Final Report

Asthma Treatment Pattern Longitudinal Analysis

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1 Background and Introduction

Asthma management guidelines from the American Thoracic Society (ATS) and the Global Initiative for Asthma (GINA) suggest a stepwise therapeutic management strategy for asthma patients[1]. The guidelines suggest that if a patient is not controlled at present time, the lowest possible treatment step should be found such that control is maintained. Operationalization of treatment steps are indicated in Appendix 2.

Gap: Although operationalization of treatment steps have been defined, these treatment patterns' association with patient demographic and clinical characteristics is unknown.

In this paper, the association between treatment step patterns and patient characteristics will be examined. Additionally, the association between asthma health outcomes with the treatment step trajectory will be assessed.

Table 1: Baseline Characteristics of Study Subjects

	Baseline Treatment Steps							
	0	1	2	3	4	5	p	test
n	3896	558	187	182	143	34		
age (mean (sd))	32.19 (18.28)	28.16 (17.43)	24.53 (17.25)	29.25 (18.32)	34.09 (16.45)	41.32 (13.84)	<0.001	
Gender (%)							0.992	
F	2265 (58.0)	315 (56.5)	103 (55.1)	99 (54.4)	83 (58.0)	21 (61.8)		
M	1634 (41.9)	243 (43.5)	84 (44.9)	83 (45.6)	60 (42.0)	13 (38.2)		
pat_region (%)							0.015	
E	1115 (28.6)	149 (26.7)	56 (29.9)	37 (20.3)	34 (23.8)	13 (38.2)		
MW	1197 (30.7)	193 (34.6)	65 (34.8)	77 (42.3)	49 (34.3)	13 (38.2)		
S	1155 (29.6)	148 (26.5)	42 (22.5)	42 (23.1)	42 (29.4)	5 (14.7)		
W	429 (11.0)	68 (12.2)	24 (12.8)	26 (14.3)	18 (12.6)	3 (8.8)		
Insurance (%)							0.442	
1	3239 (83.1)	460 (82.4)	155 (82.9)	149 (81.9)	119 (83.2)	24 (70.6)		
2	12 (0.3)	5 (0.9)	1 (0.5)	1 (0.5)	1 (0.7)	0 (0.0)		
3	163 (4.2)	25 (4.5)	4 (2.1)	10 (5.5)	5 (3.5)	2 (5.9)		
4	16 (0.4)	3 (0.5)	1 (0.5)	2 (1.1)	3 (2.1)	0 (0.0)		
5	448 (11.5)	62 (11.1)	24 (12.8)	19 (10.4)	15 (10.5)	8 (23.5)		
6	18 (0.5)	3 (0.5)	2 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)		
baseline_cost (mean (sd))	2332.40 (8456.03)	1976.91 (5186.50)	1627.84 (3147.64)	2033.80 (6760.94)	2273.61 (4161.81)	3005.02 (4810.03)	0.741	
CCI (mean (sd))	0.29 (0.62)	0.15 (0.48)	0.13 (0.43)	0.20 (0.55)	0.24 (0.74)	0.35 (0.65)	<0.001	

2 Method

Data is from IMS PharMetrics Plus claims data[2]. The original data encompasses 55,870 subjects but a random sample of 5,000 subjects were sampled for the analysis. The study period is from January 2006∼December 2013. Patient inclusion/exclusion criteria are indicated in the Appendix 6.1. The primary outcomes of interest are treatment step(ordinal) and asthma health events categorized as dichotomous and nominally; No event and event (i.e. asthma-related hospitalization, asthma-related emergency department visit, asthma-related outpatient exacerbation, and outpatient visit for lower respiratory infection treated with antibiotics). Specific details of the variables are in the Appendix 6.2. After enrollment into the study (index time), the treatment step changes according to asthma severity. The initial baseline characteristics are indicated in Appendix 6.1.

Initial data summary of demographic characteristics were examined to get a sense of the underlying assumptions and trends in the data. Data were modeled using a generalized linear mixed model(GzLMM) framework for both outcomes of interests. A priori selection of covariates of interest were age, gender, charlson comorbidity index (CCI), region and insurance type.

Treatment Step Outcome Model: Polynomial effect of time(in years as continuous), from linear to sextic term, were considered for the modeling of the treatment step outcome and up to cubic term for modeling of the asthma exacerbation event. Sensitivity analyses were conducted regarding the addition of polynomial terms and indicated age, year, CCI, and insurance was

robust while gender was significant while region became insignificant beyond the quintic term. Random intercept and random slope for year by subject were incorporated. The model utilized a multinomial distribution with a cumulative logit link and assuming a proportional odds[3].
Asthma Exacerbation Outcome Model: Interaction between treatment step by year was included to allow the trajectory of treatment steps to vary over time, whereas for the treatment step outcome interaction term of different covariates by year were considered but not included due to lack of significance. Random intercept and random slope for year by subject were incorporated. Models were chosen based on AIC. A range of covariance structure for the random effects were examined that best describes the correlation of the random effects. Analysis method for exacerbation was done using both a binomial distribution (logit link) and a multinomial distribution (generalized logit link). Data were analyzed using SAS PROC GLIMMIX and R packages 'lme4'.

How was the GzLMM fit?

3 Results

The final model to identify the association between asthma treatment steps and patient characteristics is written as

$$\begin{aligned} logit(P(Y_i < c)) = \theta_c - \beta_1 baseage_i - \beta_2 CCI_i - (\beta_3 + b_{i1}) year_{ij} - \beta_4 Insurance_i - \\ gender_k - b_{i0} - \beta_5 year^2 - \beta_6 year^3 - \beta_7 year^4 - \beta_8 year^5 - \\ \beta_{10} year^6 \ i = 1, .., n; c = 1, ..., C-1 \ where \ C = 6 \ steps; k = 1, 2; l = 1, ..., r_i; \\ \theta_j = Threshold \ variable; \ b \sim N(0, G); \ G \ structure \ VC \end{aligned} \tag{1}$$

The association between year (including and all higher order polynomial terms for year), age, gender, and CCI were significantly associated with the treatment steps ($p<0.05$, Appendix 6.3.1).

With the proportional odds assumption, the odds of patients being in treatment step 0 is the highest (0.60) and being in treatment step 5 is the lowest (0.01) after adjusting for covariates. Over all response levels, 1 year increase showed smaller odds of being in greater treatment steps (1 to 5) by 0.916 times. Similarly, over all response levels, females displayed a smaller odds of being in higher treatment steps by 0.894 times. Although a very small effect, over all response levels, 1 year increase in baseline age showed greater odds of being in greater treatment steps by 1.002 times. Similarly, over all response levels, 1 unit increase in CCI showed greater odds of being in greater treatment steps by 1.053 times. Sensitivity analyses results indicate that after adding the quintic term for year, the association between gender becomes significant (previously not significant) while the effect of region becomes non-significant. The random effects covariance structure was kept as variance component (VC) due to the fact that the AIC for the VC model was better than the unstructured (UN) model.

Table 2: Proportional Odds of Treatment Step

Treatment.Step	P(Y≥x)	P(Y=x)
5	0.0064	0.01
4	0.0621	0.06
3	0.1312	0.07
2	0.2343	0.10
1	0.3963	0.16
0	1	0.60
	SUM	1.00

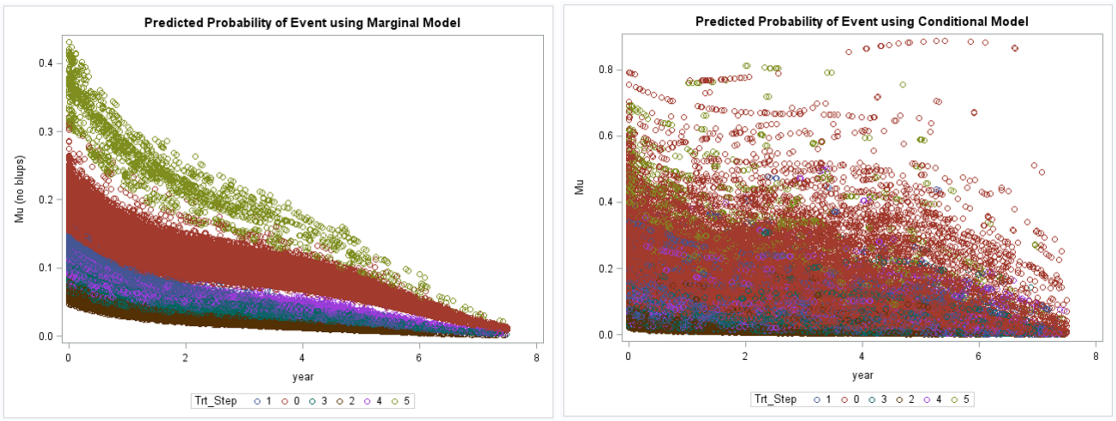
So in table it is important to define Y and x. Also, possible quick (one or 2 word) def's for treatment steps.

The final model to identify the association between asthma exacerbation events (binary) and

asthma treatment steps adjusting for relevant covariates can be written as

$$\log(\frac{p}{1-p}) = \beta_0 + \beta_1 baseage_i + \beta_2 CCI_i + \beta_3 Insurance_i + (\beta_4 + b_{i1}) year_{ij} + \tag{2}$$
$$\beta_5 year_{ij}^2 + \beta_6 year_{ij}^3 + gender_k + \beta_7 TS_{ij} + \beta_8 TS_{ij} * year_{ij} + b_{i0}$$
$$i = 1, .., n; k = 1, 2; j = 1, ..., r_i;$$

In this model, baseline age and Insurance type was not statistically significantly associated but year (and all polynomial terms for year), treatment step, year by treatment step interaction, gender, region, and CCI were statistically significantly associated (Appendix 6.3.2). Figure 1 indicates the results from the asthma exacerbation event predicted probabilities by treatment steps. The marginal model that takes into account the population average predicted values (Fig 1a) identifies higher probability of event for treatment step 5 and 0 over time compared to the other treatment steps. The conditional model (Fig 1b) is displayed to portray the difficulty in identifying any trends regarding subject-specific predicted probabilities of event over time.



(a) Marginal Model (b) Conditional Model

Figure 1: Population and Subject-specific Predicted Probabilities of Event by Treatment Step

The final model to identify the association between asthma exacerbation events (nominal) and asthma treatment steps adjusting for relevant covariates can be written as

$$\log(\frac{p_{ijc}}{p_{ij1}}) = \beta_0 + \beta_1 baseage_i + \beta_2 CCI_i + \beta_3 Insurance_i + (\beta_4 + b_{i1}) time_{ij} + \beta_5 time_{ij}^2 \tag{3}$$
$$+ \beta_6 time_{ij}^3 + gender_k + \beta_7 region_i + \beta_8 TS_{ij} + \beta_9 TS_{ij} * time_{ij} + b_{i0}$$
$$for\ c = 2, 3, .., 5;\ i = `, .., n; k = 1, 2; l = 1, ..., r_i;)$$

The generalized logit model indicates that every variable included is statistically significantly associated with asthma exacerbation event (Appendix 6.3.3). Since the interaction term is significant, compared to no asthma exacerbation event, treatment step 1 subjects have a overall lower odds of asthma exacerbation events (i.e. 0.812 times lesser odds of event 1 compared to event 0) for 1 year increase in time. Subjects with 1 unit increase in CCI value have a higher odds of event 1, 3, and 4 (1.157, 1.040, and 1.096 times greater odds) compared to no asthma exacerbation event. Females compared to males had a higher asthma exacerbation event odds compared to no asthma exacerbation event; 1.914 times greater odds of event 1 vs. 0, 1.133 times greater odds of event 2 vs. 0, 1.297 greater odds of event 3 vs. 0, and 1.253 greater odds of event 4 vs. 0.

4 Discussion

From the results indicated for the treatment steps outcome, the reduction in the odds of being in the higher treatment steps for increase in year since diagnosis and being female vs. male while increase in the odds of being in the higher treatment steps for increasing CCI and age units are clear. As indicated in Table 2, the probability of subjects being in higher treatment step is successively smaller which may be a result due to the fact that most asthma patients are in the lower treatment steps or because there are difficulties in capturing the true population of those in higher treatment steps within a claims database. The limitations to the analysis of the treatment steps may be the fact that the proportional odds assumption does not allow for different fixed or random effect slopes for each sub-models (categories of treatment steps). With more powerful (memory efficient) computing facility a nominal mixed model that estimates separate intercept, fixed, and random effects for each sub-model would allow for more flexibility.

From the results indicated for the asthma exacerbation events (binary), the plots indicate that the probability of event is highest for those in treatment step 5 and 0 which is also visible in the SAS output. This follows that an asthma exacerbation event for a typical person at one year since diagnosis with an age of 40, male, from region 4, with 1 CCI, and private insurance, in treatment step 5 can be computed as

$$\begin{aligned} \eta_{ij} &= -1.5110 - 0.5416 * 1 + 0.1472 * 1 - 0.01720 * 1 \\ &\quad + 0.8883 - 0.06917 * 1 + 0.000998 * 40 + 0.05947 * 1 \\ &= -1.0343 \\ P(Event|\eta_{ij}) &= \frac{e^{-1.0343}}{1 + e^{-1.0343}} = 0.2623 \end{aligned} \tag{4}$$

Because asthma exacerbation events are categorized into more categories, we are losing specificity and power regarding estimating each event probability thus we have used the nominal model below. What is 'below'? Are you talking about a new approach?

The generalized logit link that allows for the estimation of event probabilities indicate that for the fixed effects, all *a priori* selected covariates displayed significance. In particular, treatment step 5 compared to step 0 with regards to the odds of asthma related outpatient exacerbation (event 3) and Outpatient visit for lower respiratory tract infection (event 4) have a odds of 6.198 and 1.916, respectively after adjusting for covariates. Overall, asthma exacerbation event odds (compared to no event) are decreasing over time for each treatment steps except for slightly higher odds of event 3 for treatment steps 0, 3 and 4. An asthma-related outpatient exacerbation event for a typical person at one year since diagnosis with an age of 40, male, from region 4, with 1 CCI, and private insurance, in treatment step 5 is 0.09259 (calculation described in Appendix 6.3.5). As indicated in the calculation and the outputs, the fixed effect and random effect terms for each event (with respect to reference event 0) is estimated separately for each sub-models.
Global limitations to each models are that the sample was only a 10% simple random sample of the whole cohort of the IMS Pharmetrics Asthma population. Also the sampling population was not stratified to include equal allocation of patients within each treatment steps. Even so, the analysis did account for enough subjects within each groups through a simple random sample survey methodology thus we assume the estimation of the fixed and random effects to be robust[4]. Adherence measures was not included and may potentially effect the effects of interests[5]. Future research should focus on including additional variables that may increase the precision of the effects of interests in this analysis.

5 Reference

Articles

[1] ED1 Bateman et al. "Global strategy for asthma management and prevention: GINA executive summary". In: *European Respiratory Journal* 31.1 (2008), pp. 143–178.

[2] IMS LifeLink. "Health Plan Claims Database. Watertown, MA: PharMetrics". In: *Inc., a unit of IMS* ().

[4] KRW Brewer. "A class of robust sampling designs for large-scale surveys". In: *Journal of the American Statistical Association* 74.368 (1979), pp. 911–915.

[5] M Robin DiMatteo et al. "Patient adherence and medical treatment outcomes: a meta-analysis". In: *Medical care* 40.9 (2002), pp. 794–811.

Books

[3] Donald Hedeker. "Multilevel models for ordinal and nominal variables". In: *Handbook of multilevel analysis*. Springer, 2008, pp. 237–274.

6 Appendix

6.1 Patient Inclusion/Exclusion Criteria

Patient entry criteria:

1. evidence of asthma at least two recorded diagnosis for asthma (icd 9:493.xx) within 1 year.
2. having at least 24 months continuous eligibility after index date (follow-up period) and at least 6 months continuous eligibility before index date (pre period) environment.
3. Age 6 64 at index.

Patient exclusion criteria:

1. diagnosed with cystic fibrosis (ICD 9; 277.0x) or chronic obstructive pulmonary diseases (491.xx, 492.xx, 494.xx and 496.xx) or respiratory tract cancer (160.xx 164.xx or 231.xx) or bronchopulmonary dysplasia (770.7x) or respiratory distress syndrome (769.xx).
2. one of the following diagnoses: Addison disease (255.4x), glomerulonephritis (580.xx to 582.xx), multiple sclerosis (340.xx), polymyositis/dermatomyositis (710.3x, 710.4x), rheumatoid arthritis (714.xx), scleroderma (710.1x), Sjogren disease (710.2x), systemic lupus erythematosus (710.0x), uveitis (360.11, 363.20 364.3x), vitiligo (709.01), Wegener granulomatosis (446.4x), Primary systemic vasculitis (447.6x), Crohn?s disease (555.0x to 555.2x, 555.9x), Ulcerative colitis (556.0x to 556.6x, 556.8x, or 556.9x), Chronic eosinophilic pneumonia (518.3x), Idiopathic pulmonary fibrosis (516.3x or 515.xx), minimal change disease (581.3x), autoimmune hepatitis (571.42), Myasthenia Gravis (358.0x), Muscular dystrophy (359.0x, 359.1x, or 359.21), Still?s disease (714.2x), Churg Strauss syndrome (446.4x), Polymyalgia rheumatica (725.xx)

Index date: The first date of asthma diagnosis with 6 months eligibility before the index date (NOTE: asthma diagnosis can occur prior to the index date, however, these diagnoses would not have 6 months eligibility prior to the dates.)

6.2 Variables

Outcomes: The primary outcome of interest is a nominal variable that includes:

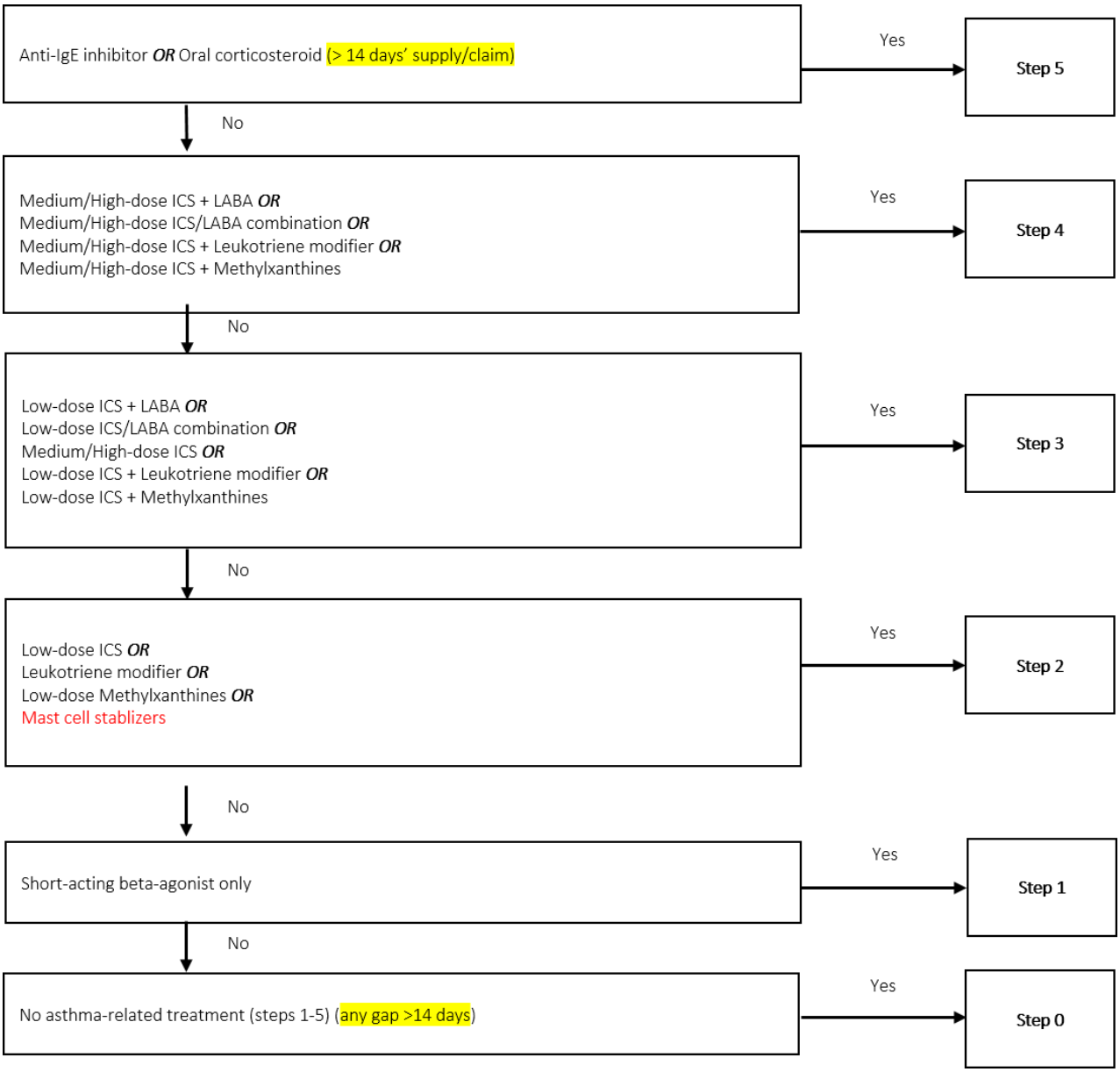
1. No event.
2. Asthma-related hospitalization.
3. Asthma-related emergency department visit.
4. Asthma-related outpatient exacerbation.
5. Outpatient visit for lower respiratory tract infection treated with antibiotics.

(See codes and definition in excel) For patients who have at least one event, we would like to have data on type of event in numeric format and number of days after the index date in numeric format. For those patients with at least one event, only the event category that are observed need to be included i.e. patients who have hospitalization and outpatient exacerbation

would only have event 1 and 3 included in the outcome file. For patient who do NOT have any events during the follow-up time, we would like to include them and have event = 0 and date = missing.

Exposure Variable: The primary exposure variable is treatment steps which is an ordinal variable characterized as:

Figure 2: Treatment Step Operationalization



6.3 Result

6.3.1 Treatment Step Outcome Model Code and Output

```
proc glimmix data=ats5k method = laplace;
class pat_id region trt_step gender (ref=first) Insurance (ref=first) ;
model trt_step(desc) = year year*year year*year*year year*year*year*year
year*year*year*year*year year*year*year*year*year*year
age gender region cci insurance / cl dist=multinomial
link=cumlogit solution oddsratio ;
random int year / subject=pat_id;
run;
```

The GLIMMIX Procedure

Model Information	
Data Set	WORK.ATS5K
Response Variable	Trt_Step
Response Distribution	Multinomial (ordered)
Link Function	Cumulative Logit
Variance Function	Default
Variance Matrix Blocked By	pat_id
Estimation Technique	Maximum Likelihood
Likelihood Approximation	Laplace
Degrees of Freedom Method	Containment

Class Level Information		
Class	**Levels**	**Values**
pat_id	5000	not printed
region	4	1 2 3 4
Trt_Step	6	5 4 3 2 1 0
gender	2	2 1
Insurance	6	2 3 4 5 6 1

Number of Observations Read	127071
Number of Observations Used	127071

Response Profile		
Ordered Value	**Trt_Step**	**Total Frequency**
1	5	2007
2	4	14746
3	3	14382
4	2	16983
5	1	21567
6	0	57386

The GLIMMIX procedure is modeling the probabilities of levels of Trt_Step having lower Ordered Values in the Response Profile table.

The GLIMMIX Procedure

Dimensions	
G-side Cov. Parameters	2
Columns in X	25
Columns in Z per Subject	2
Subjects (Blocks in V)	5000
Max Obs per Subject	218

Optimization Information	
Optimization Technique	Dual Quasi-Newton
Parameters in Optimization	24
Lower Boundaries	2
Upper Boundaries	0
Fixed Effects	Not Profiled
Starting From	GLM estimates

Iteration History					
Iteration	**Restarts**	**Evaluations**	**Objective Function**	**Change**	**Max Gradient**
0	**0**	4	369727.82762	.	27463999
1	**0**	20	369650.23517	77.59244562	1269214
2	**0**	3	369531.90241	118.33276105	952914.5
3	**0**	4	368944.10694	587.79546886	4742728
4	**0**	2	368938.31124	5.79570191	177018.9
5	**0**	4	368926.54894	11.76229713	8425602
6	**0**	4	368832.92388	93.62506896	3593685
7	**0**	3	368815.67325	17.25062600	3858958
8	**0**	3	368809.86226	5.81098492	1639345
9	**0**	4	368776.64285	33.21941786	967411.3
10	**0**	3	368766.46638	10.17647134	1093555
11	**0**	3	368761.87798	4.58840009	1154419
12	**0**	4	368735.51094	26.36703151	6193821
13	**0**	2	368689.60041	45.91052998	1993494
14	**0**	2	368609.53827	80.06214343	12169852
15	**0**	2	368474.21266	135.32561281	15493797
16	**0**	3	368382.32337	91.88928765	3047879
17	**0**	3	368376.9189	5.40446605	368707.7
18	**0**	3	368375.49548	1.42342215	56936.47
19	**0**	3	368375.12272	0.37276638	238308.7

The GLIMMIX Procedure

Iteration History					
Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
20	0	4	368368.66085	6.46186168	1198528
21	0	2	368358.27116	10.38969221	200638.4
22	0	4	368330.43835	27.83281178	2050466
23	0	2	368295.29415	35.14420311	917311.3
24	0	3	368291.87525	3.41889758	115156.6
25	0	3	368291.56566	0.30958581	57880.58
26	0	2	368291.17988	0.38578593	307823.3
27	0	6	368278.89074	12.28913823	1137693
28	0	3	368272.70706	6.18368094	64378.17
29	0	3	368270.54988	2.15717882	460457.9
30	0	3	368270.05868	0.49120186	5863.071
31	0	2	368270.00698	0.05169391	60806.76
32	0	4	368269.73194	0.27504285	46274.01
33	0	8	368209.36182	60.37011939	3804796
34	0	3	368202.15136	7.21046506	26366.22
35	0	3	368202.07224	0.07911162	41608.5
36	0	4	368201.22566	0.84658907	387083.2
37	0	2	368199.98593	1.23972886	43344.37
38	0	2	368198.08396	1.90196335	669240.2
39	0	2	368194.92194	3.16202421	385278.2
40	0	3	368193.43504	1.48689824	151122.2
41	0	2	368190.8609	2.57413804	72778.56
42	0	4	368174.77244	16.08846525	13213.17
43	0	2	368160.6776	14.09484081	162067.5
44	0	3	368159.56421	1.11338983	62536.92
45	0	3	368159.53538	0.02882947	1665.365
46	0	2	368159.52157	0.01381007	5266.117

Convergence criterion (GCONV=1E-8) satisfied.

Fit Statistics	
-2 Log Likelihood	368159.5
AIC (smaller is better)	368207.5
AICC (smaller is better)	368207.5
BIC (smaller is better)	368363.9

The GLIMMIX Procedure

Fit Statistics	
CAIC (smaller is better)	368387.9
HQIC (smaller is better)	368262.3

Fit Statistics for Conditional Distribution	
-2 log L(Trt_Step | r. effects)	358054.0

Covariance Parameter Estimates			
Cov Parm	Subject	Estimate	Standard Error
Intercept	pat_id	0.3364	0.01319
year	pat_id	0.02498	0.002144

Solutions for Fixed Effects												
Effect	Trt_Step	region	gender	Insurance	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept	5				-5.0425	0.04084	4988	-123.48	<.0001	0.05	-5.1226	-4.9624
Intercept	4				-2.7135	0.03489	4988	-77.77	<.0001	0.05	-2.7819	-2.6451
Intercept	3				-1.8896	0.03439	4988	-54.95	<.0001	0.05	-1.9570	-1.8222
Intercept	2				-1.1840	0.03414	4988	-34.68	<.0001	0.05	-1.2509	-1.1170
Intercept	1				-0.4209	0.03403	4988	-12.37	<.0001	0.05	-0.4877	-0.3542
year					2.2785	0.06234	5000	36.55	<.0001	0.05	2.1563	2.4007
year*year					-2.8209	0.06730	117E3	-41.91	<.0001	0.05	-2.9528	-2.6889
year*year*year					1.4492	0.02791	117E3	51.92	<.0001	0.05	1.3945	1.5039
year*year*year*year					-0.3642	0.004869	117E3	-74.80	<.0001	0.05	-0.3738	-0.3547
yea*yea*yea*yea*year					0.04381	0.000298	117E3	146.77	<.0001	0.05	0.04322	0.04439
ye*ye*ye*yea*yea*yea					-0.00202	0	117E3	-Infty	<.0001	.	.	.
age					0.001777	0.000674	117E3	2.64	0.0084	0.05	0.000456	0.003097
gender			2		-0.1120	0.02416	117E3	-4.64	<.0001	0.05	-0.1593	-0.06465
gender			1		0	.	.	.	.	.	.	.
region		1			-0.00330	0.03173	117E3	-0.10	0.9171	0.05	-0.06550	0.05889
region		2			0.04494	0.03015	117E3	1.49	0.1360	0.05	-0.01414	0.1040
region		3			0.04778	0.04135	117E3	1.16	0.2479	0.05	-0.03327	0.1288
region		4			0	.	.	.	.	.	.	.
CCI					0.05195	0.01869	117E3	2.78	0.0054	0.05	0.01531	0.08858
Insurance				2	0.05794	0.1295	117E3	0.45	0.6545	0.05	-0.1958	0.3117
Insurance				3	-0.1135	0.05802	117E3	-1.96	0.0504	0.05	-0.2272	0.000198
Insurance				4	-0.2690	0.1623	117E3	-1.66	0.0974	0.05	-0.5870	0.04905

The GLIMMIX Procedure

Solutions for Fixed Effects

Effect	Trt_Step	region	gender	Insurance	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Insurance				5	-0.05288	0.03681	117E3	-1.44	0.1508	0.05	-0.1250	0.01925
Insurance				6	-0.08152	0.1738	117E3	-0.47	0.6391	0.05	-0.4223	0.2592
Insurance				1	0	.	.	.	.	.	.	.

The GLIMMIX Procedure

Odds Ratio Estimates

region	gender	Insurance	year	age	CCI	_region	_gender	_Insurance	_year	_age	_CCI	Estimate	DF
			2.8235	31.308	0.3256				1.8235	31.308	0.3256	0.916	5000
			1.8235	32.308	0.3256				1.8235	31.308	0.3256	1.002	117E3
			1.8235	31.308	1.3256				1.8235	31.308	0.3256	1.053	117E3
	2		1.8235	31.308	0.3256		1		1.8235	31.308	0.3256	0.894	117E3
1			1.8235	31.308	0.3256	4			1.8235	31.308	0.3256	0.997	117E3
2			1.8235	31.308	0.3256	4			1.8235	31.308	0.3256	1.046	117E3
3			1.8235	31.308	0.3256	4			1.8235	31.308	0.3256	1.049	117E3
		2	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	1.060	117E3
		3	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.893	117E3
		4	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.764	117E3
		5	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.948	117E3
		6	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.922	117E3

Effects of continuous variables are assessed as one unit offsets from the mean.
The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

Odds Ratio Estimates

region	gender	Insurance	year	age	CCI	_region	_gender	_Insurance	_year	_age	_CCI	95% Confidence Limits	
			2.8235	31.308	0.3256				1.8235	31.308	0.3256	0.896	0.936
			1.8235	32.308	0.3256				1.8235	31.308	0.3256	1.000	1.003
			1.8235	31.308	1.3256				1.8235	31.308	0.3256	1.015	1.093
	2		1.8235	31.308	0.3256		1		1.8235	31.308	0.3256	0.853	0.937
1			1.8235	31.308	0.3256	4			1.8235	31.308	0.3256	0.937	1.061
2			1.8235	31.308	0.3256	4			1.8235	31.308	0.3256	0.986	1.110
3			1.8235	31.308	0.3256	4			1.8235	31.308	0.3256	0.967	1.138
		2	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.822	1.366
		3	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.797	1.000
		4	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.556	1.050
		5	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.882	1.019
		6	1.8235	31.308	0.3256			1	1.8235	31.308	0.3256	0.656	1.296

Effects of continuous variables are assessed as one unit offsets from the mean.
The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

The GLIMMIX Procedure

Type III Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
year	1	5000	1336.14	<.0001
year*year	1	117E3	1756.85	<.0001
year*year*year	1	117E3	2695.29	<.0001
year*year*year*year	1	117E3	5594.35	<.0001
yea*yea*yea*yea*year	1	117E3	21540.1	<.0001
ye*ye*ye*yea*yea*yea	1	117E3	Infty	<.0001
age	1	117E3	6.96	0.0084
gender	1	117E3	21.49	<.0001
region	3	117E3	1.30	0.2720
CCI	1	117E3	7.72	0.0054
Insurance	5	117E3	1.72	0.1263

6.3.2 Asthma Exacerbation Outcome (Binary) Model Code and Output

```
proc glimmix data=ats5k method=laplace;
class pat_id region trt_step (ref=first) gender (ref=first) Insurance (ref=first);
model eventb(descending)= year year*year year*year*year trt_step year*trt_step
age gender region cci insurance / cl dist=binary link=logit solution oddsratio;
random intercept year / subject=pat_id type=vc;
output out=glimmixout    pred( blup ilink)=PredProb
                                                    pred(noblup ilink)=PredProb_PA
                                                    lcl( blup ilink)=lclpp
                                                    lcl(noblup ilink)=lclpp_pa
                                                    ucl( blup ilink)=uclpp
                                                    ucl(noblup ilink)=uclpp_pa
;
run;
```

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Model Information	
Data Set	WORK.ATS5K
Response Variable	eventb
Response Distribution	Binary
Link Function	Logit
Variance Function	Default
Variance Matrix Blocked By	pat_id
Estimation Technique	Maximum Likelihood
Likelihood Approximation	Laplace
Degrees of Freedom Method	Containment

Class Level Information		
Class	**Levels**	**Values**
pat_id	5000	not printed
region	4	1 2 3 4
Trt_Step	6	1 2 3 4 5 0
gender	2	2 1
Insurance	6	2 3 4 5 6 1

Number of Observations Read	127071
Number of Observations Used	127071

Response Profile		
Ordered Value	**eventb**	**Total Frequency**
1	1	13128
2	0	113943
The GLIMMIX procedure is modeling the probability that eventb='1'.		

Dimensions	
G-side Cov. Parameters	2
Columns in X	30
Columns in Z per Subject	2
Subjects (Blocks in V)	5000
Max Obs per Subject	218

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Optimization Information	
Optimization Technique	Dual Quasi-Newton
Parameters in Optimization	27
Lower Boundaries	2
Upper Boundaries	0
Fixed Effects	Not Profiled
Starting From	GLM estimates

Iteration History

Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
0	**0**	4	76144.460312	.	70029.53
1	**0**	6	76023.389369	121.07094242	16801.61
2	**0**	2	76014.653041	8.73632868	5370.165
3	**0**	2	76012.460215	2.19282557	2906.322
4	**0**	2	76011.600469	0.85974634	1801.538
5	**0**	4	76011.090612	0.50985703	2382.051
6	**0**	4	76003.61545	7.47516172	9530.061
7	**0**	2	76000.009805	3.60564455	10484.17
8	**0**	2	75995.250587	4.75921839	925.1498
9	**0**	2	75990.268614	4.98197330	2903.227
10	**0**	3	75989.869417	0.39919699	340.0565
11	**0**	2	75989.748126	0.12129070	1715.753
12	**0**	4	75988.019397	1.72872906	4483.81
13	**0**	4	75981.146818	6.87257944	8926.001
14	**0**	4	75963.797188	17.34962996	967.9277
15	**0**	3	75963.555641	0.24154688	992.339
16	**0**	4	75962.937548	0.61809276	1404.775
17	**0**	4	75953.196539	9.74100853	3215.378
18	**0**	2	75937.325966	15.87057368	1484.145
19	**0**	3	75933.067523	4.25844284	1290.764
20	**0**	3	75932.649541	0.41798159	242.4842
21	**0**	3	75932.616854	0.03268745	239.0126
22	**0**	4	75932.483975	0.13287850	641.5407
23	**0**	4	75932.170776	0.31319920	428.6978
24	**0**	6	75923.83339	8.33738637	4723.262
25	**0**	3	75919.056495	4.77689465	622.6395

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Iteration History					
Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
26	**0**	2	75916.090711	2.96578452	2261.725
27	**0**	3	75915.572808	0.51790258	152.1451
28	**0**	3	75915.566189	0.00661876	154.9122
29	**0**	6	75915.403784	0.16240499	690.5761
30	**0**	2	75915.204937	0.19884775	149.893
31	**0**	4	75913.394297	1.81063969	959.4266
32	**0**	2	75912.476147	0.91814989	626.521
33	**0**	2	75912.031865	0.44428165	535.9055
34	**0**	2	75911.523147	0.50871822	172.3872
35	**0**	4	75910.113745	1.40940221	502.2428
36	**0**	3	75909.608113	0.50563187	55.25517
37	**0**	3	75909.605968	0.00214496	56.4542
38	**0**	6	75909.293927	0.31204097	380.0369
39	**0**	3	75909.078907	0.21502000	51.39027
40	**0**	4	75908.559092	0.51981484	751.1296
41	**0**	2	75908.068145	0.49094751	269.6479
42	**0**	3	75907.889671	0.17847386	208.7954
43	**0**	4	75905.791384	2.09828671	164.8597
44	**0**	3	75905.766933	0.02445116	55.41086
45	**0**	3	75905.765529	0.00140393	55.72902
46	**0**	4	75905.750032	0.01549737	61.58598
47	**0**	4	75905.686432	0.06359955	47.76409
48	**0**	6	75903.947082	1.73935051	1158.749
49	**0**	3	75903.827241	0.11984031	96.48244
50	**0**	3	75903.823133	0.00410818	107.9256
51	**0**	2	75903.819893	0.00323991	49.14238
52	**0**	3	75903.819108	0.00078548	33.35748
53	**0**	8	75902.887147	0.93196034	460.5382

Convergence criterion (GCONV=1E-8) satisfied.

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Fit Statistics	
-2 Log Likelihood	75902.89
AIC (smaller is better)	75956.89
AICC (smaller is better)	75956.90
BIC (smaller is better)	76132.85
CAIC (smaller is better)	76159.85
HQIC (smaller is better)	76018.56

Fit Statistics for Conditional Distribution	
-2 log L(eventb | r. effects)	68450.53
Pearson Chi-Square	102022.4
Pearson Chi-Square / DF	0.80

Covariance Parameter Estimates			
Cov Parm	Subject	Estimate	Standard Error
Intercept	pat_id	0.6367	0.02955
year	pat_id	0.05044	0.005702

Solutions for Fixed Effects												
Effect	region	Trt_Step	gender	Insurance	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept					-1.5110	0.05023	4989	-30.08	<.0001	0.05	-1.6094	-1.4125
year					-0.5416	0.04076	4999	-13.29	<.0001	0.05	-0.6215	-0.4617
year*year					0.1472	0.01852	117E3	7.95	<.0001	0.05	0.1109	0.1835
year*year*year					-0.01720	0.002183	117E3	-7.88	<.0001	0.05	-0.02148	-0.01292
Trt_Step		1			-0.5221	0.04267	117E3	-12.24	<.0001	0.05	-0.6057	-0.4385
Trt_Step		2			-1.2339	0.06396	117E3	-19.29	<.0001	0.05	-1.3593	-1.1085
Trt_Step		3			-0.9512	0.06169	117E3	-15.42	<.0001	0.05	-1.0721	-0.8303
Trt_Step		4			-0.8203	0.06046	117E3	-13.57	<.0001	0.05	-0.9388	-0.7018
Trt_Step		5			0.8883	0.08866	117E3	10.02	<.0001	0.05	0.7146	1.0621
Trt_Step		0			0	.	.	.	.	.	.	.
year*Trt_Step		1			-0.1134	0.02169	117E3	-5.23	<.0001	0.05	-0.1559	-0.07088
year*Trt_Step		2			-0.1363	0.03540	117E3	-3.85	0.0001	0.05	-0.2056	-0.06689
year*Trt_Step		3			-0.03052	0.02990	117E3	-1.02	0.3074	0.05	-0.08913	0.02809
year*Trt_Step		4			-0.00506	0.02736	117E3	-0.19	0.8532	0.05	-0.05868	0.04855
year*Trt_Step		5			-0.06917	0.03940	117E3	-1.76	0.0792	0.05	-0.1464	0.008053

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Solutions for Fixed Effects												
Effect	region	Trt_Step	gender	Insurance	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
year*Trt_Step		0			0	.	.	.	.	.	.	.
age					0.000998	0.000999	117E3	1.00	0.3176	0.05	-0.00096	0.002956
gender			2		0.2368	0.03597	117E3	6.58	<.0001	0.05	0.1663	0.3073
gender			1		0	.	.	.	.	.	.	.
region	1				-0.1722	0.04666	117E3	-3.69	0.0002	0.05	-0.2636	-0.08070
region	2				-0.1979	0.04439	117E3	-4.46	<.0001	0.05	-0.2849	-0.1109
region	3				-0.1975	0.06160	117E3	-3.21	0.0013	0.05	-0.3182	-0.07672
region	4				0	.	.	.	.	.	.	.
CCI					0.05947	0.02703	117E3	2.20	0.0278	0.05	0.006493	0.1124
Insurance				2	-0.1004	0.1988	117E3	-0.50	0.6136	0.05	-0.4901	0.2893
Insurance				3	0.02018	0.08727	117E3	0.23	0.8172	0.05	-0.1509	0.1912
Insurance				4	-0.05596	0.2429	117E3	-0.23	0.8178	0.05	-0.5320	0.4201
Insurance				5	0.07230	0.05413	117E3	1.34	0.1817	0.05	-0.03379	0.1784
Insurance				6	-0.01448	0.2647	117E3	-0.05	0.9564	0.05	-0.5333	0.5043
Insurance				1	0	.	.	.	.	.	.	.

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Odds Ratio Estimates													
region	Trt_Step	gender	Insurance	year	age	CCI	_region	_Trt_Step	_gender	_Insurance	_year	_age	_CCI
				1.8235	32.308	0.3256					1.8235	31.308	0.3256
				1.8235	31.308	1.3256					1.8235	31.308	0.3256
	1			1.8235	31.308	0.3256		0			1.8235	31.308	0.3256
	2			1.8235	31.308	0.3256		0			1.8235	31.308	0.3256
	3			1.8235	31.308	0.3256		0			1.8235	31.308	0.3256
	4			1.8235	31.308	0.3256		0			1.8235	31.308	0.3256
	5			1.8235	31.308	0.3256		0			1.8235	31.308	0.3256
	1			2.8235	31.308	0.3256		1			1.8235	31.308	0.3256
	2			2.8235	31.308	0.3256		2			1.8235	31.308	0.3256
	3			2.8235	31.308	0.3256		3			1.8235	31.308	0.3256
	4			2.8235	31.308	0.3256		4			1.8235	31.308	0.3256
	5			2.8235	31.308	0.3256		5			1.8235	31.308	0.3256
	0			2.8235	31.308	0.3256		0			1.8235	31.308	0.3256
		2		1.8235	31.308	0.3256			1		1.8235	31.308	0.3256
1				1.8235	31.308	0.3256	4				1.8235	31.308	0.3256
2				1.8235	31.308	0.3256	4				1.8235	31.308	0.3256
3				1.8235	31.308	0.3256	4				1.8235	31.308	0.3256
			2	1.8235	31.308	0.3256				1	1.8235	31.308	0.3256
			3	1.8235	31.308	0.3256				1	1.8235	31.308	0.3256
			4	1.8235	31.308	0.3256				1	1.8235	31.308	0.3256
			5	1.8235	31.308	0.3256				1	1.8235	31.308	0.3256
			6	1.8235	31.308	0.3256				1	1.8235	31.308	0.3256

Effects of continuous variables are assessed as one unit offsets from the mean.
The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Odds Ratio Estimates													
region	Trt_Step	gender	Insurance	year	age	CCI	_region	_Trt_Step	_gender	_Insurance	_year	_age	Estimate
				1.8235	32.308	0.3256					1.8235	31.308	1.001
				1.8235	31.308	1.3256					1.8235	31.308	1.061
	1			1.8235	31.308	0.3256		0			1.8235	31.308	0.482
	2			1.8235	31.308	0.3256		0			1.8235	31.308	0.227
	3			1.8235	31.308	0.3256		0			1.8235	31.308	0.365
	4			1.8235	31.308	0.3256		0			1.8235	31.308	0.436
	5			1.8235	31.308	0.3256		0			1.8235	31.308	2.143
	1			2.8235	31.308	0.3256		1			1.8235	31.308	0.776
	2			2.8235	31.308	0.3256		2			1.8235	31.308	0.758
	3			2.8235	31.308	0.3256		3			1.8235	31.308	0.843
	4			2.8235	31.308	0.3256		4			1.8235	31.308	0.865
	5			2.8235	31.308	0.3256		5			1.8235	31.308	0.811
	0			2.8235	31.308	0.3256		0			1.8235	31.308	0.869
		2		1.8235	31.308	0.3256			1		1.8235	31.308	1.267
1				1.8235	31.308	0.3256	4				1.8235	31.308	0.842
2				1.8235	31.308	0.3256	4				1.8235	31.308	0.820
3				1.8235	31.308	0.3256	4				1.8235	31.308	0.821
			2	1.8235	31.308	0.3256				1	1.8235	31.308	0.904
			3	1.8235	31.308	0.3256				1	1.8235	31.308	1.020
			4	1.8235	31.308	0.3256				1	1.8235	31.308	0.946
			5	1.8235	31.308	0.3256				1	1.8235	31.308	1.075
			6	1.8235	31.308	0.3256				1	1.8235	31.308	0.986

Effects of continuous variables are assessed as one unit offsets from the mean.
The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Odds Ratio Estimates													
region	Trt_Step	gender	Insurance	year	age	CCI	_region	_Trt_Step	_gender	_Insurance	_year	_age	DF
				1.8235	32.308	0.3256					1.8235	31.308	117E3
				1.8235	31.308	1.3256					1.8235	31.308	117E3
	1			1.8235	31.308	0.3256		0			1.8235	31.308	117E3
	2			1.8235	31.308	0.3256		0			1.8235	31.308	117E3
	3			1.8235	31.308	0.3256		0			1.8235	31.308	117E3
	4			1.8235	31.308	0.3256		0			1.8235	31.308	117E3
	5			1.8235	31.308	0.3256		0			1.8235	31.308	117E3
	1			2.8235	31.308	0.3256		1			1.8235	31.308	117E3
	2			2.8235	31.308	0.3256		2			1.8235	31.308	117E3
	3			2.8235	31.308	0.3256		3			1.8235	31.308	117E3
	4			2.8235	31.308	0.3256		4			1.8235	31.308	117E3
	5			2.8235	31.308	0.3256		5			1.8235	31.308	117E3
	0			2.8235	31.308	0.3256		0			1.8235	31.308	117E3
		2		1.8235	31.308	0.3256			1		1.8235	31.308	117E3
1				1.8235	31.308	0.3256	4				1.8235	31.308	117E3
2				1.8235	31.308	0.3256	4				1.8235	31.308	117E3
3				1.8235	31.308	0.3256	4				1.8235	31.308	117E3
			2	1.8235	31.308	0.3256				1	1.8235	31.308	117E3
			3	1.8235	31.308	0.3256				1	1.8235	31.308	117E3
			4	1.8235	31.308	0.3256				1	1.8235	31.308	117E3
			5	1.8235	31.308	0.3256				1	1.8235	31.308	117E3
			6	1.8235	31.308	0.3256				1	1.8235	31.308	117E3

Effects of continuous variables are assessed as one unit offsets from the mean.
The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Odds Ratio Estimates

region	Trt_Step	gender	Insurance	year	age	CCI	_region	_Trt_Step	_gender	_Insurance	_year	_age	95% Confidence Limits	
				1.8235	32.308	0.3256					1.8235	31.308	0.999	1.003
				1.8235	31.308	1.3256					1.8235	31.308	1.007	1.119
	1			1.8235	31.308	0.3256		0			1.8235	31.308	0.454	0.513
	2			1.8235	31.308	0.3256		0			1.8235	31.308	0.207	0.249
	3			1.8235	31.308	0.3256		0			1.8235	31.308	0.335	0.398
	4			1.8235	31.308	0.3256		0			1.8235	31.308	0.403	0.472
	5			1.8235	31.308	0.3256		0			1.8235	31.308	1.901	2.416
	1			2.8235	31.308	0.3256		1			1.8235	31.308	0.738	0.816
	2			2.8235	31.308	0.3256		2			1.8235	31.308	0.704	0.816
	3			2.8235	31.308	0.3256		3			1.8235	31.308	0.791	0.899
	4			2.8235	31.308	0.3256		4			1.8235	31.308	0.815	0.917
	5			2.8235	31.308	0.3256		5			1.8235	31.308	0.747	0.880
	0			2.8235	31.308	0.3256		0			1.8235	31.308	0.839	0.900
		2		1.8235	31.308	0.3256			1		1.8235	31.308	1.181	1.360
1				1.8235	31.308	0.3256	4				1.8235	31.308	0.768	0.922
2				1.8235	31.308	0.3256	4				1.8235	31.308	0.752	0.895
3				1.8235	31.308	0.3256	4				1.8235	31.308	0.727	0.926
			2	1.8235	31.308	0.3256				1	1.8235	31.308	0.613	1.336
			3	1.8235	31.308	0.3256				1	1.8235	31.308	0.860	1.211
			4	1.8235	31.308	0.3256				1	1.8235	31.308	0.587	1.522
			5	1.8235	31.308	0.3256				1	1.8235	31.308	0.967	1.195
			6	1.8235	31.308	0.3256				1	1.8235	31.308	0.587	1.656

Effects of continuous variables are assessed as one unit offsets from the mean.
The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

Type III Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
year	1	4999	206.10	<.0001
year*year	1	117E3	63.18	<.0001
year*year*year	1	117E3	62.04	<.0001
Trt_Step	5	117E3	181.38	<.0001
year*Trt_Step	5	117E3	8.15	<.0001
age	1	117E3	1.00	0.3176
gender	1	117E3	43.34	<.0001

Predicted Probability of Event using Marginal Model

The GLIMMIX Procedure

Type III Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
region	3	117E3	8.17	<.0001
CCI	1	117E3	4.84	0.0278
Insurance	5	117E3	0.44	0.8176

6.3.3 Asthma Exacerbation Outcome (Nominal) Model Code and Output

```
proc glimmix data=ats5k method=laplace;
class pat_id region trt_step (ref=first) gender (ref=first)
 Insurance (ref=first) event(ref=first);
model event(event=first)= year year*year year*year*year trt_step
year*trt_step age gender cci / cl dist=multinomial link=glogit solution oddsratio;
random intercept / subject=pat_id type=vc group=event;
output out=glimouth2     pred( blup ilink)=PredProb
                                                pred(noblup ilink)=PredProb_PA;
run;
```

The GLIMMIX Procedure

Model Information	
Data Set	WORK.ATS5K
Response Variable	Event
Response Distribution	Multinomial (nominal)
Link Function	Generalized Logit
Variance Function	Default
Variance Matrix Blocked By	pat_id
Estimation Technique	Maximum Likelihood
Likelihood Approximation	Laplace
Degrees of Freedom Method	Containment

Class Level Information		
Class	**Levels**	**Values**
pat_id	5000	not printed
region	4	1 2 3 4
Trt_Step	6	1 2 3 4 5 0
gender	2	2 1
Insurance	6	2 3 4 5 6 1
Event	5	0 1 2 3 4

Number of Observations Read	127071
Number of Observations Used	127071

Response Profile		
Ordered Value	**Event**	**Total Frequency**
1	0	113943
2	1	1506
3	2	2569
4	3	3671
5	4	5382
In modeling category probabilities, Event='0' serves as the reference category.		

The GLIMMIX Procedure

Dimensions	
G-side Cov. Parameters	4
Columns in X	80
Columns in Z per Subject	4
Subjects (Blocks in V)	5000
Max Obs per Subject	218

Optimization Information	
Optimization Technique	Dual Quasi-Newton
Parameters in Optimization	72
Lower Boundaries	4
Upper Boundaries	0
Fixed Effects	Not Profiled
Starting From	GLM estimates

The GLIMMIX Procedure

Iteration History					
Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
0	0	4	109293.15353	.	47682.7
1	0	8	108763.82019	529.33334827	61676.87
2	0	2	108227.76892	536.05126327	23895.05
3	0	2	108123.56099	104.20793610	28482.59
4	0	2	108064.58722	58.97376548	12648.89
5	0	2	108044.04682	20.54039880	4151.284
6	0	3	108037.44822	6.59860766	2181.349
7	0	3	108035.29903	2.14918894	716.7374
8	0	2	108033.8504	1.44862895	4479.968
9	0	4	108027.91898	5.93141370	2779.14
10	0	4	107972.31901	55.59997737	3753.409
11	0	3	107967.82249	4.49651496	992.1321
12	0	3	107966.86985	0.95263999	1283.915
13	0	4	107964.29025	2.57960401	2859.16
14	0	6	107799.62275	164.66749828	24524.53
15	0	3	107714.0117	85.61105259	5046.863
16	0	3	107695.157	18.85470009	2654.59
17	0	2	107663.88391	31.27308448	6129.069
18	0	2	107636.39251	27.49140574	5197.68
19	0	3	107628.96517	7.42734009	1675.965
20	0	2	107616.8998	12.06536426	3621.775
21	0	4	107500.49777	116.40203037	28161.79
22	0	2	107384.40234	116.09543203	17690.38
23	0	3	107358.57227	25.83007408	4427.178
24	0	3	107355.57286	2.99940777	984.0913
25	0	3	107354.42479	1.14807133	2059.864
26	0	6	107314.7078	39.71698346	9576.635
27	0	2	107279.16866	35.53914334	10021.17
28	0	2	107267.19068	11.97797522	15707.23
29	0	4	107225.52708	41.66360490	4985.91
30	0	3	107204.51731	21.00976998	3944.143
31	0	2	107168.03945	36.47785471	2029.934
32	0	3	107159.54473	8.49472185	1257.748
33	0	3	107158.50308	1.04165282	1295.471
34	0	4	107155.21688	3.28619693	2626.517

The GLIMMIX Procedure

Iteration History					
Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
35	**0**	4	107126.40459	28.81229261	4507.055
36	**0**	3	107116.52479	9.87980394	581.3195
37	**0**	3	107116.18405	0.34073869	230.7877
38	**0**	2	107115.87978	0.30426910	814.9521
39	**0**	4	107112.69063	3.18915369	2148.192
40	**0**	4	107059.22009	53.47053951	1738.08
41	**0**	3	107051.47823	7.74185678	1501.352
42	**0**	3	107050.39119	1.08703970	251.7038
43	**0**	3	107050.29915	0.09203579	321.7092
44	**0**	6	107042.42604	7.87310978	4705.613
45	**0**	2	107035.05947	7.36657342	1121.822
46	**0**	3	107032.96446	2.09501350	1087.189
47	**0**	4	106996.50971	36.45474723	2403.311
48	**0**	3	106990.51679	5.99292374	1617.02
49	**0**	2	106988.70211	1.81467815	2614.599
50	**0**	2	106986.09047	2.61163731	364.905
51	**0**	3	106985.99786	0.09260589	173.5554
52	**0**	6	106981.10077	4.89709120	2788.935
53	**0**	2	106978.92257	2.17820574	2255.873
54	**0**	2	106977.69031	1.23225739	1255.58
55	**0**	3	106976.97246	0.71784509	185.2949
56	**0**	4	106966.44999	10.52247975	1657.105
57	**0**	3	106965.82016	0.62982129	509.4262
58	**0**	3	106965.39864	0.42152090	582.3073
59	**0**	2	106964.67062	0.72802156	449.7027
60	**0**	3	106964.43297	0.23765330	409.8338
61	**0**	6	106951.80826	12.62470717	3392.013
62	**0**	3	106946.72142	5.08683719	200.7972
63	**0**	2	106946.32363	0.39779405	1698.563
64	**0**	4	106944.6945	1.62913296	314.6401
65	**0**	2	106943.64474	1.04975675	409.8008
66	**0**	3	106943.29873	0.34601178	176.7378
67	**0**	2	106943.17547	0.12326138	744.3389
68	**0**	6	106935.78084	7.39462234	2840.665
69	**0**	2	106932.48895	3.29189479	1794.848

The GLIMMIX Procedure

Iteration History					
Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
70	**0**	2	106928.85338	3.63557004	214.699
71	**0**	2	106925.61944	3.23394121	2659.283
72	**0**	2	106924.11782	1.50162044	1394.342
73	**0**	2	106923.55031	0.56750927	998.4062
74	**0**	2	106923.04544	0.50487299	318.8234
75	**0**	3	106922.99049	0.05494269	108.8831
76	**0**	6	106921.04641	1.94408128	3818.985
77	**0**	2	106919.51474	1.53166736	1278.616
78	**0**	3	106919.22927	0.28547244	83.38022
79	**0**	2	106918.86568	0.36359362	1604.603
80	**0**	4	106912.67363	6.19204886	699.7656
81	**0**	3	106911.69352	0.98010762	217.364
82	**0**	3	106911.65212	0.04140074	63.7145
83	**0**	2	106911.62658	0.02554014	141.9504
84	**0**	6	106910.42282	1.20375753	2065.525
85	**0**	2	106909.03758	1.38524728	742.7019
86	**0**	2	106907.2144	1.82317426	1144.455
87	**0**	4	106903.38607	3.82833454	652.599
88	**0**	3	106903.10641	0.27966014	52.07572
89	**0**	3	106903.09869	0.00771468	55.12641
90	**0**	6	106901.93711	1.16158378	1561.267
91	**0**	3	106901.21459	0.72252207	147.7142
92	**0**	2	106900.78051	0.43407443	486.2497
93	**0**	4	106894.98603	5.79448495	809.6247
94	**0**	3	106893.62482	1.36120447	260.1634
95	**0**	3	106893.5552	0.06962750	62.60641
96	**0**	3	106893.54846	0.00673600	61.54285
97	**0**	6	106893.38875	0.15970680	567.3507
98	**0**	2	106893.16429	0.22445919	58.97746
99	**0**	2	106892.83105	0.33324405	732.1445
100	**0**	4	106889.66635	3.16469620	2118.328
101	**0**	3	106887.78694	1.87941094	76.35449
102	**0**	3	106887.78258	0.00436210	36.09058
103	**0**	6	106887.60075	0.18183001	822.3285
104	**0**	2	106887.4274	0.17335062	237.7375

The GLIMMIX Procedure

Iteration History					
Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
105	**0**	3	106887.39755	0.02985236	81.25536
106	**0**	6	106884.69311	2.70443224	742.0014
107	**0**	3	106884.53127	0.16184485	53.09613
108	**0**	3	106884.52863	0.00263668	62.8864
109	**0**	4	106884.5026	0.02603796	86.6203
110	**0**	3	106884.49837	0.00422620	24.67487
111	**0**	4	106884.47449	0.02388330	82.67395
112	**0**	2	106884.43716	0.03732848	57.33618
113	**0**	4	106884.35815	0.07900596	190.2585
114	**0**	4	106883.6307	0.72745318	422.0418
115	**0**	2	106882.59897	1.03173304	89.60135
116	**0**	3	106882.4591	0.13986872	42.68477
117	**0**	3	106882.45528	0.00381749	25.78807
118	**0**	4	106882.44167	0.01361009	42.6621

Convergence criterion (GCONV=1E-8) satisfied.

Estimated G matrix is not positive definite.

Fit Statistics	
-2 Log Likelihood	106882.4
AIC (smaller is better)	107024.4
AICC (smaller is better)	107024.5
BIC (smaller is better)	107487.2
CAIC (smaller is better)	107558.2
HQIC (smaller is better)	107186.6

Fit Statistics for Conditional Distribution	
-2 log L(Event | r. effects)	95561.59

The GLIMMIX Procedure

Covariance Parameter Estimates				
Cov Parm	Subject	Group	Estimate	Standard Error
Intercept	pat_id	Event 1	4.0823	0.3004
Intercept	pat_id	Event 2	0	.
Intercept	pat_id	Event 3	1.1476	0.06909
Intercept	pat_id	Event 4	0.8497	0.04442

Solutions for Fixed Effects											
Effect	Event	Trt_Step	gender	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept	1			-6.2847	0.1581	19984	-39.75	<.0001	0.05	-6.5945	-5.9748
Intercept	2			-2.4067	0.05435	19984	-44.28	<.0001	0.05	-2.5132	-2.3002
Intercept	3			-3.5684	0.07556	19984	-47.23	<.0001	0.05	-3.7165	-3.4203
Intercept	4			-2.7509	0.05840	19984	-47.10	<.0001	0.05	-2.8654	-2.6364
year	1			0.3169	0.1118	107E3	2.84	0.0046	0.05	0.09782	0.5359
year	2			-0.6361	0.07969	107E3	-7.98	<.0001	0.05	-0.7923	-0.4799
year	3			-0.8306	0.06945	107E3	-11.96	<.0001	0.05	-0.9667	-0.6944
year	4			-0.6793	0.05802	107E3	-11.71	<.0001	0.05	-0.7931	-0.5656
year*year	1			-0.1027	0.04805	107E3	-2.14	0.0327	0.05	-0.1968	-0.00847
year*year	2			0.1202	0.03841	107E3	3.13	0.0018	0.05	0.04490	0.1955
year*year	3			0.2922	0.03031	107E3	9.64	<.0001	0.05	0.2327	0.3516
year*year	4			0.2217	0.02620	107E3	8.46	<.0001	0.05	0.1703	0.2730
year*year*year	1			0.006715	0.005400	107E3	1.24	0.2137	0.05	-0.00387	0.01730
year*year*year	2			-0.01051	0.004749	107E3	-2.21	0.0268	0.05	-0.01982	-0.00121
year*year*year	3			-0.02812	0.003490	107E3	-8.06	<.0001	0.05	-0.03496	-0.02128
year*year*year	4			-0.02249	0.003104	107E3	-7.25	<.0001	0.05	-0.02857	-0.01641
Trt_Step	1	1		-1.9545	0.2255	107E3	-8.67	<.0001	0.05	-2.3964	-1.5126
Trt_Step	2	1		-1.1968	0.1055	107E3	-11.34	<.0001	0.05	-1.4036	-0.9899
Trt_Step	3	1		0.09468	0.07005	107E3	1.35	0.1765	0.05	-0.04263	0.2320
Trt_Step	4	1		-0.1976	0.05908	107E3	-3.34	0.0008	0.05	-0.3134	-0.08179
Trt_Step	1	2		-2.5546	0.3204	107E3	-7.97	<.0001	0.05	-3.1825	-1.9266
Trt_Step	2	2		-2.7078	0.2105	107E3	-12.86	<.0001	0.05	-3.1204	-2.2953
Trt_Step	3	2		-0.5975	0.1049	107E3	-5.70	<.0001	0.05	-0.8031	-0.3919
Trt_Step	4	2		-0.8266	0.08540	107E3	-9.68	<.0001	0.05	-0.9940	-0.6593
Trt_Step	1	3		-2.5400	0.3211	107E3	-7.91	<.0001	0.05	-3.1694	-1.9106
Trt_Step	2	3		-2.0354	0.1923	107E3	-10.58	<.0001	0.05	-2.4124	-1.6584
Trt_Step	3	3		-0.2914	0.09881	107E3	-2.95	0.0032	0.05	-0.4850	-0.09771

The GLIMMIX Procedure

Solutions for Fixed Effects

Effect	Event	Trt_Step	gender	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Trt_Step	4	3		-0.6174	0.08316	107E3	-7.42	<.0001	0.05	-0.7804	-0.4544
Trt_Step	1	4		-2.0898	0.3010	107E3	-6.94	<.0001	0.05	-2.6796	-1.4999
Trt_Step	2	4		-2.0266	0.1922	107E3	-10.54	<.0001	0.05	-2.4033	-1.6499
Trt_Step	3	4		-0.1505	0.09383	107E3	-1.60	0.1086	0.05	-0.3344	0.03336
Trt_Step	4	4		-0.4791	0.08368	107E3	-5.73	<.0001	0.05	-0.6431	-0.3151
Trt_Step	1	5		-1.4323	0.5211	107E3	-2.75	0.0060	0.05	-2.4536	-0.4110
Trt_Step	2	5		-0.8141	0.2826	107E3	-2.88	0.0040	0.05	-1.3679	-0.2602
Trt_Step	3	5		2.0221	0.1134	107E3	17.83	<.0001	0.05	1.7998	2.2444
Trt_Step	4	5		0.7649	0.1277	107E3	5.99	<.0001	0.05	0.5146	1.0152
Trt_Step	1	0		0	.	.	.	.	.	.	.
Trt_Step	2	0		0	.	.	.	.	.	.	.
Trt_Step	3	0		0	.	.	.	.	.	.	.
Trt_Step	4	0		0	.	.	.	.	.	.	.
year*Trt_Step	1	1		-0.1589	0.1127	107E3	-1.41	0.1584	0.05	-0.3798	0.06191
year*Trt_Step	2	1		-0.4779	0.09200	107E3	-5.19	<.0001	0.05	-0.6582	-0.2976
year*Trt_Step	3	1		-0.1294	0.03267	107E3	-3.96	<.0001	0.05	-0.1934	-0.06533
year*Trt_Step	4	1		-0.1136	0.02924	107E3	-3.88	0.0001	0.05	-0.1709	-0.05625
year*Trt_Step	1	2		-0.06049	0.1617	107E3	-0.37	0.7084	0.05	-0.3774	0.2565
year*Trt_Step	2	2		-0.02047	0.1286	107E3	-0.16	0.8735	0.05	-0.2724	0.2315
year*Trt_Step	3	2		-0.1932	0.05581	107E3	-3.46	0.0005	0.05	-0.3026	-0.08377
year*Trt_Step	4	2		-0.1717	0.04735	107E3	-3.63	0.0003	0.05	-0.2645	-0.07889
year*Trt_Step	1	3		0.1034	0.1310	107E3	0.79	0.4301	0.05	-0.1534	0.3601
year*Trt_Step	2	3		-0.3923	0.1562	107E3	-2.51	0.0120	0.05	-0.6985	-0.08608
year*Trt_Step	3	3		-0.08161	0.04553	107E3	-1.79	0.0731	0.05	-0.1708	0.007631
year*Trt_Step	4	3		-0.04324	0.03890	107E3	-1.11	0.2663	0.05	-0.1195	0.03300
year*Trt_Step	1	4		-0.06626	0.1418	107E3	-0.47	0.6402	0.05	-0.3441	0.2116
year*Trt_Step	2	4		-0.2439	0.1296	107E3	-1.88	0.0598	0.05	-0.4978	0.01005
year*Trt_Step	3	4		-0.03589	0.03833	107E3	-0.94	0.3491	0.05	-0.1110	0.03924
year*Trt_Step	4	4		-0.06610	0.03837	107E3	-1.72	0.0850	0.05	-0.1413	0.009113
year*Trt_Step	1	5		-0.03979	0.2394	107E3	-0.17	0.8680	0.05	-0.5089	0.4294
year*Trt_Step	2	5		-0.07828	0.1649	107E3	-0.47	0.6349	0.05	-0.4014	0.2448
year*Trt_Step	3	5		-0.1085	0.04697	107E3	-2.31	0.0209	0.05	-0.2006	-0.01644
year*Trt_Step	4	5		-0.06279	0.05603	107E3	-1.12	0.2624	0.05	-0.1726	0.04702
year*Trt_Step	1	0		0	.	.	.	.	.	.	.
year*Trt_Step	2	0		0	.	.	.	.	.	.	.

The GLIMMIX Procedure

Solutions for Fixed Effects

Effect	Event	Trt_Step	gender	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
year*Trt_Step	3	0		0	.	.	.	.	.	.	.
year*Trt_Step	4	0		0	.	.	.	.	.	.	.
age	1			0.02322	0.002776	107E3	8.36	<.0001	0.05	0.01778	0.02866
age	2			-0.00441	0.001158	107E3	-3.81	0.0001	0.05	-0.00668	-0.00214
age	3			-0.00011	0.001562	107E3	-0.07	0.9444	0.05	-0.00317	0.002953
age	4			-0.00160	0.001260	107E3	-1.27	0.2051	0.05	-0.00407	0.000873
gender	1		2	0.6492	0.1031	107E3	6.30	<.0001	0.05	0.4471	0.8513
gender	2		2	0.1248	0.04190	107E3	2.98	0.0029	0.05	0.04265	0.2069
gender	3		2	0.2602	0.05716	107E3	4.55	<.0001	0.05	0.1482	0.3722
gender	4		2	0.2257	0.04618	107E3	4.89	<.0001	0.05	0.1351	0.3162
gender	1		1	0	.	.	.	.	.	.	.
gender	2		1	0	.	.	.	.	.	.	.
gender	3		1	0	.	.	.	.	.	.	.
gender	4		1	0	.	.	.	.	.	.	.
CCI	1			0.1460	0.06829	107E3	2.14	0.0325	0.05	0.01217	0.2799
CCI	2			-0.02623	0.03405	107E3	-0.77	0.4412	0.05	-0.09297	0.04051
CCI	3			0.03921	0.04382	107E3	0.89	0.3709	0.05	-0.04667	0.1251
CCI	4			0.09205	0.03410	107E3	2.70	0.0070	0.05	0.02521	0.1589

Odds Ratio Estimates

Event	Trt_Step	gender	year	age	CCI	_Trt_Step	_gender	_year	_age	_CCI	Estimate	DF	95% Confidence Limits	
1			1.8235	32.308	0.3256			1.8235	31.308	0.3256	1.023	107E3	1.018	1.029
2			1.8235	32.308	0.3256			1.8235	31.308	0.3256	0.996	107E3	0.993	0.998
3			1.8235	32.308	0.3256			1.8235	31.308	0.3256	1.000	107E3	0.997	1.003
4			1.8235	32.308	0.3256			1.8235	31.308	0.3256	0.998	107E3	0.996	1.001
1			1.8235	31.308	1.3256			1.8235	31.308	0.3256	1.157	107E3	1.012	1.323
2			1.8235	31.308	1.3256			1.8235	31.308	0.3256	0.974	107E3	0.911	1.041
3			1.8235	31.308	1.3256			1.8235	31.308	0.3256	1.040	107E3	0.954	1.133
4			1.8235	31.308	1.3256			1.8235	31.308	0.3256	1.096	107E3	1.026	1.172
1	1		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.106	107E3	0.079	0.142
2	1		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.126	107E3	0.099	0.162
3	1		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.868	107E3	0.787	0.958
4	1		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.667	107E3	0.613	0.726
1	2		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.070	107E3	0.046	0.105

The GLIMMIX Procedure

Odds Ratio Estimates

Event	Trt_Step	gender	year	age	CCI	_Trt_Step	_gender	_year	_age	_CCI	Estimate	DF	95% Confidence Limits	
2	2		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.064	107E3	0.046	0.089
3	2		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.387	107E3	0.331	0.452
4	2		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.320	107E3	0.282	0.363
1	3		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.095	107E3	0.065	0.141
2	3		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.064	107E3	0.043	0.096
3	3		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.644	107E3	0.561	0.739
4	3		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.498	107E3	0.445	0.559
1	4		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.110	107E3	0.075	0.159
2	4		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.084	107E3	0.061	0.117
3	4		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.806	107E3	0.713	0.910
4	4		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.549	107E3	0.491	0.614
1	5		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.222	107E3	0.115	0.428
2	5		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.384	107E3	0.243	0.607
3	5		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	6.198	107E3	5.316	7.227
4	5		1.8235	31.308	0.3256	0		1.8235	31.308	0.3256	1.916	107E3	1.611	2.279
1	1		2.8235	31.308	0.3256	1		1.8235	31.308	0.3256	0.812	107E3	0.648	1.017
2	1		2.8235	31.308	0.3256	1		1.8235	31.308	0.3256	0.483	107E3	0.400	0.583
3	1		2.8235	31.308	0.3256	1		1.8235	31.308	0.3256	0.937	107E3	0.875	1.005
4	1		2.8235	31.308	0.3256	1		1.8235	31.308	0.3256	0.876	107E3	0.823	0.932
1	2		2.8235	31.308	0.3256	2		1.8235	31.308	0.3256	0.896	107E3	0.651	1.233
2	2		2.8235	31.308	0.3256	2		1.8235	31.308	0.3256	0.763	107E3	0.591	0.984
3	2		2.8235	31.308	0.3256	2		1.8235	31.308	0.3256	0.879	107E3	0.787	0.983
4	2		2.8235	31.308	0.3256	2		1.8235	31.308	0.3256	0.826	107E3	0.751	0.909
1	3		2.8235	31.308	0.3256	3		1.8235	31.308	0.3256	1.055	107E3	0.812	1.370
2	3		2.8235	31.308	0.3256	3		1.8235	31.308	0.3256	0.526	107E3	0.386	0.717
3	3		2.8235	31.308	0.3256	3		1.8235	31.308	0.3256	0.983	107E3	0.896	1.079
4	3		2.8235	31.308	0.3256	3		1.8235	31.308	0.3256	0.940	107E3	0.867	1.018
1	4		2.8235	31.308	0.3256	4		1.8235	31.308	0.3256	0.890	107E3	0.673	1.179
2	4		2.8235	31.308	0.3256	4		1.8235	31.308	0.3256	0.610	107E3	0.472	0.789
3	4		2.8235	31.308	0.3256	4		1.8235	31.308	0.3256	1.029	107E3	0.951	1.114
4	4		2.8235	31.308	0.3256	4		1.8235	31.308	0.3256	0.918	107E3	0.849	0.993
1	5		2.8235	31.308	0.3256	5		1.8235	31.308	0.3256	0.914	107E3	0.571	1.465
2	5		2.8235	31.308	0.3256	5		1.8235	31.308	0.3256	0.720	107E3	0.519	0.997
3	5		2.8235	31.308	0.3256	5		1.8235	31.308	0.3256	0.957	107E3	0.869	1.054

The GLIMMIX Procedure

Odds Ratio Estimates

Event	Trt_Step	gender	year	age	CCI	_Trt_Step	_gender	_year	_age	_CCI	Estimate	DF	95% Confidence Limits	
4	5		2.8235	31.308	0.3256	5		1.8235	31.308	0.3256	0.921	107E3	0.823	1.031
1	0		2.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.951	107E3	0.883	1.026
2	0		2.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.778	107E3	0.731	0.829
3	0		2.8235	31.308	0.3256	0		1.8235	31.308	0.3256	1.067	107E3	1.014	1.123
4	0		2.8235	31.308	0.3256	0		1.8235	31.308	0.3256	0.981	107E3	0.939	1.025
1		2	1.8235	31.308	0.3256		1	1.8235	31.308	0.3256	1.914	107E3	1.564	2.343
2		2	1.8235	31.308	0.3256		1	1.8235	31.308	0.3256	1.133	107E3	1.044	1.230
3		2	1.8235	31.308	0.3256		1	1.8235	31.308	0.3256	1.297	107E3	1.160	1.451
4		2	1.8235	31.308	0.3256		1	1.8235	31.308	0.3256	1.253	107E3	1.145	1.372

Type III Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
year	4	107E3	99.78	<.0001
year*year	4	107E3	42.56	<.0001
year*year*year	4	107E3	29.51	<.0001
Trt_Step	20	107E3	63.35	<.0001
year*Trt_Step	20	107E3	4.45	<.0001
age	4	107E3	21.78	<.0001
gender	4	107E3	22.25	<.0001
CCI	4	107E3	3.27	0.0109

6.3.4 Marginal and Conditional Model Predicted Probability Graph

```
title 'Predicted Probability of Event using Marginal Model';
proc sgplot data=glimmixout;
        scatter x=year y=PredProb_PA / group=trt_step;
run;

title 'Predicted Probability of Event using Conditional Model';
proc sgplot data=glimmixout;
        scatter x=year y=PredProb / group=trt_step;
run;
```

6.3.5 Asthma Exacerbation Outcome (Nominal) Model Exacerbation Event 3 Probability Calculation

$$
\begin{aligned}
z_{ij1} &= -6.2847 - 0.3169 * 1 - 0.1027 * 1 + 0.006715 * 1 \\
&\quad - 1.4323 - 0.03979 * 1 + 0.02322 * 40 + 0.1460 * 1 \\
&= -7.09488 \\
z_{ij2} &= -2.4067 - 0.6361 * 1 + 0.1202 * 1 - 0.01051 * 1 \\
&\quad - 0.8141 - 0.07828 * 1 - 0.00441 * 40 - 0.02623 * 1 \\
&= -4.02812 \\
z_{ij3} &= -3.5684 - 0.8306 * 1 + 0.2922 * 1 - 0.02812 * 1 \\
&\quad + 2.0221 - 0.1085 * 1 - 0.00011 * 40 + 0.03921 * 1 \\
&= -2.18651 \\
z_{ij4} &= -2.7509 - 0.6793 * 1 + 0.2217 * 1 - 0.02249 * 1 \\
&\quad + 0.7649 - 0.06279 * 1 - 0.00160 * 40 + 0.09205 * 1 \\
&= -2.50083
\end{aligned} \tag{5}
$$

$$
P(Event = 3|z_{ij}) = \frac{e^{-2.18651}}{1 + e^{-2.18651} + e^{-7.09488} + e^{-4.02812} + e^{-2.50083}} = 0.09259
$$