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An Analysis Of Patterns And Predictors Associated With Patient Compliance Using Group-Based Trajectory Modeling

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Abstract

The purpose of the study was to identify differential trajectories of patient compliance in a clinical trial and to determine demographic and health risk factors associated with compliance trajectory membership. The data was obtained from an 18 month, double-blinded, placebo-controlled trial looking at the long-term impact of increased dietary protein on bone mass in older men and women. Two hundred and eight subjects were randomized to either a protein treatment or carbohydrate placebo group. Statistical analysis utilized a group-based trajectory modeling framework to identify distinct clusters of individuals who follow similar compliance trajectories over time. Post hoc analysis using multinomial and standard logistic regression models were conducted to incorporate risks factors associated with compliance group membership. A four-group trajectory model was selected and determined that reported adverse event was a significant risk factor. This analysis will provide supplementation to the standard intention-to-treat analysis to understand how efficacy is driven by compliance and will pave the way to improve compliance in subsequent protein-supplemented trials.

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1. Introduction

Osteoporosis, a skeletal disorder characterized by low bone density and micro-architectural deterioration of bone tissue, affects over 10 million persons in the United States.[1] This predisposition increases the risk of osteoporotic fractures, a major cause of morbidity and disability in the elderly.[2] It is projected that by 2025, the direct costs of inpatient medical services and nursing home care will exceed $27 billion in hip fractures alone, not to mention indirect costs associated with loss of productivity and a reduction in quality of life due to disability.[3,4] The World Health Organization (WHO) defines osteoporosis based on a measurement of bone mineral density (BMD), where individuals with BMD levels more than 2.5 standard deviations below the young adult reference mean are considered to have osteoporosis.[5] The dual-energy X-ray absorptiometry (DEXA) is currently regarded as the gold standard to measure BMD.[5]

Nutrition plays an important role in the development and maintenance of bone mass and the prevention and treatment of osteoporosis.[1,2,5,6] Calcium is one of the main bone-forming minerals and contributors in the attainment of peak bone mass, and vitamin D is also required for optimal calcium absorption.[1,2,6] There is evidence to suggest the importance of dietary protein as a key nutrient in the regulation of calcium metabolism and homeostasis.[7–11] A systematic review of 18 cross sectional surveys indicated a significantly positive association between dietary protein and lumbar spine BMD, a clinically meaningful outcome (r_{pooled} =0.143, 95% CI: 0.10, 0.20).[12] This was validated through a meta-analysis of six randomized placebo-controlled trials, indicating a positive influence of protein supplementation on lumbar spine BMD.[12] However, the long-term effects of dietary protein on skeletal health and fracture risk remains uncertain.[12] Furthermore, in many of these intervention-based trials, compliance with respect to protein supplementation has not been thoroughly examined. Since elevated BMD is demonstrated through increased dietary protein consumption, BMD is arguably driven by compliance. This suggests a dose-response relationship between compliance and BMD; better compliance of dietary protein results in a greater increase in BMD. Therefore, monitoring compliance is essential to establishing clinical efficacy.[13] Identifying the long-term patterns of compliance may pave the way to determine thresholds for treatment efficacy.[14]

This provides the motivation for an analysis to (1) identify differential trajectories of patient compliance in a long-term randomized clinical trial (RCT) and to (2) determine demographic and health risk factors associated with compliance trajectory membership. The analysis will provide insight to develop strategies for future RCTs to improve patient compliance in protein-supplemented trials. The analysis will also provide supplementation to the standard intention-to-treat (ITT) analysis.[15] The principle of ITT requires that all subjects be analyzed based on their original randomization scheme regardless of their confounding experience.[16] The proposed analysis may help to explain the therapeutic mechanisms of the treatment and to address different types of questions that are not explained by an ITT analysis.[16] For example, if poor compliance can be traced to an unpleasant aftertaste of the treatment, this can be easily remedied by motivating subjects to focus on the long-term benefits despite the unpleasant aftertaste or even improving the taste of the treatment in subsequent studies.[16]

Statistical methods, such as group-based trajectory modeling (GBTM), have been developed to identify distinct clusters of individuals who follow similar trajectories over time.[17] GBTM has been used in the fields of psychology and sociology, and more recently, it has been seen in clinical studies to capture heterogeneity in treatment responses longitudinally.[18,19] GBTM draws from well developed methodologies including hierarchical and latent class models.[20] Several studies have looked at patient compliance in a variety of clinical applications using GBTM,[14,21–23] which adds to the motivation in using this methodology for the proposed analysis.

2. Materials and Methods

Study Participants and Procedures

A data set was obtained from an 18 month, double-blinded, placebo-controlled trial looking at the long-term impact of increased dietary protein on bone mass in older men and women.[24] Two-hundred and eight English speaking men and women over the ages of 70 and 60 years were selected for the trial, respectively. The subjects were recruited from central and southern-central Connecticut, and the study sites were located at Yale University and the University of Connecticut's Health Center (UCHC). Subjects were selected because they naturally consumed a moderately low, but adequate protein diet (0.6-1.0 g/kg). After baseline measurements (BMD,

heart rate, blood pressure, and height and weight) and screening and safety biochemistries from blood and urine samples were taken at the initial visit, eligible subjects were invited back for randomization proceedings. Subjects were randomized to either a protein treatment or carbohydrate placebo group. Both supplements were formulated to be identical in appearance, taste, texture, and caloric content. It was expected that subjects consume 40 g of the protein or carbohydrate powder daily by mixing it into their food or drink. Registered dietitians provided nutritional counseling during the initial and follow-up visits to (1) stabilize the subjects' calcium and vitamin D intake and to cease all other nutritional supplements that may affect bone homeostasis, (2) incorporate the powder supplements into their diets and provide weight management, and (3) monitor compliance of treatment. After randomization, subjects were followed up after 1.5, 3, 6, 9, 12, 15, and 18 months. It should be noted that at the time the data was received, the study was still active. Therefore, the analysis was performed blinded and did not take into account treatment groups.

Measures

For the purposes of this analysis, the outcome variable was percent compliance. The following covariates were considered as potential predictors of compliance trajectory membership: baseline DEXA lumbar vertebrae 2-4 (L2-4) BMD, BMD T-score, age, gender, study site, reported adverse event, physical function measured by the Estimated Populations for Epidemiologic Studies of Elderly (EPESE) battery, and self-reported history of depression and/or anxiety.

(1) Percent Compliance

After randomization, patients were dispensed a batch of the supplement either containing the protein or carbohydrate powder. It was expected that subjects consume 40 g of the powder daily, and so the appropriate amount was dispensed and recorded accordingly. Subjects were asked to bring any unconsumed powder with them during follow-up visits to be weighed. The amount consumed was calculated as the amount dispensed during the previous visit minus the unconsumed amount during the follow-up visit. The expected amount consumed was calculated as 40 g of powder multiplied by the days between each visit. Therefore percent compliance was calculated as:

$$\textit{Percent Compliance} = (\textit{Amount Consumed} / \textit{Expected Amount}) \times 100$$

Compliance data was available after the second visit, and repeated measurements were taken during visits 3, 4, 5, 6, 7, 8, and 9 (i.e. during months 1.5, 3, 6, 9, 12, 15, and 18). Occasionally, there were subjects who consumed more than 40 g of powder daily, on average. Since these subjects exceed the expected amount and therefore were fully compliant, they were considered as having one-hundred percent compliance. Conversely, missing data from subjects that had dropped out of the study or stopped treatment but remained in the study for follow-ups were considered to be fully non-compliant. These subjects were recorded as having zero percent compliance.

(2) DEXA L2-4 BMD and T-score

The DEXA L2-4 BMD (g/ cm^2) was the primary endpoint of the clinical trial. Measurements were taken initially during the screening visit and remeasured after 9 and 18 months (visits 6 and 9). Baseline BMD was only considered for this analysis to evaluate the initial disease severity. In addition, the T-score, a clinically relevant tool for diagnosing osteoporosis, was also considered. A T-score is defined as the number of standard deviations from the mean BMD in relation to a young healthy adult population.[5] Since subjects were considered to have osteoporosis if their T-score was less than -2.5, this variable was categorized to $\leq$ -2.5 as having clinically diagnosed osteoporosis and > -2.5 as having moderately low (osteopenia) to normal BMD levels.

(3) Demographic and Other Health Measurements

Since women are at greater risk of developing osteoporosis,[25] the trial over-sampled women to men that were 60 and 70 years of age or older, respectively. The study sites were located either at Yale University or UCHC. Adverse events were recorded at baseline and follow-up visits. An adverse event is defined as any injurious falls to the ground that resulted in bruises, strains, cuts and abrasion, back pain, and/or fractures.[24] A record of any adverse event and its severity was kept throughout the trial. The baseline reported adverse event was only used in the analysis. Self-reported history of depression and/or anxiety was also considered as relevant predictor. Finally, physical performance among older populations was measured by the EPESE battery, which consisted of three domains of lower extremity function to assess gait speed, standing balance, and time to rise from a chair five times.[26–28] Within each domain, a score of 0 denoted an inability to

complete the test, while a score of 4 represented the highest level of performance; the maximum total EPESE score was 12.[28]

3. Statistical Analysis

Statistical analysis encompassed (1) descriptive statistics of the study characteristics, (2) model selection for determining the compliance trajectory groups using GBTM, and (3) statistical inference for determining predictors associated with compliance trajectory membership using multinomial and standard logistic regression models. All data analysis was carried out using SAS version 9.2 and PROC TRAJ, a SAS macro for GBTM developed by Bobby L. Jones.[19]

Group-Based Trajectory Modeling

Group-based trajectory modeling (GBTM), also referred to as latent class growth modeling, is a statistical tool used to identify distinct clusters of individuals, called trajectory groups, who follow a similar developmental trajectory on an outcome of interest.[17,19] Trajectory groups can be thought of as unobserved (latent) longitudinal strata where population variability is captured by the differential trajectories across groups.[17,29] GBTM uses a semi-parametric group-based approach that draws from two well-developed methodologies – hierarchical modeling and latent curve analysis.[20] The key difference among these models is that hierarchical and latent class models utilizes multivariate continuous distributions to explain the population-level variability in growth, while GBTM uses a multinomial-based strategy to identify relatively homogeneous clusters of developmental trajectories.[20] GBTM is a special case of growth mixture models (GMM) in that it assumes no random effects in each of the group's trajectories; GMM relaxes this assumption and allows for variation within each of the trajectory groups.[17,30] GBTM has been widely used in the fields of developmental and abnormal psychology as well as modeling behavior in sociological and criminological studies.[19] More recently, GBTM has been applied to clinical research to map the developmental course of symptoms and to assess heterogeneity in response to clinical interventions.[17]

Derivation of the Group-Based Trajectory Model[19,31,32]

Let $Y_i = \{y_{i1}, y_{i2}, y_{i3} \ldots y_{iT}\}$ denote the repeated measurements of individual *i* over T measurements. Since measurements are reassessed at each visit *t* (i.e. 1st, 2nd, 3rd visit, etc.), it is expected that the number of visits be the same across individuals. GBTM assumes that individuals fall within a particular group *J* such that

$$P(Y_i) = \sum_{j=1}^{J} \pi_j P(Y_i|J = j) = \sum_{j=1}^{J} \pi_j P^j(Y_i)$$

where π_j is the probability of membership in group *j*, and $P^j(Y_i)$ is the conditional probability of Y_i given membership in group *j*. The model makes a strong assumption that measurements for individual *i* are independent of each other, conditional on membership in group *j*. Therefore, $P^j(Y_i) = \prod_{t=1}^{T} p^{jt}(y_{it})$. π_j is estimated using a multinomial logit function to ensure that the probabilities fall between 0 and 1:

$$\pi_j = \frac{e^{\theta_j}}{\sum_{j=1}^{J} e^{\theta_j}}$$

where θ_1 is initialized at 0. GBTM is able to handle continuous (censored normal), count (zero-inflated Poisson), and binary outcome data by selecting a form of $p^{jt}(y_{it})$ to fit the appropriate data type. For continuous data, GBTM uses a polynomial relationship between the outcome and time variable:

$$y_{it}^{*j} = \beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3 + \beta_4^j Time_{it}^4 + \varepsilon_{it}$$

where y_{it}^{*j} is a latent variable and link between the outcome and time variable, and ε_{it} is a random error term that follows a normal distribution with mean of zero and constant variance σ^2. Many statistical packages that performs GBTM allows specification of the order trajectories up to the fourth degree polynomial.[19,30,31]

Model Selection of Compliance Trajectories using PROC TRAJ

GBTM can be applied to a variety of statistical packages including SAS and Mplus.[19,30,31] For the purposes of this analysis, PROC TRAJ, a SAS macro developed by Bobby L. Jones[19] was used to perform GBTM to estimate the compliance trajectories. PROC TRAJ assigns group membership to each individual where the posterior probability of membership to that group is the

highest.[19] Parameter estimates are based on maximum likelihood via the quasi-Newton optimization procedure, and standard errors are approximated by a fist-order Taylor series expansion.[23] PROC TRAJ allows specification of the trajectories up to the fourth degree polynomial.[19,31] It includes subjects with missing longitudinal data and time-varying covariates; however missing time-stable covariates are excluded from the analysis.[19] Covariates can be incorporated into the model either by adding them simultaneously in the PROC TRAJ statement, or by performing post-hoc analysis using a multinomial logistic regression model. In this analysis, both methods were performed to compare the consistency of the results.

Model selection involved a two-step process to determine the best model for each trajectory group (i.e. best model containing 1-, 2-, 3-group trajectories, etc.) and the best overall model with PROC TRAJ. The strategy outlined by Andruff et al.[32] to determine the best model for each trajectory group utilized a combination of visual inspection of the fitted compliance trajectories overlaid with the mean trajectories at each time point, and tests of significance on whether or not the time parameter estimates differed from zero. The significance level α was set at 0.05. For each trajectory group, a third order polynomial model was fitted. A new model was refitted of increased or decreased order depending on the significance of the third order parameter estimates. This process was repeated until the highest order term achieved significance, and the fitted model appeared adequate from the trajectory plot. Once a best model was chosen for each trajectory group, the best overall model was selected using the Bayesian Information Criteria (BIC) and the log Bayes factor to compare models. The log Bayes factor is approximated as:

$$\log\ Bayes\ factor = 2log_e(B_{10}) \approx 2(\Delta BIC)$$

where ΔBIC is the difference between the BIC of the larger model (alternative) model and the BIC of the smaller (null) model.[19] The log Bayes factor is interpreted as the degree of evidence favoring the larger model and is shown in the table below.

Interpretation of the Log Bayes Factor

Log Bayes Factor	Evidence against H_0
0 to 2	Weak
2 to 6	Positive
6 to 10	Strong
> 10	Very Strong

To ensure that PROC TRAJ accurately assigned each individual to the appropriate trajectory group, Nagin outlined four criteria to assess model adequacy: (1) the estimated probability of group membership ($\hat{\pi}_j$) should correspond closely to the proportion classified in that group based on the highest posterior probability, (2) the confidence intervals around $\hat{\pi}_j$ should be reasonably tight, (3) the average posterior probability (AvePP) of group membership for individuals assigned to each group should exceed the 0.7 threshold, and (4) the odds of correct classification (OCC) should exceed the minimum threshold of 5.[17,18] For each group *j*, the OCC is calculated as:

$$OCC_j = \frac{AvePP/(1 - AvePP)}{\hat{\pi}_j/(1 - \hat{\pi}_j)}$$

Simultaneous and Post-hoc Analysis using Multinomial and Standard Logistic Regression

GBTM allows the group membership probabilities to vary as a function of time-stable characteristics for an individual, and therefore covariates can be added simultaneously in the PROC TRAJ statement to predict trajectory group membership.[31] Measured covariates were included in the model simultaneously to determine the impact of a given risk factor on the probability of group membership in a specified trajectory group compared to a reference group.[31] Given that the trajectory groups followed a multinomial distribution, post-hoc analysis using multinomial logistic regression was also conducted to determine whether the measured covariates were significant predictors of compliance trajectory group membership. The results of the simultaneous and post-hoc analysis were compared for consistency. Furthermore, the groups in the multinomial analysis were collapsed into a binary outcome variable indicating compliant or non-compliant subjects. A standard logistic regression model was then performed to take into account potential predictors for compliance. The Hosmer and Lemeshow Chi-square test for goodness of fit was used to assess model adequacy, and the R^2 and max-rescaled R^2 was also reported. Since R^2 only achieves a maximum value of less than 1 when discrete variables are included in a logistic regression model, the max-rescaled R^2 provides a more accurate assessment of model fit.[33]

3. Results

Description of the Sample

Two-hundred and eight subjects were considered for the analysis to identify differential trajectories of patient compliance and to determine risk factors associated with compliance group membership. A description of the study participants can be found in Table 1. The mean age of the subjects was 69.8 ± 6.2 years. As females are at higher risk of developing osteoporosis, they were over-sampled and comprised of 85.6% of the study subjects. The majority of the subjects (92.2%) had a T-score greater than -2.5, indicating that they did not have clinically diagnosed osteoporosis at the beginning of the study. The mean EPESE score was 11.3 ± 1.1. Eighty-two subjects reported an adverse event at baseline, while only 23 reported any history of depression and/or anxiety.

Model Selection for Determining Compliance Trajectory Groups

Model selection for GBTM was assessed by comparing the BIC, log Bayes factor, and estimated group proportions for five trajectory models (i.e. 1-, 2-, 3-, 4-, and 5-group models) (Table 2). A 6-group model failed to achieve convergence and was not included in the model selection. The second group of the 5-group model contained only 2.14% of the total sample; therefore, the sample size was not large enough to perform further analysis with multinomial logistic regression. As a result, the 4-group model was chosen as the best model as it identified four distinct trajectories with estimated group proportions well over the 5% threshold (Group 1: 23.5%, Group 2: 36.9%, Group 3: 19.8%, and Group 4: 19.8%).

A plot of the individual trajectories of percent compliance at each visit (Figure 1) indicated a large degree of heterogeneity among the subject-specific percent compliance. After performing GBTM, the fitted model was able to identify four distinct trajectory groups (Figure 2). Group 1 (red) was identified as “severely noncompliant.” Percent compliance within group 3 (blue) decreased over time and these subjects were termed “delayed noncompliant.” Groups 2 (green) and 4 (black) showed consistently moderate to high levels of compliance and were identified as “moderately compliant” and near-perfect compliant” subjects, respectively. For comparison, a panel of the 1-, 2-, 3-, and 5-group fitted models can be found in Figure 3.

The parameter estimates of the differential trajectories over time from the 4-group model are shown in Table 3. The estimates of the highest degree polynomial within each group were found be to significant ($p < 0.001$). To ensure that GBTM accurately assigned each individual to the appropriate trajectory group, diagnostics were performed to check for model adequacy in Table 4. The estimated probabilities of group membership and the proportion classified to that group showed close correspondence with each other. The width of the 95% confidence intervals of the estimated probabilities appeared reasonably narrow, and the AvePP and OCC significantly met the minimum thresholds of 0.7 and 5, respectively. Therefore, the diagnostics suggest that GBTM was successful in accurately assigning each individual to the appropriate trajectory group.

Predictors of Compliance Group Membership

Bivariate analysis of the study characteristics across the four trajectory groups is shown in Table 5. There were no significant associations between the compliance trajectory groups and the study characteristics. Although not significant ($p = 0.268$), there were a greater proportion of subjects with clinically diagnosed osteoporosis (T-score $\leq$ -2.5) among the severely (14.6 %) and delayed (7.7%) noncompliant groups compared to the moderately (5.3%) and near-perfect compliant groups (4.8%). The continuous DEXA measurement for BMD showed a consistent and slightly more significant association ($p = 0.092$). Over half of the subjects within the delayed noncompliant group (53.7%) reported an adverse event at baseline in comparison to the severely noncompliant (32.7%), moderately compliant (36.8%), and near-perfect compliant (38.1) subjects (p-value = 0.198).

PROC TRAJ has the capabilities to simultaneously identify differential trajectory groups and take into account potential risk factors; however, when this was applied, convergence was not achieved past two trajectory groups. Therefore, the results of the post hoc analysis were only shown. One-hundred and sixty eight subjects with complete data were included in multinomial logistic regression. Given that the T-score calculation was based off of the DEXA BMD and therefore were highly correlated with each other, two separate models were performed. Table 6 shows the multivariate regression model that includes the BMD T-score (model 1), while Table 7 shows the model containing DEXA BMD (model 2).

The near-perfect compliant group was set as the reference group. None of the predictors measured were found to be significant for model 1. When controlling for all other variables, subjects who were severely noncompliant were 3.36 times more likely to have clinically diagnosed osteoporosis (T-score $\leq$ -2.5) compared to those with near-perfect compliance (p = 0.176, 95% CI: 0.58, 19.34). Subjects with delayed noncompliance were more likely to report an adverse event compared to subjects with near-perfect compliance (AOR = 2.27, 95% CI: 0.81, 6.34). On the other hand, DEXA BMD was found to be significant in model 2 (p = 0.036). The severely (AOR = 0.26, 95% CI: 0.02, 3.89) and delayed (AOR = 0.64, 95% CI: 0.04, 11.02) noncompliant groups were associated with lower BMD levels, while the moderately compliant group (AOR = 6.66, 95% CI: 0.67, 65.8) showed increased BMD levels compared to the near-perfect compliant group. However, none of these estimates were significant, and the wide 95% confidence intervals suggest that the reliability of the estimates is questionable. The significance of the Wald Chi-square test implies significant associations for DEXA BMD comparing a different reference group.

Since the severely and delayed noncompliant groups were presumably represented by noncompliant subjects, and the moderately and near-perfect compliant groups as the compliant subjects, the four groups were collapsed into a binary outcome. The probability of noncompliance (i.e. comparison of noncompliant versus compliant group) was modeled using standard logistic regression for models 1 and 2 (Tables 8 and 9). For both models, reported adverse event was significantly associated with noncompliance (model 1: p = 0.033, model 2: p = 0.35). Noncompliant subjects were 51% less likely to have reported an adverse event compared to compliant subjects (model 1: AOR = 0.49, 95% CI: 0.25, 0.94, model 2: AOR = 0.49, 95% CI: 0.26, 0.95). However, the max-rescaled R^2 of both multinomial (model 1: max-rescaled R^2 = 0.164, model 2: max-rescaled R^2 = 0.173) and standard logistic regression (model 1: max-rescaled R^2 = 0.075, model 2: max-rescaled R^2 = 0.082) models did not indicate an adequate fit of the data, suggesting that other important risk factors were overlooked in explaining the variability of the compliance trajectory groups.

4. Discussion

GBTM was able to accurately identify four distinct compliance trajectory groups – severely noncompliant, delayed noncompliant, moderately compliant, and near-perfect compliant groups. However, because the parameter estimates for the risk factors did not achieve convergence when added simultaneously to PROC TRAJ, the results of the simultaneous and post hoc analysis were not compared. Jones argues that the post-hoc analysis does not account for the uncertainty in group assignment and this could lead to bias; incorporating the predictors simultaneously accounts for this automatically.[19] Nonetheless, the procedure was shown to accurately identify four distinct trajectory groups that follow a multinomial distribution based on the model diagnostics for GBTM, and so the post hoc analysis was justified.

While there were no significant predictors of compliance group membership within the first multinomial logistic model, DEXA BMD was found to be a significant predictor within the second model. The wide variability around the 95% confidence intervals as well as the limited number of subjects diagnosed with osteoporosis, on the other hand, suggest that the estimates may not be reliable. As a result of the inclusion/exclusion criteria, relatively healthy subjects were selected for the trial. This was evident as subjects had a mean EPESE score of 11.3, and these scores were found not to be statistically different across the four compliance groups ($p = 0.719$). The main inclusion criterion was that they naturally consumed a moderately low, but adequate protein diet. The trial excluded subjects with a BMD T-score of < -2.5 with the exception of subjects who declined treatment for anti-osteoporotic medications throughout the trial. Thus, only 16 out of 208 subjects were found to have clinically diagnosed osteoporosis. This greatly limits the statistical power to conduct a multinomial logistic regression analysis and to compare the four compliance groups. GBTM is preferable when the sample size is greater than 300,[18] and so this adds to a limitation in the analysis.

The nature of the clinical trial also limited the analysis in terms of potential risk factors that could have been analyzed to predict compliance group membership. The trial restricted subjects to those with normal BMI levels (i.e. excluded BMI levels < 19 and > 32). An investigation of whether or not subjects with low BMI were more likely to comply with the treatment protocol

compared to those with normal to high levels would have provided much insight. Data on reported history of gastrointestinal disorders (i.e. Crohn's disease, colitis, ulcers) was also available to determine whether the supplements had an adverse effect on these individuals, making them less likely to be compliant. Unfortunately, there were not enough subjects that responded to these questions, and so this was not considered in the analysis. Socioeconomic status (SES), measured by education level, might also have been an important predictor as there is a direct correlation between education and health.[34] Subjects with higher education levels are more likely to be health conscious, and so they might be motivated to take the supplements regularly if they knew it would be beneficial to their health. However, subjects within the clinical trial comprised of mainly retired and working class individuals, and so SES data was not available.

A major limitation to this analysis was that the clinical trial was still active at the time the data was received. As a result, the analysis did not take into account the treatment effect as a predictor because the study had been blinded to the treatment allocation. Data on the treatment group would have provided insight to uncover potential discrepancies in compliance between the protein and carbohydrate groups. If it was shown that subjects who received the protein treatment were more likely to fall within the noncompliant groups (i.e. severely and delayed noncompliance) compared to the compliant groups (i.e. moderate and near-perfect compliance), this may help to explain why the treatment was not efficacious to increase BMD levels. It is possible that efficacy for the treatment effect was undermined by compliance. Equally, if subjects who received the protein treatment were more likely to be compliant compared to the carbohydrate-supplemented group, then the magnitude for the association between BMD levels and the treatment effect might have been overestimated. Therefore, understanding the mechanisms behind compliance is essential to establishing clinical efficacy.

While there were no significant predictors of compliance group membership in the multinomial logistic models, reported adverse events was found to be a significant predictor in the standard logistic regression models. Subjects who had reported an adverse event throughout the trial were more likely to be compliant with their treatment. This makes intuitive sense because subjects who believe that they are more susceptible to having lower BMD because of an adverse event

will more likely comply with the medication in hopes of increasing their BMD levels. This idea is known as the Becker's health belief model. It postulates that the likelihood that patients follow a health regimen is related to their motivation and incentive to do so.[35] The motivation and incentive, in this case, is alleviating their adverse event, and so subjects are more likely to comply with the protein or carbohydrate supplements.

In summary, the analysis using the GBTM methodology will provide supplementation to the clinical trial to explain how efficacy is driven by compliance. By identifying the differential effects in reporting an adverse event at baseline and its impact on compliance, subgroup analysis can be performed to compare BMD levels over time between subjects who did and did not reported an adverse event at baseline. If it is shown that subjects who reported an adverse event had a greater treatment difference of increased BMD compared to those who did not report an adverse event, then future studies can be develop to target subjects with adverse events. But because of the low sample size and the risk of type I error, subgroup analysis should be approached with caution; these analysis are merely speculative and must be followed up with confirmatory studies[16] Nevertheless, exploring trajectory groups using GBTM is advantageous in identifying more direct thresholds of compliance for establishing clinical efficacy.

Table 1. Description of the Sample[a]

Characteristic	N = 208[b]
Age (years)	69.8 ± 6.2
Gender	
Male	30 (14.4)
Female	178 (85.6)
Study Site	
Yale	66 (31.7)
UCHC	142 (68.3)
DEXA L2-4 BMD (g/cm^2)	1.2 ± 0.2
T-score	
≤ -2.5	16 (7.8)
> -2.5	188 (92.2)
Adverse Event	
Yes	82 (39.4)
No	126 (60.6)
EPESE Score	11.3 ± 1.1
History of Depression/ Anxiety	
Yes	23 (13.3)
No	150 (86.7)

[a] Table values are mean ± SD for continuous variables and n (%) for categorical variables

[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding

Table 2. Model Selection using BIC, Log Bayes Factor, and Estimated Group Proportions Using GBTM in Determining Compliance Trajectory Groups

			Estimated Group Proportions				
Number of Groups	BIC	Log Bayes Factor	Group 1	Group 2	Group 3	Group 4	Group 5
1	-4328.50		100.00				
2	-3755.63	1145.74	41.98	58.02			
3	-3722.41	66.44	40.93	16.09	42.98		
4	**-3602.30**	**240.22**	**23.50**	**36.87**	**19.81**	**19.82**	
5	-3589.89	24.82	23.62	2.14	19.29	41.05	13.90

Table 3. Final Model Containing the 4-Group Compliance Trajectories

Group	Parameter Estimate[a] (95% CI)	t-statistic	P-value
Severely Noncompliant			
Intercept	170.19 (112.87 , 227.51)	5.82	< 0.001
Linear	-52.60 (-70.43 , -34.77)	-5.78	< 0.001
Delayed Noncompliant			
Intercept	33.84 (-38.66 , 106.34)	0.92	0.361
Linear	31.96 (-0.13 , 64.05)	1.95	0.051
Quadratic	-6.15 (-9.48 , -2.82)	-3.62	< 0.001
Moderately Compliant			
Intercept	76.75 (71.35 , 82.15)	27.88	< 0.001
Near-Perfect Compliant			
Intercept	114.98 (103.31 , 126.65)	31.47	< 0.001

[a] Parameter estimates denote the differential time polynomial

Table 4. Model Diagnostics for GBTM

Group	Group Membership Model Estimates (95% CI)	Proportion Classified in Group	Average Posterior Probability[a]	Odds of Correct Classification[b]
Severely Noncompliant	0.24 (0.17 , 0.30)	0.24	0.979	156
Delayed Noncompliant	0.20 (0.14 , 0.26)	0.20	0.964	107
Moderately Compliant	0.37 (0.26 , 0.48)	0.37	0.917	19
Near-Perfect Compliant	0.20 (0.09 , 0.30)	0.20	0.858	24

[a] Average posterior probability for each group should exceed the minimum threshold of 0.7
[b] Minimum odds of correct classification should exceed 5

Table 5. Description of the Sample by Compliance Trajectory Group

Characteristic	Compliance Trajectory Groups[ab]				P-value[c]
	Severely Noncompliant (n = 49)	Delayed Noncompliant (n = 41)	Moderately Compliant (n = 76)	Near-Perfect Compliant (n = 42)	
Age	70.3 ± 6.7	69.0 ± 6.3	69.6 ± 6.4	70.6 ± 5.1	0.639
Gender					0.079
Male	7 (14.3)	3 (7.3)	9 (11.8)	11 (26.2)	
Female	42 (85.7)	38 (92.7)	67 (88.2)	31 (73.8)	
Study Site					0.944
Yale	15 (30.6)	14 (34.2)	25 (32.9)	12 (28.6)	
UCHC	34 (69.4)	27 (65.9)	51 (67.1)	30 (71.4)	
DEXA L2-4 BMD (g/cm^2)	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.3	1.2 ± 0.2	0.092
T-score					0.268
≤ -2.5	7(14.6)	3 (7.7)	4 (5.3)	2 (4.8)	
> -2.5	41 (85.4)	36 (92.3)	71 (94.7)	40 (95.2)	
Adverse Event					0.198
Yes	16 (32.7)	22 (53.7)	28 (36.8)	16 (38.1)	
No	33 (67.4)	19 (46.3)	48 (63.2)	26 (61.9)	
EPESE Score	11.3 ± 1.2	11.2 ± 1.4	11.4 ± 0.9	11.3 ± 1.1	0.719
History of Depression/ Anxiety					0.283
Yes	5 (12.2)	8 (23.5)	6 (9.4)	4 (11.8)	
No	36 (87.8)	26 (76.5)	58 (90.6)	30 (88.2)	

[a] Table values are mean ± SD for continuous variables and n (%) for categorical variables

[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding

[c] P-values are calculated using the Pearson Chi-Square or Fisher's Exact test for categorical variables and One-Way ANOVA for continuous variables

Table 6. Multinomial Logistic Regression Model 1: Predictors of Compliance Group Membership (N = 168)[ab]

	Severely Noncompliant		Delayed Noncompliant		Moderately Compliant			
Variable	AOR	95% CI	AOR	95% CI	AOR	95% CI	Wald χ^2_3	P-value
Age	1.04	(0.95 , 1.13)	1.00	(0.91 , 1.09)	1.04	(0.96 , 1.12)	1.57	0.666
Gender	0.31	(0.08 , 1.27)	0.28	(0.06 , 1.37)	0.35	(0.10 , 1.16)	4.40	0.222
Study Site	0.86	(0.23 , 3.30)	1.62	(0.44 , 6.01)	1.98	(0.64 , 6.19)	2.74	0.433
Osteoporosis (T-score)	3.36	(0.58 , 19.34)	0.81	(0.09 , 7.06)	0.40	(0.05 , 3.18)	6.96	0.073
Adverse Event	0.76	(0.28 , 2.08)	2.27	(0.81 , 6.34)	0.71	(0.29 , 1.76)	6.88	0.076
EPESE Score	0.95	(0.60 , 1.51)	0.85	(0.53 , 1.36)	1.14	(0.73 , 1.79)	1.89	0.596
History of Depression/ Anxiety	1.12	(0.27 , 4.71)	2.34	(0.60 , 9.07)	0.71	(0.17 , 2.90)	3.79	0.285

[a] Near-perfect compliant group was set as the reference group

[b] $R^2 = 0.153$; max-rescaled $R^2 = 0.164$

Table 7. Multinomial Logistic Regression Model 2: Predictors of Compliance Group Membership (N = 168)[ab]

	Severely Noncompliant		Delayed Noncompliant		Moderately Compliant			
Variable	AOR	95% CI	AOR	95% CI	AOR	95% CI	Wald χ^2_3	P-value
Age	1.04	(0.95 , 1.14)	1.00	(0.91 , 1.10)	1.02	(0.94 , 1.11)	1.22	0.748
Gender	0.36	(0.08 , 1.53)	0.31	(0.06 , 1.55)	0.26	(0.07 , 0.94)	4.76	0.190
Study Site	0.97	(0.26 , 3.62)	1.44	(0.38 , 5.47)	2.35	(0.73 , 7.57)	3.45	0.328
DEXA L2-4 BMD (g/cm^2)	0.26	(0.02 , 3.89)	0.64	(0.04 , 11.02)	6.66	(0.67 , 65.8)	8.56	0.036
Adverse Event	0.69	(0.26 , 1.87)	2.27	(0.81 , 6.35)	0.77	(0.31 , 1.91)	6.94	0.074
EPESE Score	0.94	(0.60 , 1.47)	0.85	(0.53 , 1.36)	1.18	(0.74 , 1.86)	2.24	0.524
History of Depression/ Anxiety	1.13	(0.27 , 4.73)	2.30	(0.59 , 8.94)	0.71	(0.17 , 2.90)	3.70	0.296

[a] Near-perfect compliant group was set as the reference group

[b] $R^2 = 0.162$; max-rescaled $R^2 = 0.173$

Table 8. Logistic Regression Model 1 (N = 168)[abc]

Variable	AOR (95% Confidence Interval)	P-value
Age	1.04 (0.98 , 1.10)	0.224
Gender	0.55 (0.21 , 1.44)	0.222
Study Site	1.19 (0.53 , 2.68)	0.680
Osteoporosis (T-score)	1.39 (0.38 , 5.03)	0.617
Adverse Event	0.49 (0.25 , 0.94)	0.033
EPESE Score	1.15 (0.84 , 1.57)	0.388
History of Depression/ Anxiety	0.53 (0.21 , 1.33)	0.172

[a] Adjusted odds ratios compared noncompliant to compliant group

[b] $R^2 = 0.055$; max-rescaled $R^2 = 0.075$

[c] Hosmer and Lemeshow Goodness of Fit $\chi^2_8 = 4.868$, p-value = 0.772

Table 9. Logistic Regression Model 2 (N = 168)[abc]

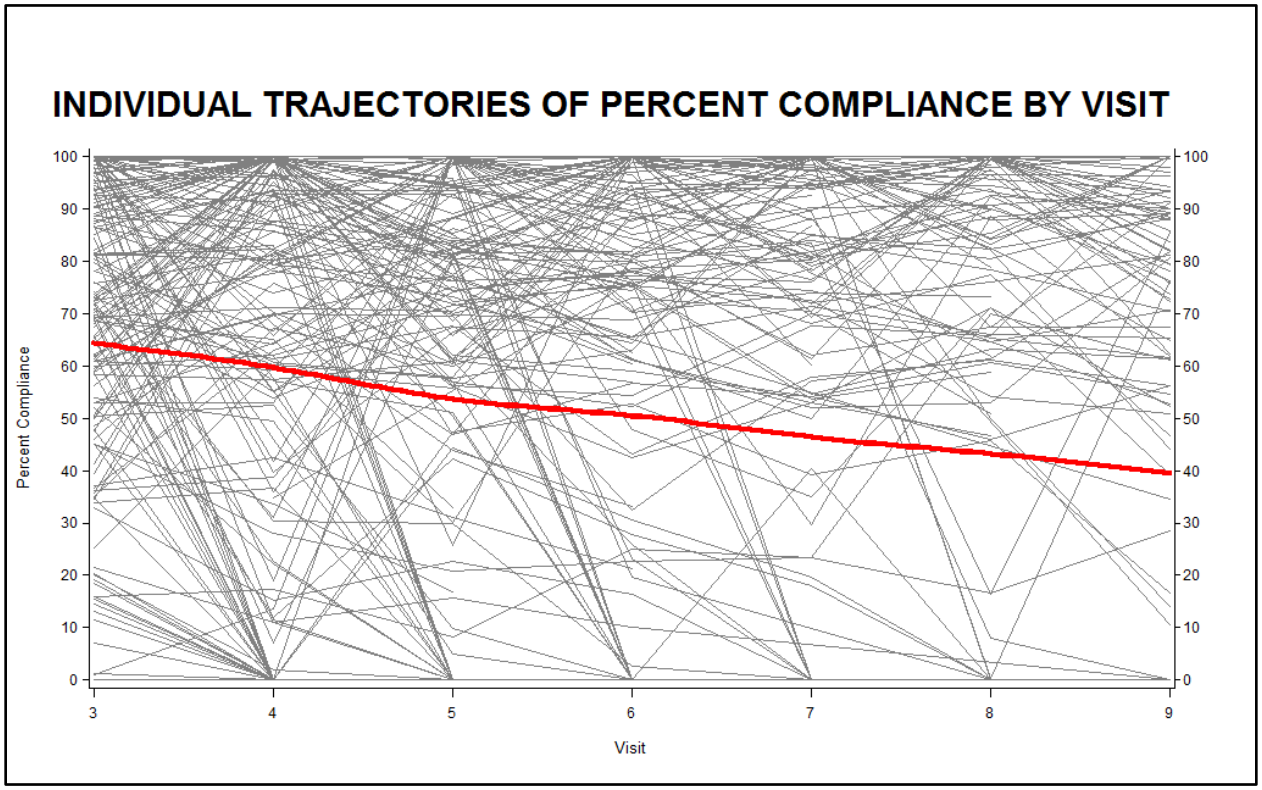
Variable	AOR (95% Confidence Interval)	P-value
Age	1.03 (0.97 , 1.09)	0.344
Gender	0.46 (0.17 , 1.27)	0.134
Study Site	1.42 (0.62 , 3.25)	0.407
DEXA L2-4 BMD (g/cm^2)	2.54 (0.46 , 13.94)	0.283
Adverse Event	0.49 (0.26 , 0.95)	0.035
EPESE Score	1.14 (0.84 , 1.56)	0.403
History of Depression/ Anxiety	0.54 (0.21 , 1.35)	0.185

[a] Adjusted odds ratios compared noncompliant to compliant group

[b] $R^2 = 0.060$; max-rescaled $R^2 = 0.082$

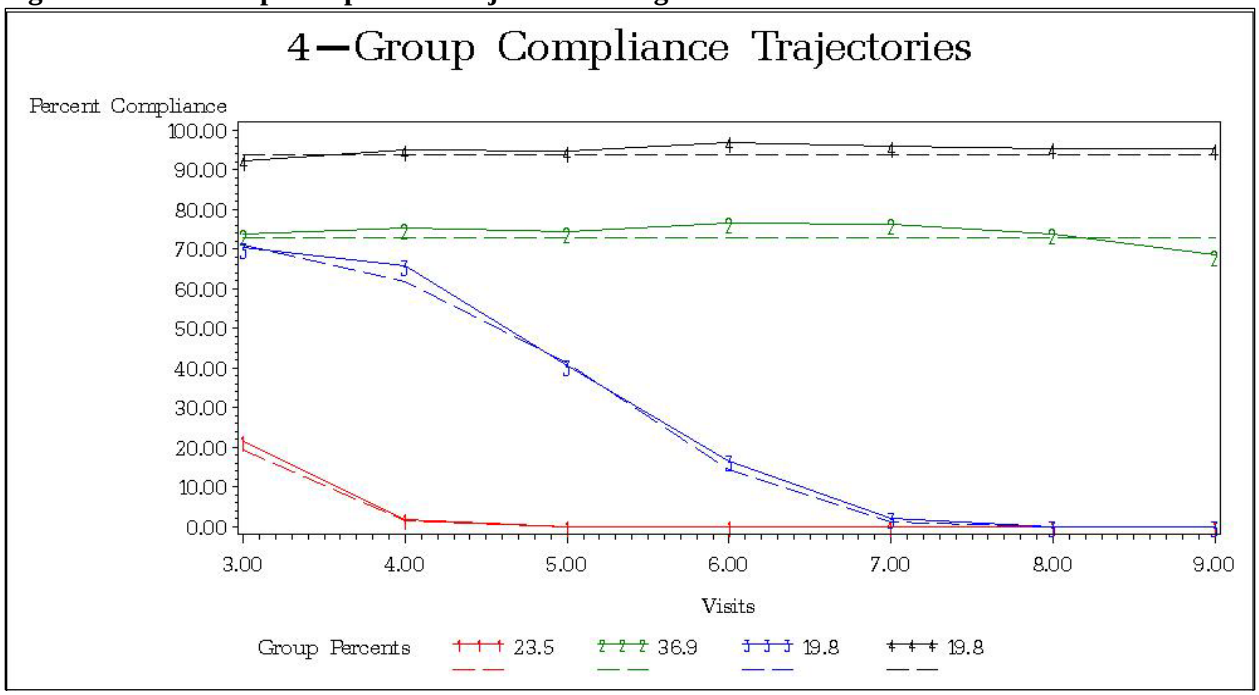
[c] Hosmer and Lemeshow Goodness of Fit $\chi^2_8 = 4.484$, p-value = 0.811

Figure 1. Individual Trajectories of Percent Compliance by Visit[a]



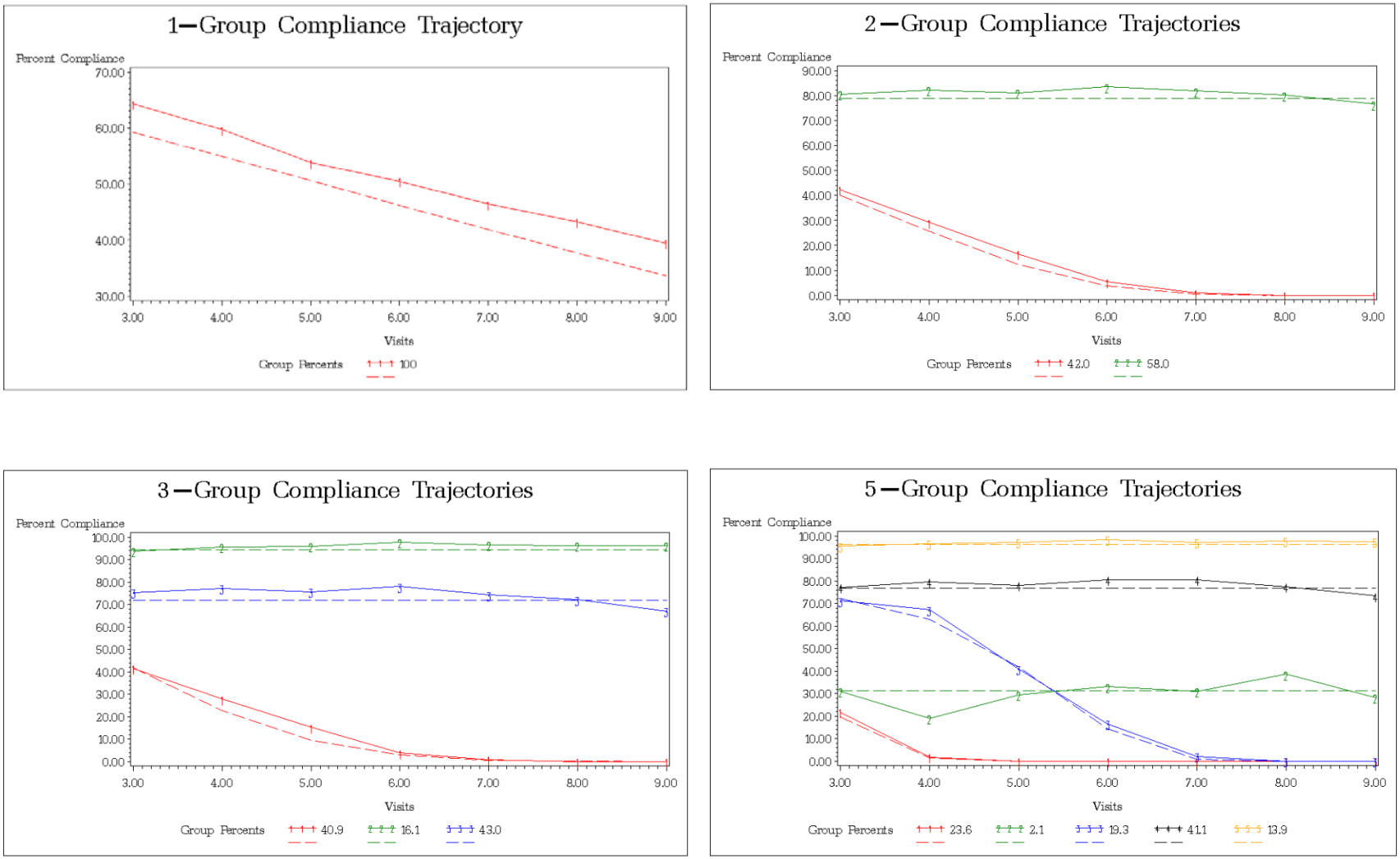
[a] Individual trajectories were plotted over the seven time points (visits) overlaid by a spline function

Figure 2. Four-Group Compliance Trajectories using GBTM[a]



[a] Dashed lines denote the fitted model using GBTM and the solid lines denote the mean percent compliance at each time point

Figure 3. One-, Two-, Three-, and Five-Group Compliance Trajectories using GBTM[a]



[a] Dashed lines denote the fitted model using GBTM and the solid lines denote the mean percent compliance at each time point

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