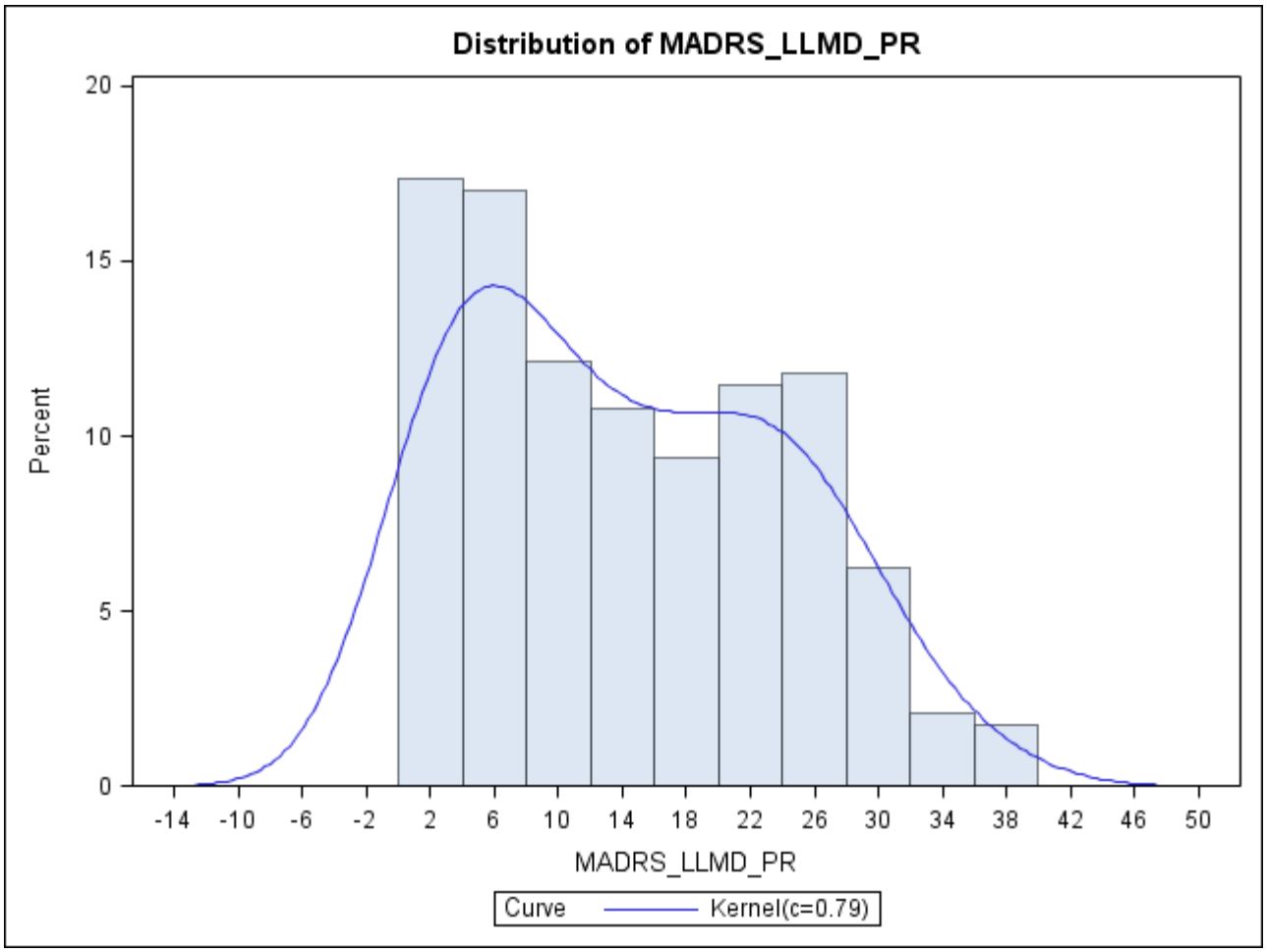

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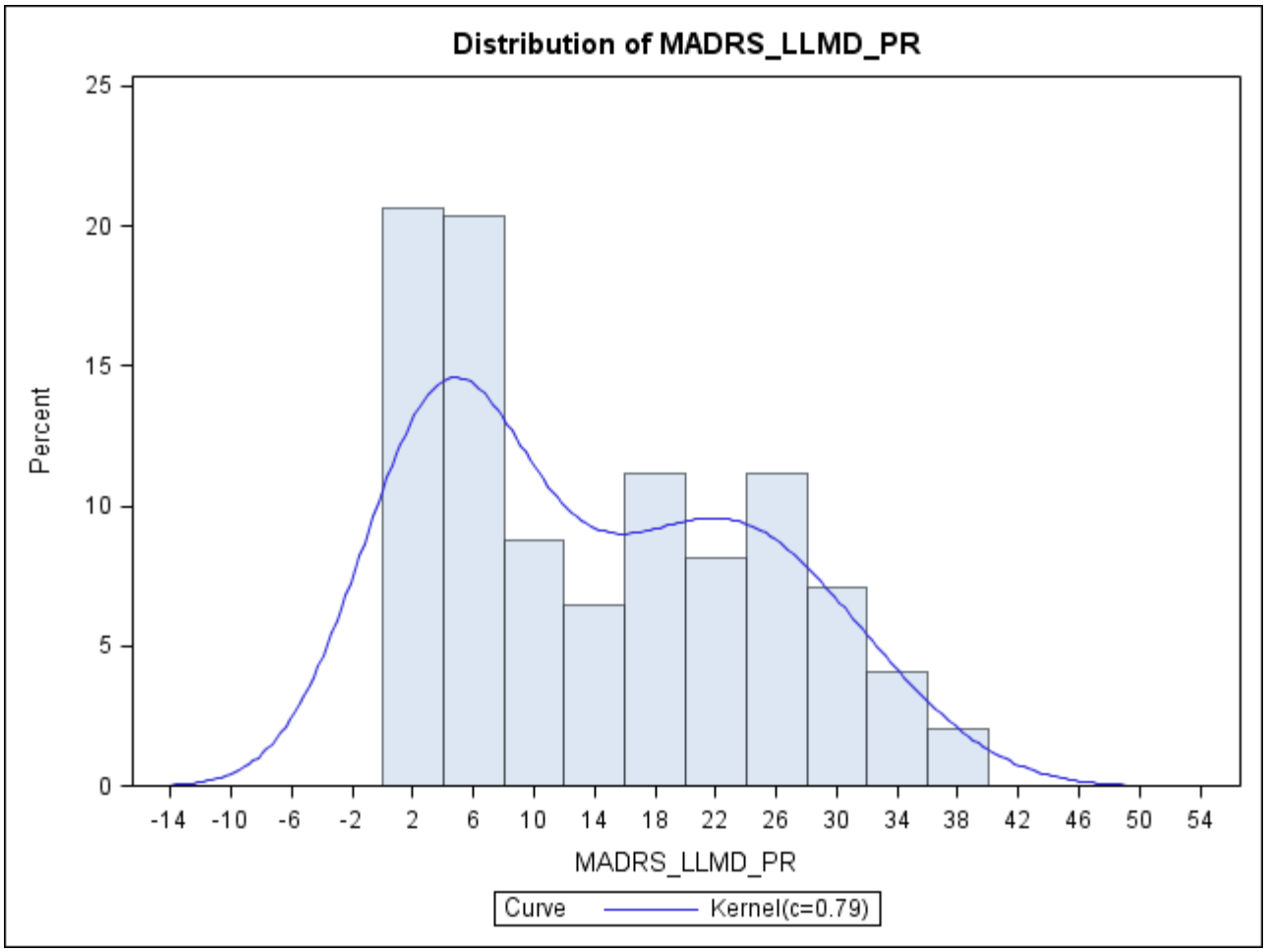
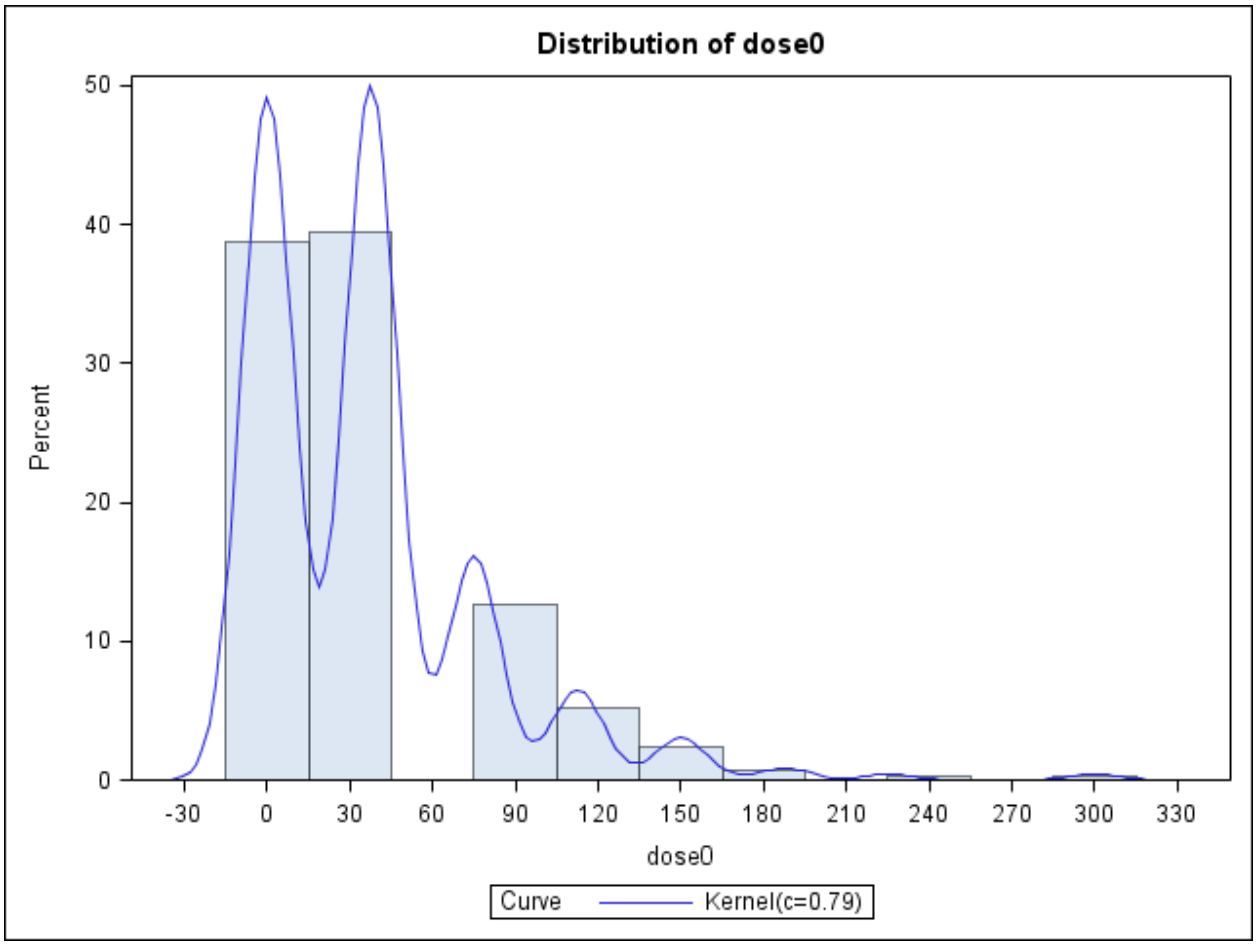
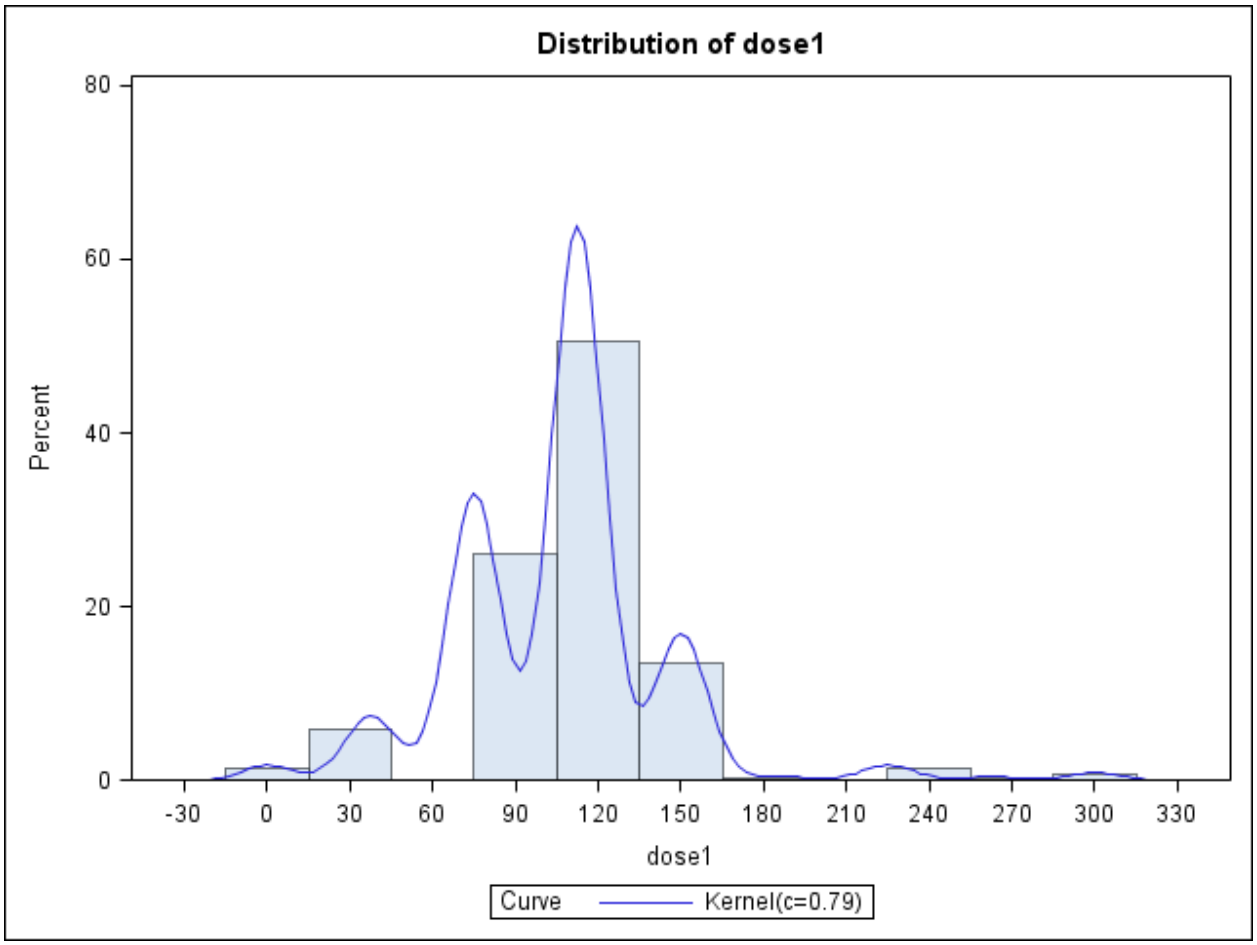


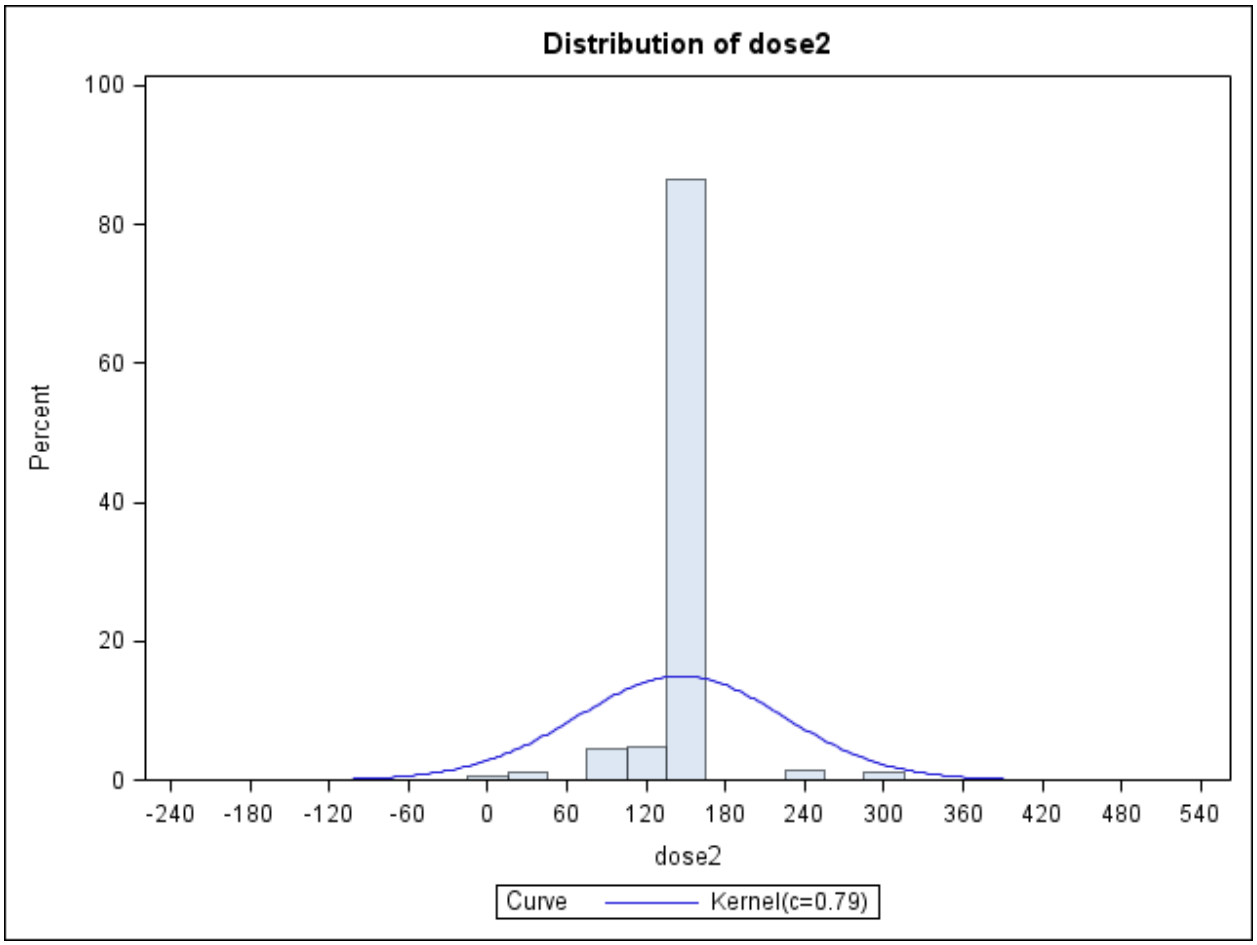
MADRS ENDPOINT



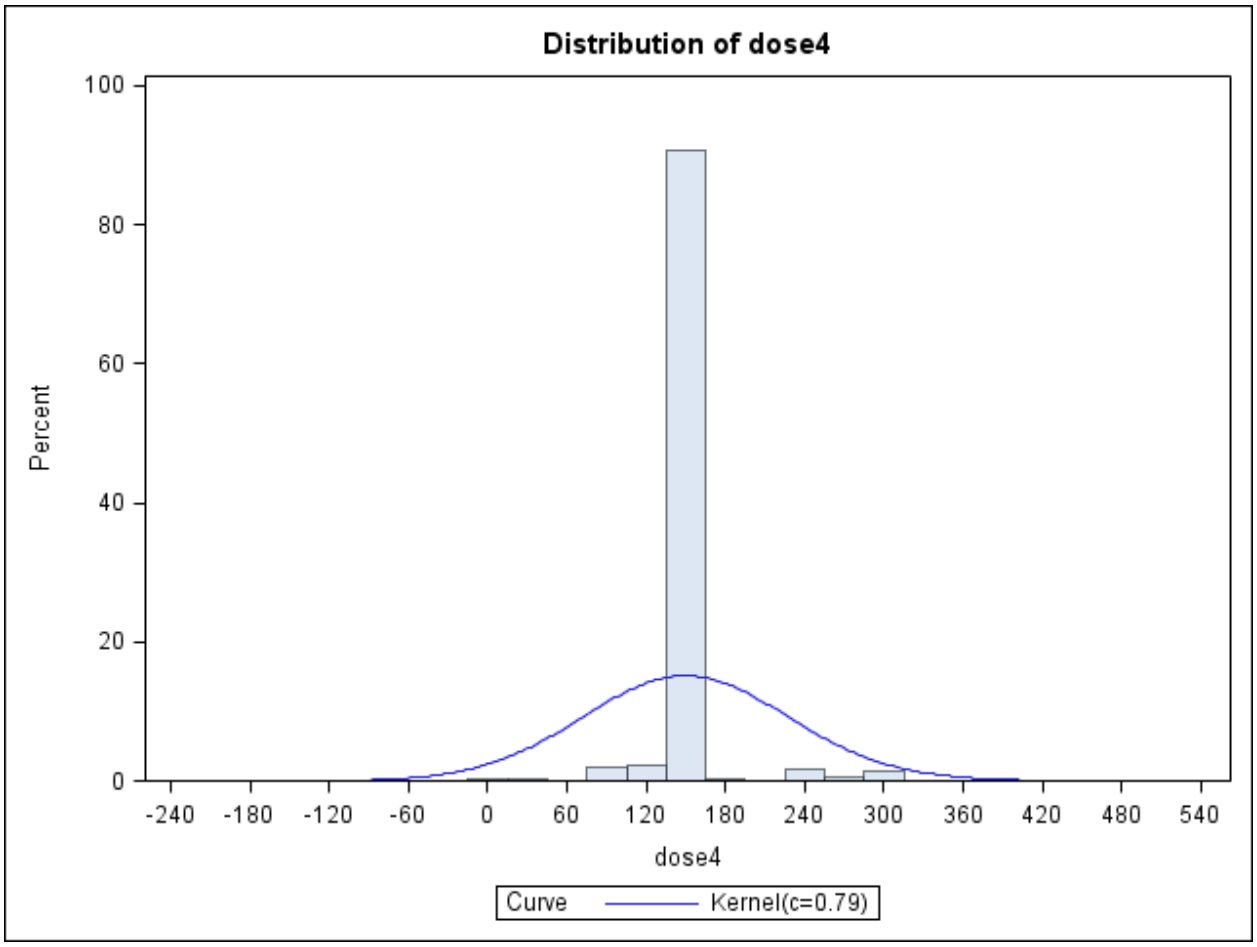
BASELINE DOSE


Distribution of dose1
Percent
80
60
40
20
0
-30
0
30
60
90
120
150
180
210
240
270
300
330
dose1
Curve
Kernel(c=0.79)

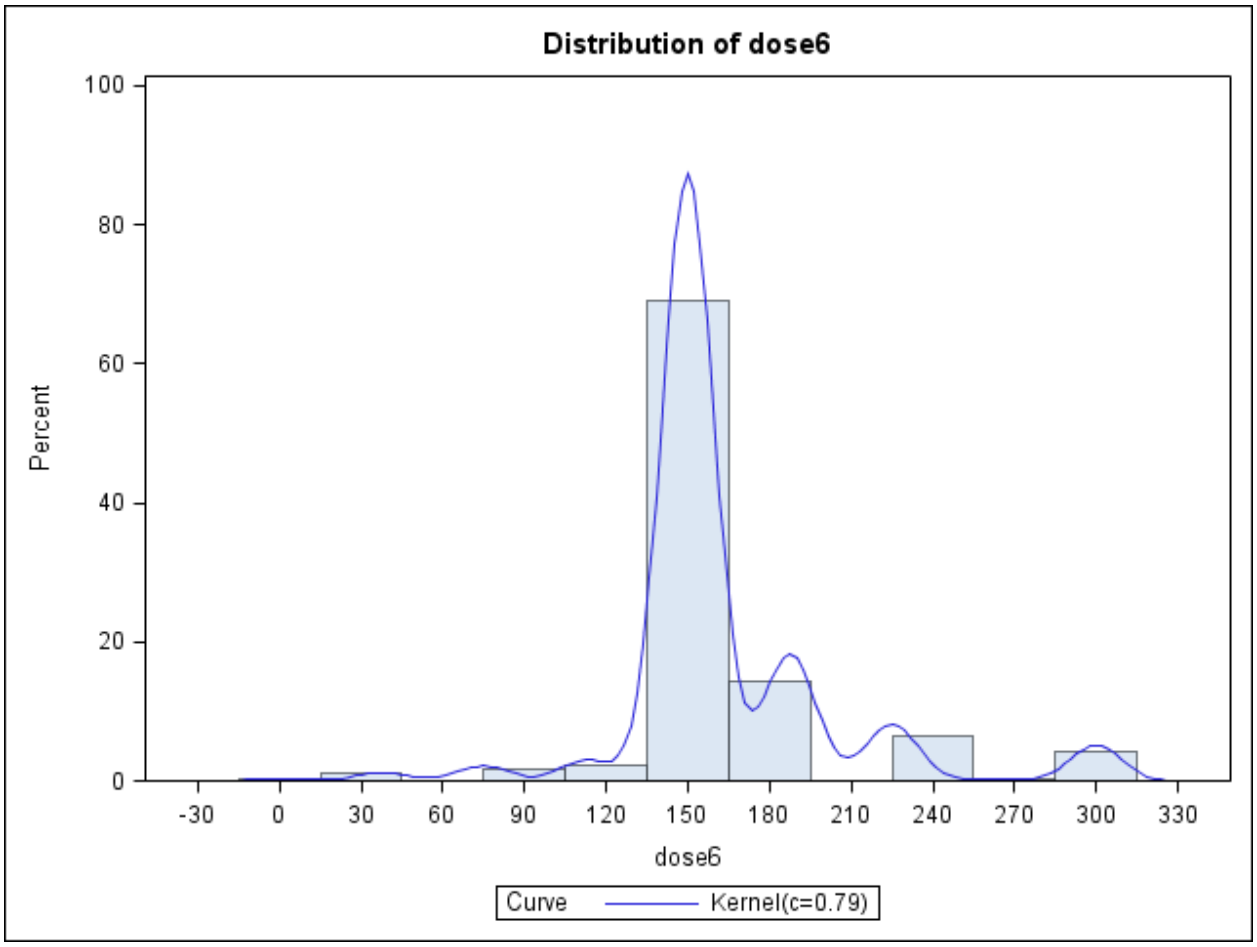
WEEK 1 DOSE


Distribution of dose2
Percent
100
80
60
40
20
0
-240
-180
-120
-60
0
60
120
180
240
300
360
420
480
540
dose2
Curve
Kernel(c=0.79)

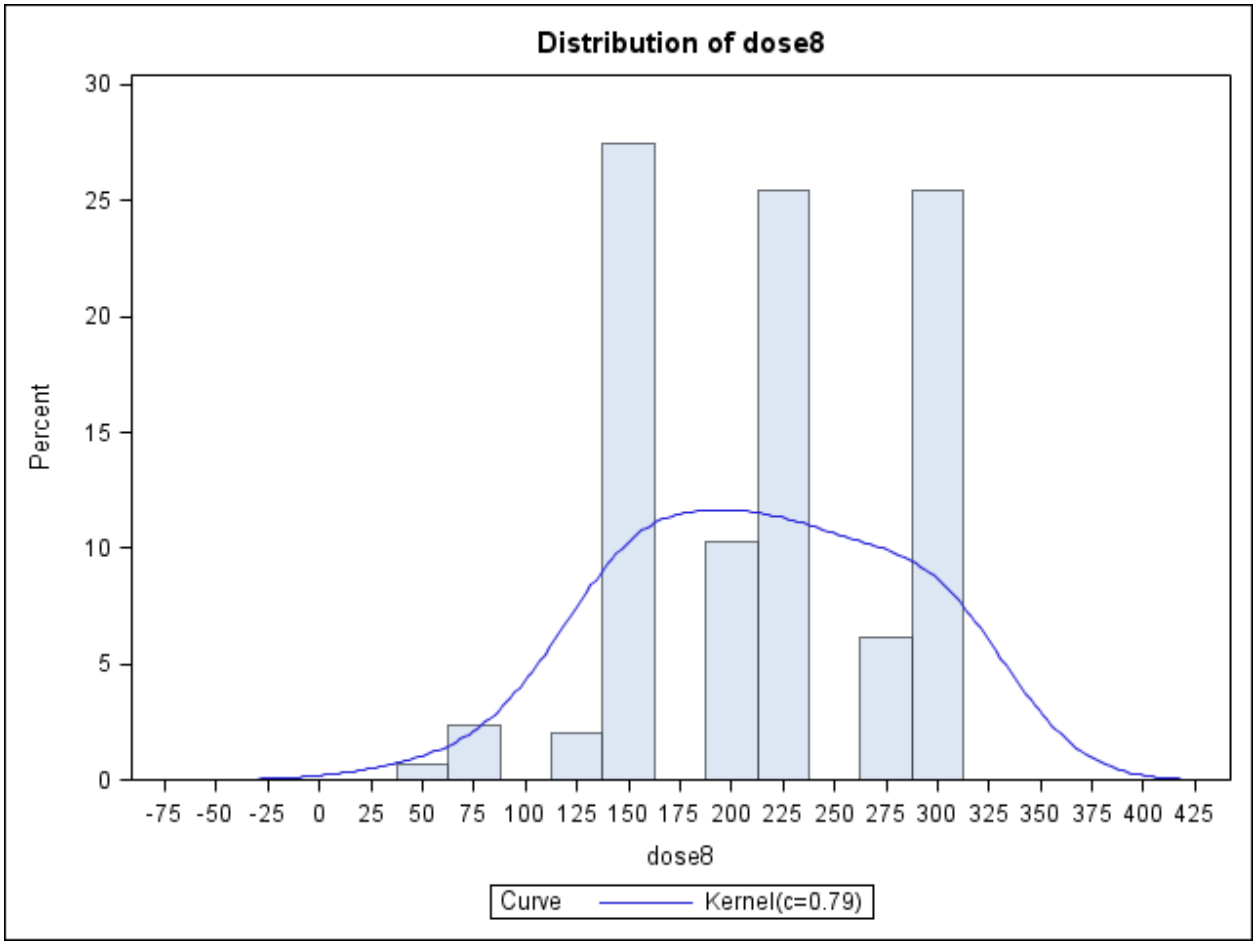
WEEK 2 DOSE


Distribution of dose4
Percent
100
80
60
40
20
0
-240
-180
-120
-60
0
60
120
180
240
300
360
420
480
540
dose4
Curve
Kernel(c=0.79)

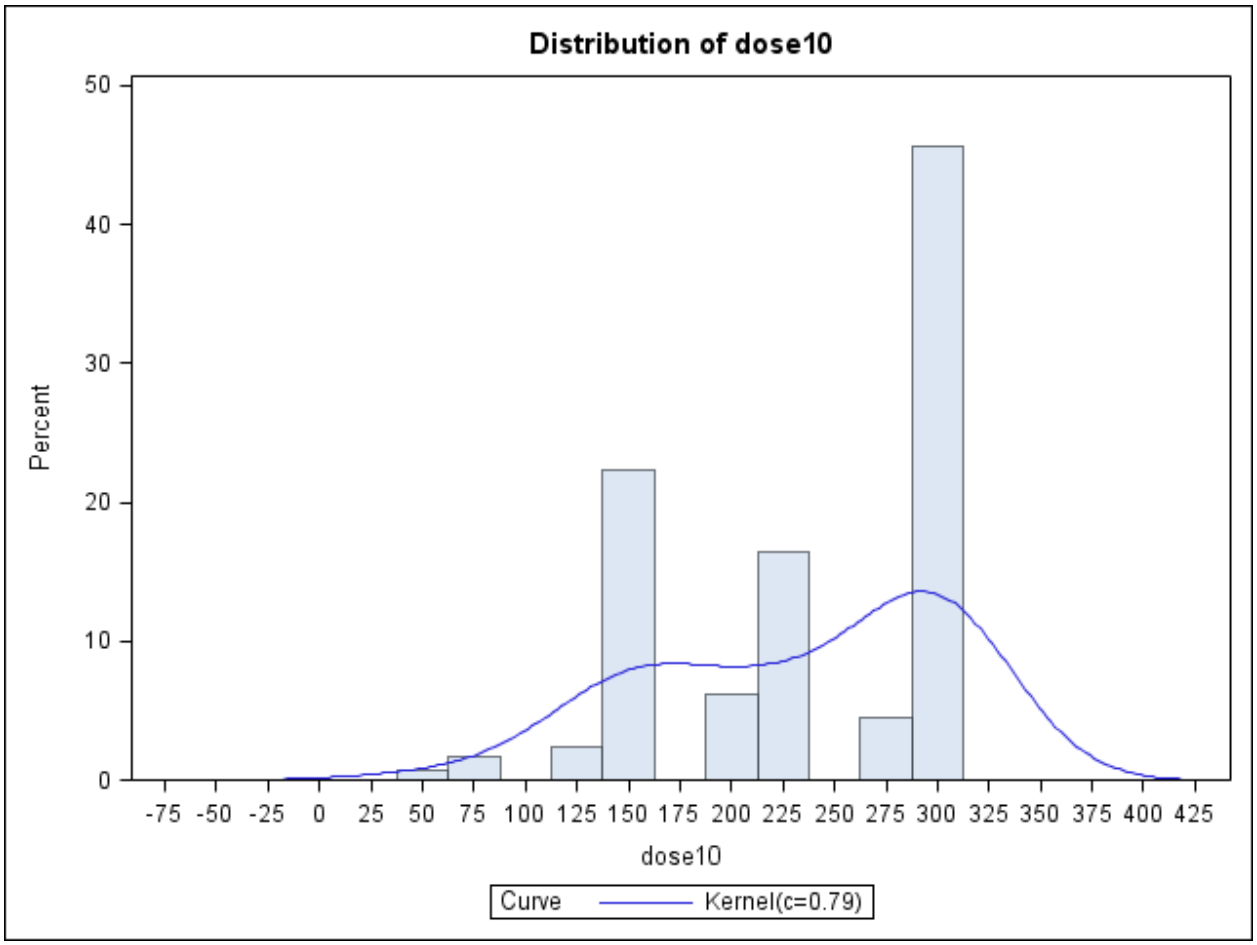
WEEK 4 DOSE


Distribution of dose6
Percent
100
80
60
40
20
0
-30
0
30
60
90
120
150
180
210
240
270
300
330
dose6
Curve
Kernel(c=0.79)

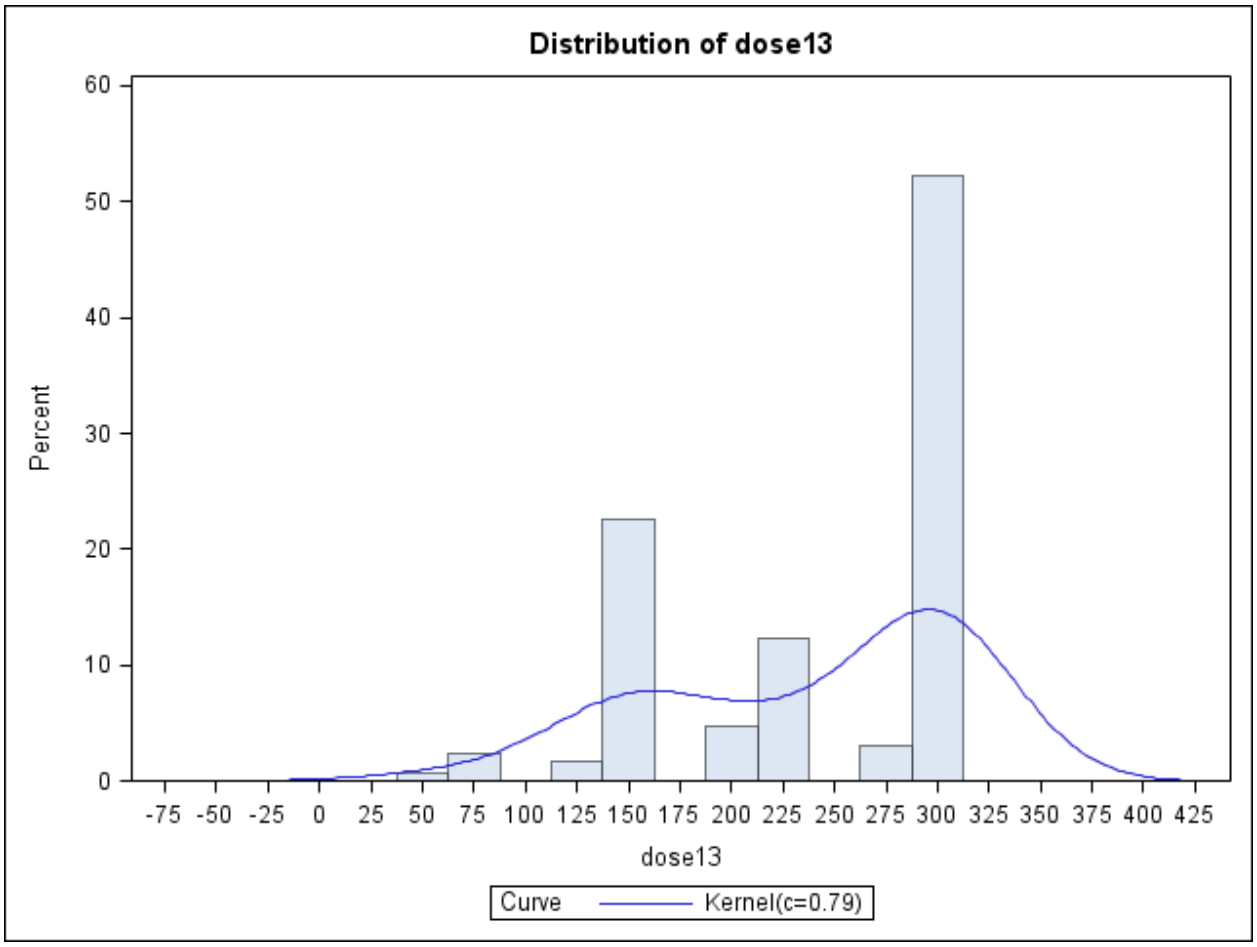
WEEK 6 DOSE


Distribution of dose8
Percent
30
25
20
15
10
5
0
-75 -50 -25 0 25 50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425
dose8
Curve
Kernel(c=0.79)

WEEK 8 DOSE


Distribution of dose10
Percent
50
40
30
20
10
0
-75 -50 -25 0 25 50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425
dose10
Curve
Kernel(c=0.79)

WEEK 10 DOSE



ENDPOINT DOSE

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