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BST 210 Group 5 We R

Severity of COVID-19 Symptoms and Anxiety and Depression

Abstract

The COVID-19 pandemic, and the restrictions required to halt spread of the infection, are associated with increased population burden of moderate to severe symptoms of depression and anxiety. According to The Lancet Commission, the prevalence of depression and anxiety globally increased 27% and 25% respectively because of the pandemic compared with pre-pandemic prevalence.[5] It is of great clinical importance to evaluate the effects of COVID-19 on mental health, so those mental health disorders could be approached with more precision by mental health providers. This study uses a dataset of 446 individuals and their socio demographic, health characteristics and COVID-19 (severity of symptoms) to build a logistic and multinomial regression model to find the association between depression, anxiety and COVID-19. After conducting a logistic regression model, we found that severity of COVID-19 symptoms is not significantly associated with anxiety. We conducted a multinomial regression model, in which there is a positive association between moderate or severe COVID-19 symptoms and higher frequency of feeling depressed. We also performed secondary analyses for physical health using a linear model and we found no association between severity of COVID-19 symptoms on duration of moderate physical activity.

Introduction

Mental health disorders are one of the principal causes of global health-related burden. As the COVID-19 pandemic rages on, it has drastically changed our lives in many aspects and it is known that it has caused a variety of psychiatric distress that may lead to long term concerns like depression and anxiety, among others.[1] Moreover, Hoosain et al. (2020) claim that individuals who were diagnosed with COVID-19 had "profound psychological distress, anxiety, depression, and other mental health problems compared to those who were not infected". Several reasons have been pointed out as risk factors for worsening mental health, such as social isolation measures and a fear of contracting the disease.

Review of literature and domain expertise

Several studies have examined the relationships between the pandemic and mental health. For example, Hoosain et al. (2020) provided a narrative review that discussed the mental health problems associated with the pandemic, as well as the problems associated with having COVID-19, and also several potential factors associated with mental health problems. This gave us a starting point as the sources cited allowed us to further our literature review. Because of the recency and urgency of the pandemic, similar questions have been posed all around the world as researchers are interested in how the pandemic has affected our mental health, especially after being infected with COVID-19. Such as Xie Y et al. (2022) which was a cohort study that examined the risks of mental health outcomes of people who had COVID-19 and found that patients who survived COVID-19 were at an increased risk of anxiety and depression.

However, the relationship between the severity of COVID-19 symptoms and mental health has been studied much less. Fisher et al. reported that there is consistent evidence from diverse countries that population prevalence rates of clinically significant symptoms of depression and anxiety are substantially higher in the context of any COVID-19-related restrictions than at non-pandemic times.

Thus, the aim of this study is to take it one step further and explore if the severity of COVID-19 has any impact on depression and anxiety. It is important to note that mental health issues often result in lower life expectancies and poorer physical health than the general population.[4] There is an urgency to strengthen mental health systems in most countries. Mitigation strategies could incorporate ways to promote mental wellbeing and target determinants of poor mental health and interventions to treat those with a mental disorder.[5] In examining this topic, we hope to elucidate whether severity of COVID-19 symptoms is a risk factor for depression and anxiety in order to have a better understanding of how the pandemic as a whole is impacting our physical and mental health.

We also spoke to a domain expert in this matter and they pointed out that many studies have looked at associations between COVID-19 and mental health and advised us to also look at physical health as a secondary analysis. When it comes to physical health, a lot of papers look at how physical activity can be a protector against COVID-19.[6] On the other hand, we are interested in how the severity of COVID-19 may influence one's physical activity. Verveen et al. (2022) looked at the health-related quality of life of people depending on their severity of COVID-19, where people with initial moderate or severe/critical COVID-19 had impaired health-related quality of life. In addition, there are some studies that have shown that maintaining a certain amount of physical activity during the pandemic can decrease mental health disorders like depression and anxiety. One important aspect to

consider is that during the COVID-19 pandemic, suspension of all sports and fitness facilities had a considerable impact on mental health.[6] For instance, a rapid review by Park AH et al. (2020) also suggested that the pandemic was linked with significant decreases in physical activity and increase of sedentary activity so as a secondary analysis, we are also examining the severity of COVID-19 on physical health specifically in terms of frequency of moderate physical activity.

Research and Analysis Methods

Data Description and Variable Selection

Our data comes from the IPUMS Health Surveys: National Health Interview Surveys (NHIS). The NHIS is a survey that collects information on the health behaviors and health of people in the US population. It has been collecting data since 1963 to the present and annually, the survey covers about 100,000 persons in 45,000 households. We extracted our variables for our primary and secondary analyses from the NHIS database.[12] Due to the sheer number of variables possible to extract, we discussed with our domain expert and looked towards our own team member, Maria, an experienced clinician, and we thought extensively about choosing only a handful that we considered to be possible confounders, effect modifiers, important covariates to adjust for, as well as our outcomes of interest. Variable definitions are provided in Supplementary Table S1.

For our primary analyses, we looked at depression which was defined to be how often the individual felt depressed and anxiety which was if the individual was ever told by a doctor or other health professional they had anxiety. For severity of COVID-19 symptoms, it was defined as the severity of COVID-19 symptoms at their worst for an individual. For our secondary analyses regarding physical activity, our outcome of interest was defined as

duration of moderate activity (minutes). Other variables we selected were age, sex, race, income, health status, emotional support, and region. Our total study after selecting these variables and removing anyone defined as not in the universe by NHIS was 446 observations. Table 1 summarizes these demographic characteristics.

Data Cleaning

For all of the variables, there is a category NIU, which stands for not in universe. NIU has different definitions for each variable. For example, the universe for duration of moderate activity is sample adults aged 18+ who do moderate physical activities while the universe for depression is sample children aged 5-17 and sample adults aged 18+. Therefore, physical activity data is unavailable for any participant younger than 18, and depression data is unavailable for any participant younger than 5. As a result, there was MAR (Missing At Random) which disappeared if we adjust for age. Because we were unable to distinguish missingness due to survey collection and missingness due to avoidance, we decided to only keep individuals who were in the universe for all variables.

Since most of our covariates are categorical, we collapsed some of the variable levels. Almost 75% of our participants identified as White and we only have a few observations in other categories, so we combined all non-white race groups. For health status, we combined “excellent” with “very good” and “good” to be the positive group and left “fair” as the neutral group and “poor” as the negative group. Similarly, we merged “sometimes”, “rarely”, and “never” to be the negative group for emotional support. Lastly, feeling depressed weekly and monthly were combined as there were fewer observations in these two categories and they are both associated with moderate depression that is less severe than daily depressive mood but more serious than yearly depressive mood.

After removing all NIUs and re-categorization, we have 446 observations of 11 variables. There are fewer than 5 missing values in most variables, 10 in emotional support, and 38 in race. Based on the 5% missingness of 22.3 observations, only race has a slightly higher missingness. As a result, we decided to conduct complete case analyses, which left us with 397 observations.

Primary Analysis (Anxiety):

For the first part of our primary analysis, we explored the association between severity of COVID-19 symptoms and anxiety. Our outcome anxiety is a binary (yes/no variable) defined as whether the individual had ever been told by a doctor or health professional they had anxiety. Based on our epidemiology knowledge, the potential confounders include age, sex, race, health status, and physical activity. Region, emotional support, and income do not satisfy the causal definition of confounder because they do not seem to relate to COVID-19 symptom severity.

Confounding and Effect modification:

Firstly, a full logistic model with all covariates was fitted to explore any statistically significant variables that are not a confounder. Using the p-value<0.05 cutoff, only race and health status were significant. Then, we computed the percentage change in COVID-19 symptom severity coefficients associated with each of the 5 potential confounders to check if they pass the 10% rule of thumb for the statistical definition of confounder. The difference was calculated as the difference between two coefficients divided by the coefficient when a confounder is included, using the formula $\frac{crude-adjusted}{adjusted} \times 100$ where adjusted is the model that includes the confounder and crude is the model not including the confounder. Age, sex, race, and health status passed the 10% test while physical activity did not. We also examined whether any of the confounders could be an effect modifier of the association between

anxiety and COVID-19 symptom severity. None of the interaction terms were statistically significant and the Likelihood Ratio tests (LRT) suggested the reduced model is sufficient. Therefore, our final model is Anxiety ~ age + sex + race + health status + covid symptom severity.

Primary Analysis (Depression):

In the second half of our primary analysis, we explored the association between severity of COVID-19 symptoms and depression, another of our mental health indicators. This new outcome depression is a categorical variable with 4 values - never, daily, weekly or monthly, and yearly. It is defined as how often an individual feels depressed. Same as above, the potential confounders based on our epidemiology knowledge are age, sex, race, health status, and physical activity. Region, emotional support, and income do not satisfy the causal definition of confounder because they do not seem to relate to COVID-19 symptom severity.

Because our outcome is a categorical variable and there is a natural ordering of how frequently one feels depressed, there are two potential models: multinomial and ordinal models. To test the proportional odds assumption for ordinal models, two separate logistic models were conducted to compare the odds ratio of feeling depressed daily versus the rest and the odds ratio of never feeling depressed versus the rest. Coefficients of the COVID-19 symptom terms significantly differ in the two models and fell out of the 95% confidence interval. Thus, we concluded that the proportional odds assumption does not hold and it is inappropriate to use any ordinal model.

Confounding and Effect modification:

After excluding ordinal models, we continued with multinomial models and assessed the 10% rule of thumb for the statistical definition of confounder. Similarly, age, race, and

health status passed this rule while physical activity did not. Sex is not operationally significant here with mostly lower than 5% change. Our domain knowledge and literature review suggested that, however, there are significant sex differences in the risk of depression and COVID-19 symptoms.[13,14] Considering the potential clinical importance of sex, we decided to include it despite not satisfying the 10% rule.

We also examined whether any of the confounders could be an effect modifier of the association between anxiety and COVID-19 symptom severity. Half of the interaction terms between health status and COVID-19 symptom severity have a significant p-value<0.05 while the other half >0.05. Likelihood Ratio tests (LRT) indicated the reduced model is sufficient and no interaction is necessary. Because the interaction leads to an addition of 20 coefficients, we decided not to include it for parsimony. Therefore, our final model is Depression ~ age + sex + race + health status + covid symptom severity.

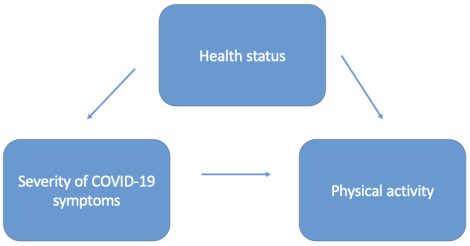
Secondary Analysis (Physical activity):

In our secondary analysis, linear regression modeling was conducted to explore the association between severity of COVID-19 symptoms and duration of moderate physical activity (minutes).

Confounding and Effect modification:

From discussing with the domain expertise, we believe that from our initial set of variables we believed anxiety, depression, region, income, or emotional support did not meet parts of the classical definition of confounding, that is, they were not associated with severity of COVID-19 symptoms and associated with duration of moderate physical activity. They were also tested for effect modification but results showed they were not effect modifiers so we did not include them in the model. A likelihood ratio test comparing the models with interaction effects to the model without also showed the smaller models were sufficient.

Because our main interest is association and interpretation of beta coefficients, we have considered potential confounders that we plan to control for in our model. For example, the health status of subjects (coded as a categorical predictor and presented in the method section above) is theorized to be a confounder on the relationship between COVID-19 severity and physical activity and additionally, it also meets the statistical definition of confounding.



Additionally, we plan on adjusting for these sociodemographic variables and factors in our consideration for potential confounders and effect modifiers: age, sex, and race. So in our initial model, we regressed duration of moderate physical activity on these predictors: severity of COVID-19 symptoms, age, sex, race, health status.

We checked the assumptions for linear regression and noticed that the normality of the residuals were violated. The residuals exhibited a right skew so we log-transformed the outcome variable. After log-transforming and refitting the model, the residuals looked normal and assumptions held. Variance inflation factor was also checked and none were above 5 so multicollinearity was not an issue. Our final model was fitting the log (duration of moderate physical activity) on these predictors: severity of COVID-19 symptoms, age, sex, race, health status. Using Cook's distance, three observations (299, 51, 429) exhibited large Cook's distances based on the rule of thumb (>12/397) and so a model was also fitted without these observations.

Findings and Analysis

Population characteristics

Table 1 summarizes the characteristics of the study population. We found that out of 446 participants, 241 (54,03%) were female and 205 (45,96%) were male. Population's age ranged from 31- 58 years with the mean being 45.12 years old. Approximately, 31.3% of the population had an income under $49,999 per year, 28.2% between $50,000 and $99,999 per year and lastly 40.3% over $100,000 per year. Most of the population were white (74,8%) and had a good health status (90.3%).

Characteristic	Patients (N=446)
Sex	
Female-no.(%)	241 (54)
Male-no.(%)	205 (46)
Age	
Median	44
Mean	45.12
Interquartile range	31-58
Income-no.(%)	
Under $49,999	140 (31.3)
$50,000-$99,999	126 (28.2)
Over $100,000	180 (40.3)
Region-no.(%)	
Northeast	70 (15.6)
Midwest	109 (24.4)
South	172 (38.6)
West	95 (21.3)
Race-no.(%)	
White	334 (74.8)
Non-white	74 (16.5)
NA	38 (8.52)
Health status-no.(%)	
Good	403 (90.3)
Fair	39 (8.7)
Poor	4 (0.9)
Emotional support - no(%)	
Always	
Usually	(25.8)
Sometimes-never	(18.4)
NA	(2.2)
Depression (frequency) - no(%)	
Never	239 (53.6)
Daily	16 (3.6)
Weekly or monthly	65 (14.6)
Yearly	125(28)
NA	1(0.2)
Anxiety	
Yes	368 (82.5)
No	78 (17.5)
Duration of physical activity(min)	
Mean	58.75
Median	45
Interquartile range	30-60

Table 1. Characteristics of Study Demographic

Covariates	Estimates
Intercept	-1.831*
Sex	
Male	-0.546
Age	-0.001
Race	
White	0.852
Health status	
Poor	2.239
Fair	1.168*
Covid-19 Symptoms	
Mild	-0.255
Moderate	-0.073
Severe	0.167

Table 2. Estimates from logistic regression model. (*) indicates p-value < 0.05.

Severity of COVID-19 symptoms and anxiety

Our final model is Anxiety ~ age + sex + race + health status + covid symptom severity. Shown in the model output in Table 2, fair health status is statistically significant with a p-value<0.005. Poor health status, sex, and race are borderline significant with p-values<0.1. COVID-19 symptoms are insignificant with p-value>0.05 and 95% CI including 1, after adjusting for other covariates.

Although our focus is an association study, which means prediction accuracy is not our priority, we still performed Goodness of Fit (GOF) and diagnostic tests to evaluate our final model. The Hosmer-Lemeshow test gave a p-value>0.1, indicating we do not have enough evidence to reject the null hypothesis that the fit of the model is adequate. We also assessed variance inflation factors which tell us the amount of one covariate that is described by other covariates in the model. VIF≤3 for all covariates so we conclude there is little collinearity in our variables.

Lastly, evaluative statistics were computed to examine the performance of the models. Our final model has the second lowest AIC and BIC values among our 7 models and its AUC is also moderately high with a value<0.65 as shown in Supplementary Table S2. If we want to further explore how to predict anxiety status associated with severity of COVID-19 symptoms, we could start with this model as it has a satisfactory model fit.

Severity of COVID-19 symptoms and depression

Our final model is Depression ~ age + sex + race + health status + covid symptom severity. In this model, poor health status for yearly depressive mood, fair health status for daily and weekly or monthly depressive mood, and moderate and severe COVID-19 symptoms for yearly depressive mood are statistically significant with a p-value<0.05.

According to the model output in Table 3, the association between severity of COVID-19 symptoms and depression could be interpreted as follows.

Daily		Weekly or monthly		Yearly	
Covariates	Estimates	Covariates	Estimates	Covariates	Estimates
Intercept	-3.640*	**Intercept**	-0.969	**Intercept**	-0.696
Sex		**Sex**		**Sex**	
Male	-0.476	Male	-0.255	Male	-0.244
Age	-0.006	**Age**	-0.018	**Age**	-0.013
Race		**Race**		**Race**	
White	1.258	White	0.407	White	0.094
Health status		**Health status**		**Health status**	
Poor	3.087	Poor	1.360	Poor	-12.426*
Fair	1.878*	Fair	1.133*	Fair	-0.303
Covid-19 Symptoms		**Covid-19 Symptoms**		**Covid-19 Symptoms**	
Mild	-1.874	Mild	-0.237	Mild	0.290
Moderate	-0.332	Moderate	0.451	Moderate	1.050*
Severe	1.065	Severe	0.455	Severe	1.012*

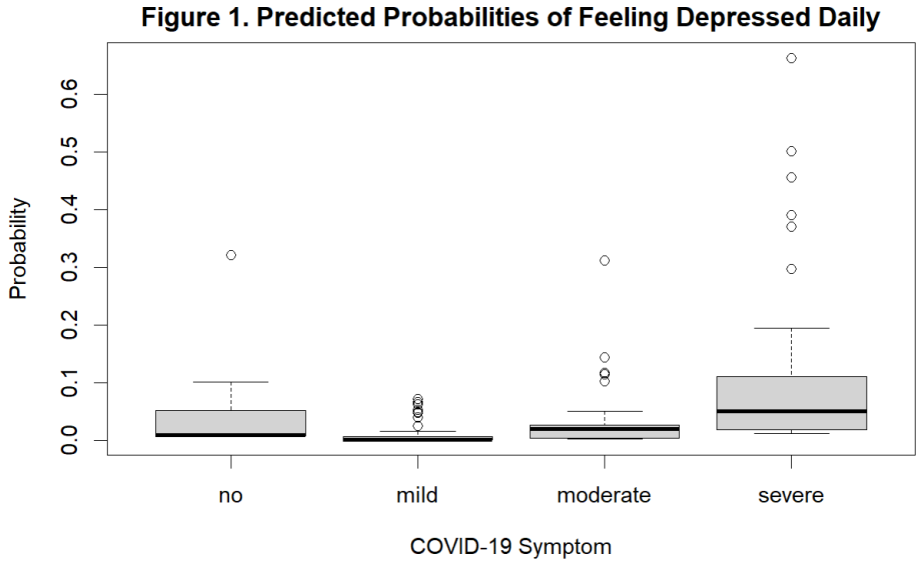
Table 3. Estimates from multinomial logistic regression model. (*) indicates p-value < 0.05.

The relative risk ratio (RRR) of feeling depressed a few times a year versus never feeling depressed is on average 2.859, for those who had moderate COVID-19 symptoms versus those who had no symptom, holding age, sex, race, and health status constant. The RRR of feeling depressed a few times a year versus never feeling depressed is on average 2.751, for those who had severe COVID-19 symptoms versus those who had no symptom, holding other covariates constant. From the relative risk ratios, it is clear that the more severe COVID-19 symptoms one has, the larger the negative effect on mental health.

To evaluate our final model, Goodness of Fit (GOF) and diagnostic tests were conducted. The Hosmer-Lemeshow test gave a p-value>0.1, indicating we do not have enough evidence to reject the null hypothesis that the fit of the model is adequate. Moreover, evaluative statistics were computed to examine the performance of the models. Our final model has relatively high AIC and BIC among our 7 models as shown in Supplementary

Table S3. If we want to further explore how to predict depression status associated with severity of COVID-19 symptoms, we should try other models that have a better model fit.

To examine the calibration of our model, the predicted probabilities of the outcome and the observed probabilities from our data were calculated and compared. The probabilities are mostly reasonably close to each other but there is overestimation and underestimation in some cases.



We also plotted the predicted probabilities for daily depressive mood (Figure 1). There is a clear difference that individuals with severe COVID-19 symptoms have on average a higher probability of feeling depressed daily. 6 outliers even have a greater than 0.3 probability. This boxplot visualizes the potential negative effect of having severe COVID-19 symptoms on mental health, specifically depression.

Severity of COVID-19 symptoms and physical activity

In our secondary analyses, after fitting our final model, we observed that none of the categories for COVID-19 symptoms were statistically significant (p-values > 0.05) so we do not have enough evidence to suggest that increased severity of covid symptoms has an effect on the duration of moderate physical activity (minutes) one engages in, on average, after

adjusting for the other covariates. The p-values for mild, moderate, and severe were 0.799, 0.750, and 0.508 respectively. Our unadjusted R-squared was 0.014 and our adjusted R-squared was -0.006 which suggests our model does not explain much of the variance of log(duration of moderate physical activity). The model without the three observations that exhibited high Cook's distance had similar results, levels of the severity of COVID-19 symptoms were still not significant.

Covariates	Estimates
Intercept	3.999
Sex	
Male	0.030
Age	-0.004
Race	
White	-0.012
Health status	
Poor	-0.141
Fair	-0.145
Covid-19 Symptoms	
Mild	0.029
Moderate	0.036
Severe	0.083

Table 4. Estimates from Linear Regression for the outcome log(duration of moderate physical activity). No estimate was deemed statistically significant at a significance level of 0.05.

Discussion

Results from our study indicate that there is no association between severity of COVID-19 symptoms and anxiety or physical activity, after adjusting for other covariates. For depression, having moderate or severe COVID-19 symptoms is associated with two times the risk of feeling depressed a few times a year versus never feeling depressed. Our study provided insight into the consequences of contracting COVID-19 and how it might affect an individual's mental health. As our model suggested a heightened risk of depressive mood associated with moderate or severe COVID-19 symptoms, it is an urgent call to take care of mental health through the lens of COVID-19 the pandemic as well as the severity of its symptoms, and it would be helpful to provide extra mental health interventions to patients with severe COVID-19 symptoms.

Limitations

This study is limited in a few ways. First of all, depression is not a confirmatory diagnosis from a physician, as defined in the survey, which makes it a subjective point of view. For future studies, assessing mental health on a scale with more severity levels and more possible symptoms to choose from might help reduce bias and bring in data more representative of the general population. Additionally, there is potential recall bias as individuals are asked to remember several pieces of information. Also, IPUMS does not have data about COVID-19 vaccination and healthcare access, which could be potential confounders in this study. In addition, working as a healthcare provider might be a possible effect modifier, but there is no data available about this. We have missing data in our race variable, which is larger than 5%, and we conducted a complete case analysis, which potentially decreased the power of the study. When referring to external validity of our study, our results might not be generalizable considering the age of the study population, but only U.S adults (older than 18 years old). One final limitation of this study is its cross-sectional nature, which makes it impossible to know the temporality of each variable. There is no information on whether contracting COVID-19 happened before one had anxiety or after, which then influences whether COVID-19 symptom is a confounder or a mediator.

This study had limitations; nevertheless, it set a sound foundation for the need to consider combined effects of contracting COVID-19 and severity of symptoms on mental health outcomes. Also, NHIS survey is highly representative of the U.S population and supports our study to potentially fill in the gap regarding severity of COVID-19 symptoms and both mental and physical health.

Future Scope

Further research could be done in assessing how PA (physical activity) was or was not favorable for mental health disorders like anxiety and depression. Considering the context that in this study we are analyzing data from 2020, we will be interested in finding out the depression and anxiety scores after everything went back to “normal” and the participants have the opportunity to increase their PA. One other approach is to conduct a longitudinal study with follow-up since it would allow temporality to be established, allow causal inferences to be made, as well as allow the ascertainment of whether COVID-19 is a cause of mental issues.

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Appendix

Code

https://github.com/yzhong0620/Applied-Regressoin-Analysis

Supplementary materials

Table S1

Variable	Definition
Age	Individual's age, in years since their last birthday
Sex	Whether the person was male or female
Race	Whether the person was White or non-White
Health status	Self-rated general health ranging from "excellent, very good, good", "fair", to "poor"
Physical activity	Duration of moderate physical activity in minutes
Anxiety	Ever told by a doctor or health professional you had any anxiety disorder
Depression	How often feel depressed ranging from "never", "a few times a year", "monthly, weekly", to "daily"
Emotional support	How often get emotional support ranging from "always", "usually", to "sometimes, rarely, never"
Income	Total combined family income ranging from "under $49,999", "$50,000-$99,999", to "over $100,000"
Region	Region of the U.S. where the housing unit containing survey participants was located: Northeast, North Central/Midwest, South, and West correspond to the U.S. regions recognized by the Census Bureau
COVID-19 Symptom	Severity of COVID-19 symptoms at their worst ranging from "no symptoms", "mild symptoms", "moderate symptoms", to "severe symptoms"

Table S2

MODEL	AIC	BIC	AUC
logis1	375.5568	443.2837	0.6869
logis2	369.6569	417.4641	0.6741
logis3	367.6626	411.4859	0.6743
logis4	369.9795	409.8188	0.6675
logis5	373.7351	413.5744	0.6338
Final Model	367.9807	403.8361	0.6684
logis7	371.9470	399.8346	0.6056

Table S3

MODEL	AIC	BIC
multi1	861.1691	1064.3498
multi2	849.6609	993.0826
multi3	846.1152	977.5851
multi4	873.0132	992.5313
multi5	841.6937	961.2118
Final Model	868.8338	976.4001
multi7	860.7692	944.4319