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Cross Sectional Analysis of Patients with Alpha-1 Antitrypsin Deficiency Enrolled in a Disease Management and Prevention Program

Jordan T. Perkins
University of Kentucky

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Jordan T. Perkins, Student

David Mannino, MD, Committee Chair

Corrine Williams, ScD, MS, Director of Graduate Studies

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Cross Sectional Analysis of Patients with Alpha-1 Antitrypsin Deficiency Enrolled in a Disease Management and Prevention Program

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the requirements for the degree of
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Jordan T. Perkins

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_____
David M. Mannino, M.D., Chair

_____
Steven R. Browning, Ph.D, Co-Chair

_____
Sabrina Brown, DrPH, Co-Chair

Table of Contents

Abbreviations

AAT   alpha-1 antitrypsin
AATD   alpha-1 antitrypsin deficiency
ADMAPP alpha-1 antitrypsin deficiency management and prevention program
BMI   body mass index
BRFG   Big Fat Reference Guide
CCI   Charlson Comorbidity Index
CI   Confidence interval
COPD   chronic obstructive pulmonary disease
OR   odds ratio
MCAR   missing completely at random
SD   standard deviation
SNP   single nucleotide polymorphism
SAS   statistical analysis system

Abstract

Background: Alpha-1 antitrypsin deficiency is a heritable genetic condition that is largely underdiagnosed and has been estimated to affect 1 out of every 5,000-7,000 people in North America. The condition is characterized by a decrease in the production or activity of the alpha-1 antitrypsin protein, increasing risk for chronic lung or liver inflammation, that may lead to disease. Currently, there is no cure for the condition and augmentation therapy, which replaces the lost protein, has shown mixed results, meaning preventive measures taken by the patient are a large component of the prescribed treatment. Thus, patients with the condition are strongly encouraged to quit smoking, reduce drinking, avoid occupations or areas that have high levels of particulate matter or toxic air pollutants as well as maintain active vaccinations against lung and liver infections like pneumonia, hepatitis A and B, and the flu to prevent complications from the condition.

Objectives: This study aims to 1) Access the associations between adherence to the AlphaNet disease management and prevention program and the prophylactic measures that are encouraged by the program and; 2) determine if any of these associations are a result of demographic and health differences between individuals who are adherent ADMAPP and those who are not.

Methods: This is a cross-sectional study of 3,526 individuals with alpha-1 antitrypsin deficiency who answered a questionnaire administered by AlphaNet from May 29th 2008 to February 14th 2015 as part of the Alpha-1 Antitrypsin Management and Prevention Program. This study focused on questions related to adherence to the program and prophylactic measures taken by the individual that are encouraged by the literature given out by the program. Only individuals who

answered questions about their adherence to the program were included in this current study. Demographic differences between the two stratified populations and an index for comorbidities were used for logistic regression analysis.

Results: After adjustment for sex, age, income, and comorbidies, compared with individuals who self-reported as being non-adherent to the disease management and prevention program, adherent individuals were more likely to be comfortable with their knowledge of the disease (OR_{adj}=4.95, 95% CI: 3.24-7.57), have read any part of the literature provided by the program (OR_{adj}=6.44, 95% CI: 5.45-7.62), and use augmentation therapy (OR_{adj}=2.08, 95% CI: 1.53-2.82). These individuals were also more likely to be vaccinated for the flu (OR_{adj}=1.34, 95% CI: 1.08-1.68), Hepatitis A (OR_{adj}=1.41, 95% CI: 1.20-1.66), and Hepatitis B (OR_{adj}=1.62, 95% CI: 1.37-1.91), as well as exercise (OR_{adj}=2.07, 95% CI: 1.74-2.47), while being less likely to be active smokers (OR_{adj}=0.47, CI: 0.31-0.70).

Conclusions: This study suggests that AlphaNet program may be a useful tool for informing and improving preventive measures taken by individuals with alpha-1 antitrypsin deficiency. Individuals who self-reported their percent adherence to the program as being nonzero were more likely to be informed about their condition and taking preventive measures, such as smoking cessation, getting vaccinated for conditions that could magnify the effects of AATD, and increases in self-reported exercise. Future studies are needed to show causality and improvement in participant outcomes such as mortality and quality of life.

Introduction

Alpha-1 antitrypsin deficiency (ATTD) was first described in 1963 by Carl-Bertil Laurell and Sten Eriksson who observed low levels of the alpha-1 antitrypsin (ATT) protein associated with the symptoms of emphysema [1]. This discovery, coupled with the association of ATTD with liver cirrhosis has led to a recognition as ATTD as being a predisposing factor for the development of liver disease and emphysema. While the condition has been identified for over 50 years, our understanding of the disease as well as the information concerning its prevalence is limited.

ATTD is a heritable condition that, as its name suggests, is a result of an individual having lower levels of the alpha-1 antitrypsin (ATT) protein. Lower levels of this protein have been linked to numerous diseases; the majority of which are related to impaired lung function and liver disease [2]. Currently there are no cures for ATTD, but several treatment options are available, most of which are the same as the ones used to treat chronic obstructive pulmonary disease (COPD) [3]. Augmentation therapy, where intravenous AAT is administered to patients, usually on a weekly basis, as well as gene therapy have also been explored as possible treatment options [3, 4], but the efficacy of these treatments is debatable; there is a lack of well-designed randomized clinical trials, among other things [5-7].

To help patients, families of patients, and healthcare providers navigate the wealth of information on AATD, individuals from AlphaNet, a not-for-profit organization founded in

1995, have developed the Alpha-1 Disease Management and Prevention Program (ADMAPP). The program provides support as well as education on the disease [8]. A large part of the education component is devoted to prophylactic measures that individuals with ATTD can take to help decrease the risk of further disease complications.

Since there is no active cure for ATTD, preventive measures are emphasized, such as smoking cessation and vaccination for certain diseases, all of which are part of the ADMAPP program. Therefore, the purpose of this analysis was to: 1) access the associations between adherence to the AlphaNet disease management and prevention program and the prophylactic measures that are encouraged by the program and; 2) determine if any of these associations are a result of demographic and health differences between individuals who are ADMAPP adherent and those who are not.

Literature Review

The following review of literature is a summary of current scientific knowledge and understanding of ATTD. It is a collection of knowledge from the molecular mechanics and genetics perspective, as well as a larger, epidemiological view of the topic. The works cited are a collection of peer-reviewed articles found on scientific literature search engines such as PubMed. The purpose of this review is to summarize the information available on ATTD that is applicable to this study and is not an exhaustive review of all the literature available.

Genetics and mechanism of action

AATD is an inherited autosomal codominant genetic condition following the Mendelian pattern of inheritance [9]. The condition is a result of a single nucleotide polymorphism (SNP) in the gene that codes for the ATT protein. These SNPs have the potential to change the amino acid composition of the protein and therefore the charge of the protein. The changes in charge alter the speed at which the proteins migrate on gel electrophoresis, which is used to characterize the specific phenotype of an individuals with ATTD [9]. The phenotypes are labeled alphabetically with the A allele having the highest rate of migration, while the more commonly observed Z allele having the slowest, and the M allele having the normal speed.[9, 10]. For clarity, the remainder of this paper will refer to the specific alleles using the common nomenclature, which is PI* (standing for protease inhibitor) followed by the allele (i.e. PI*ZZ for the homozygous Z allele phenotype).

The specific phenotype that a patient with ATTD has is clinically significant, as each is correlated with the degree of severity of the condition [10]. For instance, the PI*SZ and PI*ZZ mutations reduce ATT levels by 25% and 15% of normal, respectively [11]. This is in contrast to the more rare PI*NullNull variant, which results in the total absence of ATT due to transcriptional or translational errors that create a protein that is ultimately degraded [9, 11].

Normally, the ATT protein functions as a serine protease inhibitor, with the most notable substrate being neutrophil elastase. Briefly, when immune cells known as neutrophils are recruited to sites of inflammation they release elastase, an enzyme with broad substrate reaction activity capable of attacking a number of host proteins as well as numerous xenobiotics like bacteria or chemicals found in smoke. The release of elastase in response to inflammation is a protective mechanism by the body, as the enzyme has numerous beneficial actions such as impairing phagocytosis of bacterial pathogens [9]. ATT helps balance the protective effects of the elastase while limiting the damage to the host.

In individuals with ATTD, levels of ATT are decreased resulting in increased host damage. Importantly, the phenotype of an individual has been found to be the best determinant of ATT level variation [12]. In addition to decreased levels of ATT, the ATT present in ATTD individuals may be dysfunctional and less capable of antiprotease activity [10].

Prevalence

The presence of ATTD varies widely among different populations [13], with the largest presence being detected in groups with European ancestry, particularly in the Scandinavia regions of

Europe [3, 14]. In addition to variable prevalence of the condition, the distribution of specific alleles also varies within populations [13]. This becomes especially important in North America where the mixed descendent population creates even more variability [15]. Prevalence approximations of ATTD in North American, especially the United States, are hindered by this fact, but it has been estimated to be as high as 1 out of every 5,000-7,000 individuals in North America for the non-PI*MM (normal) phenotypes [16].

The figures for ATTD prevalence are further complicated by the lack of testing for the condition. Recent findings showing an increased prevalence in a wide array of countries indicate the impression of ATTD being a relatively rare disease may be a function of lack of testing. In addition, it has been estimated that 10-35% of individuals with certain alleles may not ever present with clinical symptoms, further decreasing chances of the condition being detected [3].These observations suggest that the condition is not rare, but rather rarely diagnosed [17].

Disease Risk

The majority of diseases associated with AATD are a result of pulmonary impairment (e.g., COPD, bronchiectasis), with a smaller proportion of patients having hepatic (e.g., cirrhosis, hepatoma) and vasculitis manifestations of the condition [2, 3, 18, 19]. Several other disease, such as coeliac disease and certain cancers, have been suggested as well, but the associations remains unclear [18]. While the specific mechanisms of the disease progression out of the scope of this study, it is important to note the systems affected by AATD.

Lung disease in patients with AATD usually manifests as emphysema or COPD and generally begins in early adulthood. The development of these diseases are often exacerbated by the presence of compounding factors such as smoking or infection [20]. Lung injury is a result of decreased levels of ATT in the lungs, which leads to unchallenged proteolytic damage to the lung tissue [3, 19]. Risk of lung disease is strongly correlated with the variant of ATTD, with PI*SZ, PI*ZZ, and PI*NullNull being the most significantly at risk [18].

While ATTD manifests as liver disease less frequently than lung disease, it can lead to serious liver dysfunction in some patients. Liver complications begin as hepatitis (inflammation of the liver) which can lead to liver cirrhosis. Unlike lung disease, the mechanism resulting in liver disease as a result of ATTD is not related to the loss of inhibitory functionality, but instead is a result of protein accumulation in the hepatocytes [18, 19]. In individuals with the PI*ZZ, and less frequently, the PI*SZ variant of ATTD, the amino acid substitution in the ATT protein causes the proteins to spontaneously polymerize, or bind together [19]. The polymerization of the protein prevents its secretion, leading to cellular inflammation and a further decrease in circulating ATT levels [18].

It is not surprising that all of the prophylactic measures suggested to ATTD patients focus on lung and liver injury prevention. ATTD patients are strongly encouraged to quit smoking, reduce drinking, avoid occupations or areas that have high levels of particulate matter or toxic air pollutants as well as maintain active vaccinations against lung and liver infections like pneumonia, hepatitis A and B, and the flu [20, 21]. With an impaired ability to respond to

xenobiotic insults, it is important that ATTD patients prevent unnecessary stress on the lungs or

liver.

Methodology

Study population

This study uses data gathered from an introductory questionnaire that individuals with ATTD in the AlphaNet system completed that has been previously described elsewhere [22]. The data set is a collection of qualitative, self-reported, questionnaire responses containing information from 4,747 unique individuals, with missing entry frequency varying between a few hundred to a few thousand. The answer date of the questionnaire ranges from May 2008 to February 2015 and contains up to 178 responses per individual. This data set includes basic demographic information (e.g. sex, race, marital status, income level), medical history (e.g. specific ATTD genetic variant, current medical conditions) and lifestyle choices (e.g. smoking, drinking, and exercise habits).

The study population was determined by the response to two questions in the questionnaire regarding adherence to the ADMAPP. Participants were ask if they currently followed the guidelines of ADMAPP as well as their estimated percentage of compliance. Any participants who responded yes or had a percent compliance as being nonzero was considered adherent, while participants who responded no or had a percent compliance of zero was considered non-adherent. After this classification process, 1,221 of the participants had missing adherence information and were therefore excluded from the study, leaving a final study population of 3,526, which was further stratified into two groups based on their self-reported compliance with the program (Figure 1).
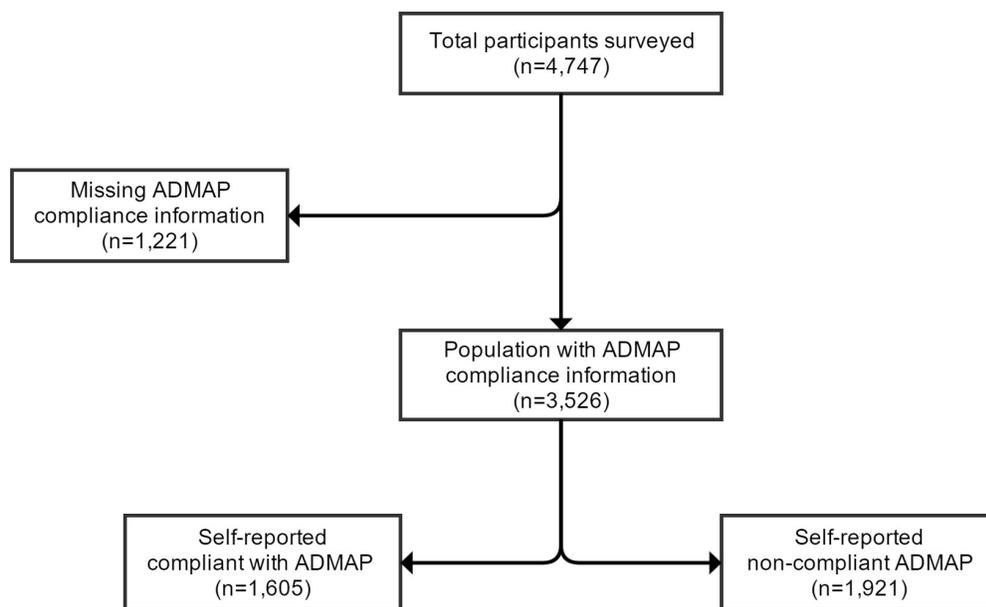
Figure 1. Flowchart of the study population.

Study Design

This is a cross sectional study aimed at identifying, assessing, and analyzing any associations found related to individuals with ATTD being compliant with the ADMAPP. The outcome of interest was on the differences in the preventive lifestyle choices between the two groups (i.e. smoking, drinking, vaccinations), health status (i.e. BMI, perceived health), and knowledge of the disease.

Variables

All of the variables used in this study were generated from self-reported data. Using this self-reported information, the following variables were used in the analysis: sex, age, race, variant of AATD, the reason they were originally tested and diagnosed for AATD, comfort level with disease knowledge, use of augmentation therapy, smoking status, drinking habits, vaccinations, BMI, perceived weight, fitness level, and health, exercise habits, heath care visits, and emergency service visits.

The outcomes variables were grouped into three categorized (Disease knowledge and treatment, exacerbating and prophylactic factors, health and health perception) based on similarities in measured outcome. Disease knowledge and treatment included self-reported comfort with current disease knowledge, as well as whether they had read any part of the BFRG and if the participant was currently using any kind of augmentation therapy. Exacerbating and prophylactic factors included current smoking status, drinking habits, as well as whether the participant had received certain vaccinations. Health and health perception included exercise habits, body mass index (BMI), health provider visits, emergency service utilization, and perceptions on various aspects the participant health.

The body mass index was calculated by dividing the weight by the square of the height and multiplying by a conversion factor of 703, per CDC guidelines [23]. The age of the participant at the time of survey completion was calculated by taking the difference between the date of birth and date the questionnaire was answered. Originally the exercise habits of individuals were broken up based on the location and regularity of the exercise. These variables were combined so

indication of exercise at any location, regardless of regularity, was categorized as an affirmative answer.

Missing and Nonsensical Data

This data set was not complete for all respondents. In order to remain transparent about this limitation, descriptive variables were reported for the individuals who were missing information for ADMAPP adherence. Currently, there is no consensus on how to statistically test for whether or not missing data is missing at random or not, which was assumed in this study. In an attempt to validate this assumption, statistical analysis was performed on differences between the study population and the missing population using various demographic and outcome variables.

To help with the issue of erroneous or nonsensical data points, several decisions regarding these data points were made, all of which are reported below.

Any variable that contained a response recorded as being unknown, was reclassified as being missing unless that was an option on the questionnaire. For questions that had sub-questions based on the answer to the original, the original answer was considered correct. For example, if an individual answered no to "Have you ever smoked cigarettes?" but had responses recorded for "How many years did you have you smoked?" or "Are you still smoking?" the responses following the original question of "Have you ever smoked cigarettes?" were marked as missing. All instances where the inch portion of a person's height were reported as being "12" were marked as missing, ultimately resulting in missing information for BMI. Finally, if self-reported

ADMAPP compliance was reported as 0 then those individuals were recoded as being non-compliant, while any compliance above 0 was considered to be compliant.

Charlson Comorbidity Index

In order to ensure differences between the two groups was not due to individuals who had more serious medical conditions being unequally distributed between the groups, the Charlson Comorbidity Index (CCI) was used. Briefly, the CCI utilizes categories of comorbidities with associated weight (Table 1) based on the risk of mortality. Mortality risk increases proportionally with the CCI score [24]. For the CCI calculations, missing or negative answers for each condition were given a score of 0, which is why there are no missing observations missing this demographic characteristic.

Table 1. The Charlson Comorbidity Index (CCI) Scoring System

Weight/Score	Condition
1	Diabetes
	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia or Alzheimer's
	Connective tissue disease
	Ulcer disease
	Mild liver disease
2	Paralysis of arms and/or legs
	Moderate or severe kidney disease
	Any tumor or cancer
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	AIDS
	Metastatic cancer

15

ADMAPP and the Big Fat Reference Guide (BFRG)

The Big Fat Reference Guide (BFRG) is a free resource provided by the AlphaNet. It is a comprehensive guide meant for patients with ATTD, their families, and medical providers and is one of the main components of the ADMAPP. Adherence with the ADMAPP is largely associated with complying with the suggestions in the BFRG. Unfortunately, the question pertaining to ADMAPP adherence did not specifically as what parts of the program the individual was compliant with, but merely an estimation of overall compliance.

Statistical analysis

Data were analyzed using SAS software, Version 8 of the SAS System for Windows. Frequencies and percentages were reported for categorical variables for the entire population as well as the subgroups within the population and were compared using chi-square tests. Continuous variables were reported as means and standards deviations; t-tests were used for comparisons. P values were reported for both continuous and categorical variables, with the significance threshold being a P value less than 0.05.

Crude odds ratios and the respective 95% confidence intervals were calculated for the variables of interest using the Proc Freq function. Adjusted odds ratios were calculated using the Proc Logistic function, controlling for age, sex, CCI, and income. Covariates were chosen based on differences in population demographics as well as potential for confounding. These covariates were then analyzed for model inclusion using a stepwise technique described elsewhere [25], the results of which are summarized in Table 2. While there was a statistically significant difference

in race between the stratified groups, the populations were almost entirely homogenous (white), therefore decided that the variable would not help our predictions. The study protocol was approved by the the Institutional Review Board at the University of Kentucky.

Results

Sample Overview

The characteristics of the total sample and sample stratified by ADMAPP compliancy as well as missing compliancy information is presented in Table 1. Overall the sample was a fairly evenly split between male and female, with no statistical differences in age, reason for original diagnosis, or the CCI between the ADMAPP compliancy stratified populations. Significant differences were observed in marital status, race, income, and specific AATD variant of the participant. By comparing the stratified populations we found majority of the selected variables were statistically different (Table 6). In addition, a choropleth map showing the number of participants per state is displayed in Figure 1, showing the geographical diversity of the population.

Disease Knowledge and Treatment

Initial analysis showed statistical differences between the stratified populations in all three of the disease knowledge and treatment outcome variables (Table 4). These variables included self-reported comfort with knowledge of the disease, whether or not they had ever read any part of the BFRG, and if they were currently using any kind of augmentation therapy. Adjustment for possible cofounders using logistic regression (Table 5) revealed individuals compliant with ADMAPP were more likely to feel comfortable about their knowledge of the disease (OR_{adj}=4.95, 95% CI: 3.24-7.57), have read any part of the BFRG (OR_{adj}=6.44, 95% CI: 5.45-

18

7.62), and twice as likely to be currently using augmentation therapy (OR_{adj}=2.08, 95% CI: 1.53-2.82).

Exacerbating and Prophylactic Factors

Initial analysis showed statistically significant differences for almost all of the exacerbating and preventive factors (Table 4). Prior to adjustment, significant increases in odds were observed in drinking status as well as all vaccination rates, while showing a decreased odds of smoking (Table 5). After adjusting for possible confounding, the increase in drinking status and pneumonia vaccination rates were no longer statistically significant. ADMAPP adherence was found to have a statistically significant, but marginal effect, on vaccination rates for flu in the last year (OR_{adj}=1.34, 95% CI: 1.08-1.68), Hepatitis A (OR_{adj}=1.41, 95% CI: 1.20-1.66), and Hepatitis B (OR_{adj}=1.62, 95% CI: 1.37-1.91). Most notably, odds of ADMAPP adherent participants still being a smoker were greatly decreased (OR_{adj}=0.47, CI: 0.31-0.70).

Health and Health Perception

Prior to logistic regression adjustment (Table 5), of all the health and health perception outcome variables examined, only exercise status (OR=2.21, 95% CI: 1.89-2.59), self-reported perception of weight (About Right vs Overweight, OR=1.17, 95% CI: 1.02-1.35), self-reported perception of physical health (Pretty fit/Getting fit/Very fit vs. Out of Shape, OR=1.68, 95% CI: 1.47-1.93), self-reported perception of overall health (Excellent/Good vs Fair/Poor, OR=1.32, 95% CI: 1.15-1.51), if participant saw a physician other than the ones listed (OR=1.29, 95% CI:1.12-1.47), and if a participant had any unscheduled physician visits (OR=1.16, 95% CI: 1.01-1.33) were

statistically significant. After adjustment, only exercise status (OR_{adj}=2.07, 95% CI: 1.74-2.47), self-reported perception of physical health (OR_{adj}=1.66, 95% CI: 1.43-1.94) if participant saw a physician other than the ones listed (OR_{adj}=1.28, 95% CI:1.10-1.50), and if a participant had any unscheduled physician visits (OR_{adj}=1.27, 95% CI: 1.08-1.48).

Discussion

Missing Completely at Random Assumption

Missing information was a significant problem in this study, with 25.72% of subjects available in the dataset having no information on ADMAPP adherence. While there is no consensus on the appropriate way to determine when missing data is considered missing completely at random (MCAR), it is an important consideration for this study. To address this issue, demographic and outcome variables were arbitrarily selected and compared between the population with ADMAPP adherence information and the missing population.

After analysis, 11 of the 16 demographic characteristics and outcomes examined (Table 6) were found to be significantly different between the two populations. While these findings suggest the data is not MCAR there is a large number of missing information within the missing population. Of the 11 variables found to significantly different, 9 had a majority of missing observations. Taken together, these findings make it difficult to conclude the nature of the missing data.

ADMAPP Adherent Participants are More Informed About AATD

Self-reported comfort with knowledge on ATTD, as well as utilization of the BFRG were associated with the largest odds ratio increase of all the outcome variables examined. The information contained within the BFRG is extensive, covering a multitude of topics that are related to ATTD and the observed increase in utilization is substantial. The guide itself is the largest part of the ADMAPP program so these results suggest that individuals are reading the guide and are retaining information from it, which may translate into prophylactic behavioral

changes. These results must be interpreted cautiously though, as this is not a validated measure of change in participant knowledge and is relative to the person answering the question. It does not measure whether or not the knowledge is correct, merely whether or not they feel comfortable with their knowledge.

Physician and Emergency Medical Service Utilization

The interpretation of the overall physician and emergency medical services utilization is difficult for this data set and must be done cautiously. For the purposes of this analysis, health provider visits (primary care, lung or liver specialist, other MD) were considered preventive measures. This was done because the BRFG suggests annual or biannual visits to a primary care physician and other physicians visits as necessary, which is the rational for doing logistic regression with physician visits being categorized as a binary outcome (did or did not use). It could be understandably argued that these same outcomes could be a negative indication.

Interestingly, in unadjusted analysis (Table 4), the average number of primary care visits was higher in the non-adherent group, although the increase is not clinically significant. Once the primary care visits were re-categorized as a binary variable, this difference was lost, leaving only a slight increase in odds of "other" physician utilization. Considering the large number of physician specialties completely unrelated to ATTD, it is impossible to confidently draw any conclusions on the implications of these findings.

Prophylactic Measures Associated with ADMAPP Adherence

Since there is currently no cure for AATD, much of the treatment information for individuals with the condition focuses on prophylactic measures that can be taken to decrease the burden of disease on the individual. Generally, these measures are focused on preventing xenobiotic and infectious insult to the lungs or liver, and healthy lifestyle choices. Ultimately, the aim is to avoid a pro-inflammatory environment.

Smoking is a major cause of inflammation in the lungs, increasing host damage due to AATD, and as such, is a major focus of the ADMAPP. This study found that ADMAPP adherent individuals were far less likely to be active smokers, which is clinically significant (Table 5). In addition, these individuals were more likely to be vaccinated for the flu in the past year, hepatitis A, hepatitis B, which can be more serious in individuals with AATD, and recommended vaccinations in the BFRG. Pneumonia vaccination rates were also significantly increased in the adherent population prior to adjustment, but were not statistically significant in the logistic regression model. Taken together these results are encouraging and suggest that the ADMAPP adherent individuals are more likely to take an active effort in reducing the chances aggravating their condition.

Perceived Health and Fitness

A number of questions on the survey dealt with the subject's perception of their general health and fitness as well as their exercise habits. The initial comparisons (Table 4) suggested several instances of distinction between the two populations. Adjustment for covariates showed

perceived fitness and exercise habits as being the only two statistically significant differences. Like the other results presented, these conclusions should also be carefully interpreted.

For the perceived fitness question, the comparison was between individuals who answered "out of shape" and those who answered any of the other options ("getting fit", "pretty fit", "very fit"). These, like many of the other questions, have subjective answers that are relative to the observer, meaning one person's definition of "pretty fit" could be another person's definition of "out of shape." This question may also be influenced by what can be referred to as "wishful thinking," meaning reporting may be based on what makes the individual feel better as opposed to reality.

While the ADMAPP adherent population was also found to be more likely to exercise, caution should also be used when correlating the two questions. The exercise observation was a combination of answers, similar to the perceived fitness question. Originally, study participants were given the option of choosing no exercise or four additional options that included various locations and regularity of exercise. These answers were combined so that any answer besides no exercise, was coded as a yes. For the purposes of this study, it was decided that the regularity of the exercise or location were not imperative to final interpretation, but the effort of exercise was.

Even with these limitations, the conclusion that ADMAPP adherent individuals are more likely to exercise and have a positive image of their fitness remains fairly strong. It was not surprising to not see a corresponding change in BMI or perceived weight. Significant changes in weight would be the result of long term changes to multiple aspects of a person's lifestyle. Considering the lack of temporality of this data, it is impossible to state how long people have been involved

in the program and therefore the impact of the program on that aspect may just not be visible at the time of the survey.

The lack of differences between the perceived health of the total populations was equally unsurprising. Health is an encompassing term and can mean many things to different people. Without the explicitly stating in the question was aspects of health the questionnaire was referring to (e.g., mental health, physical health, conditions unrelated to AATD), a statistically significant difference would be difficult to interpret in the proper context.

Limitations

There are several important limitations of this study that should be considered along with the results. First, all of the information, including the medical history, was collected via a self-report questionnaire which brings into question the validity of the information provided. The self-report nature of the study brings in recall bias (how accurate a person was able to remember information), reporting bias (selective revealing or suppressing of information by the participant), as well as a degree of social desirability bias (participants providing answers that they think are correct or desired). The data also lacked a longitudinal component, meaning the associations presented cannot be used to infer causality. In addition to this, there was also a significant proportion of missing data and nonsensical entries, which are discussed in the methodology section. The proportion of missing entries for the question concerning ADMAPP compliance was 25.72%, meaning our results may under- or overestimate the true results.

Conclusions

While missing observations continue to be a limitation of this study, the large sample size and observations about the missing population alleviate some of the concerns about the missing information. As this study indicates an association between ADMAPP adherence several preventive outcomes, future studies need to be conducted using longitudinal data on this population to determine if this relationship is causal. Ultimately, The results of this study display the positive impact the ADMAPP can have on individuals with AATD. Individuals who self-reported their percent adherence to the program as being nonzero were more likely to be informed about their condition and taking preventive measures, such as smoking cessation, getting vaccinated for conditions that could magnify the effects of AATD, and increases in self-reported exercise.

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Additional Tables

Table 2. Covariates determined to be significant for each outcome

	Age	Sex	Income	CCI
Disease Knowledge and Treatment				
Comfort with disease knowledge (Comfortable vs not comfortable)			Y	Y
Have read any part of BFRG (Yes vs No)			Y	Y
Use augmentation therapy (Yes vs No)	Y		Y	
Exacerbating and Prophylactic Factors				
Still smoking (Yes vs No)	Y		Y	
Drinker (Yes vs No)		Y	Y	Y
Vaccinations				
Pneumonia in last 6 years (Yes vs No)	Y		Y	
Flu vaccine in last year (Yes vs No)	Y		Y	
Hepatitis A (Yes vs No)	Y	Y	Y	Y
Hepatitis B (Yes vs No)	Y	Y	Y	
Health and Health Perception				
Exercise (Yes vs No)	Y		Y	Y
BMI				
(Normal vs Overweight/Obese)	Y	Y	Y	Y
(Normal vs Underweight)			Y	
Perceived weight				
(About Right vs Underweight)	Y		Y	Y
(About Right vs Overweight)	Y	Y	Y	Y
Perceived fitness (Pretty fit/Getting fit/Very fit vs Out of Shape)	Y	Y	Y	Y
Perceived health (Good/Excellent vs Poor/Fair)	Y		Y	Y
Health care provider visits				
Primary care ($\geq$ 1 visit vs 0 visits)	Y	Y	Y	Y
Lung specialist ($\geq$ 1 visit vs 0 visits)	Y	Y		
Liver specialist ($\geq$ 1 visit vs 0 visits)	Y			Y
Other MD ($\geq$ 1 visit vs 0 visits)	Y	Y	Y	Y
Emergency services utilization over past year				
Hospital admittance (Yes vs No)	Y		Y	Y
ICU admittance (Yes vs No)	Y		Y	Y
ER (Yes vs No)	Y		Y	Y
Unscheduled MD visit (Yes vs No)	Y		Y	Y
Percent significant	83.3%	37.5%	91.7%	70.8%

Table 3. Descriptive characteristics and statistics of the study population

	Total Population n=4,747 # (%)	Non-Adherent ADMAPP Users n=1,921 # (%)	Adherent ADMAPP Users n=1.605 # (%)	P-Values	Missing n=1,221 # (%)
Sex				0.059	
Male	2397 (50.50)	1,026 (53.41)	806 (50.22)		565 (46.27)
Female	2135 (44.98)	873 (45.45)	780 (48.60)		482 (39.48)
Missing	215 (4.53)	22 (1.15)	19 (1.18)		174 (14.25)
Age (Mean ± SD)	56.67 ± 11.76	56.34 ± 12.19	56.96 ± 11.22	0.117	56.82 ± 11.77
Marital status				**0.004**	
Married	2,787 (58.71)	1,141 (59.40)	1,042 (64.92)		604 (49.47)
Single	1,640 (34.55)	715 (37.22)	531 (33.08)		394 (32.27)
Missing	320 (6.74)	65 (3.38)	32 (1.99)		223 (18.26)
Race				**<0.001**	
White	4,399 (92.67)	1,825 (95.00)	1,563 (97.38)		1,011 (82.80)
Non-White	107 (2.25)	61 (3.18)	24 (1.50)		22 (1.80)
Missing	241 (5.08)	35 (1.82)	18 (1.12)		188 (15.40)
Income				**<0.001**	
<$20,000	1,150 (33.55)	564 (35.97)	371 (28.06)		215 (39.96)
$20,000-$40,000	910 (26.55)	414 (26.40)	361 (27.31)		135 (25.09)
$40,000-$$60,000	572 (16.69)	267 (17.03)	234 (17.70)		71 (13.20)
$60,000-$80,000	341 (9.95)	147 (9.38)	147 (11.12)		47 (8.74)
$80,000-$100,000	191 (5.57)	75 (4.78)	84 (6.35)		32 (5.95)
>$100,000	264 (7.70)	101 (6.44)	125 (9.46)		38 (7.06)
Missing	1,319	353	283		683
AATD variant				**<0.001**	
PI*ZZ	2,507 (52.81)	1,036 (53.93)	1,022 (63.68)		449 (36.77)
PI*MZ	522 (11.00)	196 (10.20)	140 (8.72)		186 (15.23)
PI*SZ	323 (6.80)	110 (5.73)	94 (5.86)		119 (9.75)
PI*ZNull	33 (0.70)	13 (0.68)	13 (0.81)		7 (0.57)
PI*NullNull	14 (0.29)	7 (0.36)	5 (0.31)		2 (0.16)
Other	162 (3.41)	54 (2.81)	55 (3.43)		53 (4.34)
Unknown	769 (16.20)	397 (20.67)	227 (14.14)		145 (11.88)
Missing	417 (8.78)	108 (5.62)	49 (3.05)		260 (21.29)
Charlson Comorbidity Index (Mean ± SD)	0.77 ± 1.28	0.78 ± 1.29	0.76 ± 1.27	0.760	0.75 ± 1.27
0	3004 (63.28)	1,200 (62.47)	1,017 (63.36)	0.927	787 (64.46)
1	725 (15.27)	308 (16.03)	240 (14.95)		177 (14.50)
2	567 (11.94)	231 (12.02)	196 (12.21)		140 (11.47)
3	218 (4.59)	84 (4.37)	75 (4.67)		59 (4.83)
4	113 (2.38)	48 (2.50)	36 (2.24)		29 (2.38)
5	53 (1.12)	20 (1.04)	20 (1.25)		13 (1.06)
≥6	67 (1.41)	30 (1.56)	21 (1.31)		16 (1.31)
Diagnosis prompt					
Early onset lung disease				0.438	
Yes	1,083 (22.81)	497 (25.87)	435 (27.10)		151 (12.37)
No	3,496 (73.65)	1,409 (73.35)	1,162 (72.40)		925 (75.76)
Missing	168 (3.54)	15 (0.78)	8 (0.50)		145 (11.88)
Emphysema				0.842	
Yes	1,127 (23.74)	471 (24.52)	390 (24.30)		266 (21.79)
No	3,452 (72.72)	1,435 (74.70)	1,207 (75.20)		810 (66.34)
Missing	168 (3.54)	15 (0.078)	8 (0.50)		145 (11.88)
Uncontrolled asthma				0.205	
Yes	593 (12.49)	235 (12.23)	220 (13.71)		138 (11.30)
No	3,986 (83.97)	1,671 (86.99)	1,377 (85.79)		938 (76.82)
Missing	168 (3.54)	15 (0.78)	8 (0.50)		145 (11.88)
Screening because relative has				0.730	
Yes	666 (14.03)	286 (14.89)	233 (14.52)		147 (12.04)
No	3,913 (82.43)	1,620 (84.33)	1,364 (84.98)		929 (76.09)
Missing	168 (3.54)	15 (0.78)	8 (0.50)		145 (11.88)
Chronic bronchitis				0.080	
Yes	672 (14.16)	272 (14.16)	262 (16.32)		138 (11.30)
No	3,907 (82.30)	1,634 (85.06)	1,335 (83.18)		938 (76.82)
Missing	168 (3.54)	15 (0.78)	8 (0.50)		145 (11.88)
Bronchiectasis				0.087	
Yes	101 (2.13)	34 (1.77)	42 (2.62)		25 (2.05)
No	4,477 (94.31)	1,872 (97.45)	1,555 (96.88)		1,050 (86.00)
Missing	169 (3.56)	15 (0.78)	8 (0.50)		146 (11.96)
COPD				0.496	
Yes	1,145 (24.12)	447 (23.27)	359 (22.37)		339 (27.76)
No	3,434 (72.34)	1,459 (75.95)	1,238 (77.13)		737 (60.36)
Missing	168 (3.54)	15 (0.78)	8 (0.50)		145 (11.88)
Cirrhosis				0.829	
Yes	40 (0.84)	12 (0.62)	11 (0.69)		17 (1.39)
No	4,538 (95.60)	1,894 (98.59)	1,586 (98.82)		1,058 (86.65)
Missing	169 (3.56)	15 (0.78)	8 (0.50)		146 (11.96)

29

Table 4. Descriptive characteristics and statistics for outcome variables of interest

	Total Population n=4,747 # (%)	Non-Adherent ADMAPP Users n=1,921 # (%)	Adherent ADMAPP Users n=1.605 # (%)	P-Values	Missing n=1,221 # (%)
Disease Knowledge/Treatment					
Comfort with disease knowledge				<0.001	
Not comfortable	268 (5.65)	147 (7.65)	36 (2.24)		85 (6.96)
Somewhat comfortable	2,109 (44.43)	960 (49.97)	574 (35.76)		575 (47.09)
Comfortable	2,114 (44.53)	782 (40.71)	974 (60.69)		358 (29.32)
Missing	256 (5.39)	32 (1.67)	21 (1.31)		203 (16.63)
Read any part of BFRG				<0.001	
Yes	1,886 (39.73)	518 (26.97)	1,126 (70.16)		242 (19.82)
No	2,180 (45.92)	1,361 (70.85)	461 (28.72)		358 (29.32)
Missing	681 (14.35)	42 (2.19)	18 (1.12)		621 (50.86)
Use augmentation therapy				<0.001	
Yes	3,750 (79.00)	1,679 (87.40)	1,500 (93.46)		571 (46.76)
No	383 (8.07)	190 (9.89)	83 (5.17)		110 (9.01)
Missing	614 (12.93)	52 (2.71)	22 (1.37)		540 (44.23)
Exacerbating and Preventive Factors					
Smoking status				0.831	
Never smoked	1,022 (21.53)	463 (24.10)	398 (24.80)		161 (13.19)
Have smoked	3,095 (65.20)	1,415 (73.66)	1,196 (74.52)		484 (39.64)
Missing	630 (13.27)	43 (2.24)	11 (0.69)		576 (47.17)
Still smoking				<0.001	
Yes	185 (5.98)	107 (5.98)	38 (3.18)		40 (8.26)
No	2,893 (93.47)	1,295 (91.52)	1,157 (96.74)		441 (91.12)
Missing	17 (0.55)	13 (0.92)	1 (0.08)		3 (0.62)
Drinking habits				0.001	
Don't drink	2,340 (49.29)	1,093 (56.90)	842 (52.46)		405 (33.17)
Drink	1,716 (36.15)	757 (39.41)	727 (45.30)		232 (19.00)
Missing	691 (14.56)	71 (3.70)	36 (2.24)		584 (47.83)
Weekly Drinks (Mean $\pm$ SD)	5.52 $\pm$ 6.69	5.79 $\pm$ 7.07	5.50 $\pm$ 6.55	0.416	4.72 $\pm$ 5.77
Vaccinations					
Pneumonia in last 6 years				0.017	
Yes	3,488 (73.48)	1,586 (82.56)	1,391 (86.67)		511 (41.85)
No	529 (11.14)	255 (13.27)	174 (10.84)		100 (8.19)
Missing	730 (15.38)	80 (4.16)	40 (2.49)		610 (49.96)
Flu vaccine in last year				<0.001	
Yes	3,522 (74.19)	1,592 (82.87)	1,409 (87.79)		521 (42.67)
No	574 (12.09)	285 (14.84)	176 (10.97)		113 (9.25)
Missing	651 (13.71)	44 (2.29)	20 (1.25)		587 (48.08)
Hepatitis A				<0.001	
Yes	1,578 (33.24)	677 (35.24)	733 (45.67)		168 (13.76)
No	1,835 (38.66)	864 (44.98)	620 (38.63)		351 (28.75)
Missing	1,334 (28.10)	380 (19.78)	252 (15.70)		702 (57.49)
Hepatitis B				<0.001	
Yes	2,225 (46.87)	957 (49.82)	1,046 (65.17)		222 (18.18)
No	1,430 (30.12)	681 (35.45)	427 (26.60)		322 (26.37)
Missing	1,092 (23.00)	283 (14.73)	132 (8.22)		677 (55.45)
General Health Information					
Body mass index (BMI)				0.274	
Underweight	212 (4.47)	91 (4.74)	76 (4.74)		45 (3.69)
Normal	1,553 (32.72)	655 (34.10)	580 (36.14)		318 (26.04)
Overweight	1,249 (26.31)	515 (26.81)	439 (27.35)		295 (24.16)
Obese	1,304 (21.78)	443 (23.06)	328 (20.44)		263 (21.54)
Missing	699 (14.73)	217 (11.30)	182 (11.34)		300 (24.57)
Perceived weight				0.084	
Underweight	482 (10.15)	225 (11.71)	184 (11.46)		73 (5.98)
About right	1,605 (33.81)	716 (37.27)	665 (41.43)		224 (18.35)
Overweight	2,009 (42.32)	930 (48.41)	736 (45.86)		343 (28.09)
Missing	651 (13.71)	50 (2.60)	20 (1.25)		581 (47.58)
Perceived fitness				<0.001	
Out of shape	1,967 (41.44)	982 (51.12)	632 (39.38)		353 (28.91)
Pretty fit	1,205 (25.38)	502 (26.13)	531 (33.08)		172 (14.09)
Getting fit	781 (16.45)	323 (16.81)	351 (21.87)		107 (8.76)
Very fit	115 (2.42)	45 (2.34)	61 (3.80)		9 (0.74)
Missing	679 (14.30)	69 (3.59)	30 (1.87)		580 (47.50)
Perceived Health				<0.001	
Poor	781 (16.45)	378 (19.68)	273 (17.01)		130 (10.65)
Fair	1,745 (36.76)	826 (43.00)	646 (40.25)		273 (22.36)
Good	1,407 (29.64)	601 (31.29)	589 (36.70)		217 (17.77)
Excellent	152 (3.20)	58 (3.02)	74 (4.61)		20 (1.64)
Missing	662 (13.95)	58 (3.02)	23 (1.43)		581 (47.58)
Exercise Habits				<0.001	
Exercise	2,720 (57.30)	1,103 (57.42)	1,192 (74.27)		425 (34.81)

Don't exercise	1,206 (25.41)	661 (34.41)	323 (20.12)		222 (18.18)
Missing	821 (17.30)	157 (8.17)	90 (5.61)		574 (47.01)
Health Provider Visits (Mean $\pm$ SD), past year					
Primary care	3.30 $\pm$ 2.00	3.32 $\pm$ 2.05	3.13 $\pm$ 1.96	**0.006**	3.53 $\pm$ 1.94
Lung specialist	3.00 $\pm$ 1.75	3.01 $\pm$ 1.74	2.94 $\pm$ 1.76	0.280	3.04 $\pm$ 1.76
Liver specialist	0.19 $\pm$ 0.79	0.17 $\pm$ 0.71	0.20 $\pm$ 0.81	0.240	0.24 $\pm$ 0.88
Other MD	1.76 $\pm$ 2.08	1.66 $\pm$ 2.08	1.81 $\pm$ 2.06	**0.048**	1.87 $\pm$ 2.11
Emergency Service Visits (Mean $\pm$ SD), past year					
Hospital admittance	0.70 $\pm$ 1.30	0.72 $\pm$ 1.35	0.63 $\pm$ 1.21	**0.046**	0.76 $\pm$ 1.34
Intensive Care Unit admittance	0.13 $\pm$ 0.50	0.13 $\pm$ 0.53	0.12 $\pm$ 0.45	0.549	0.13 $\pm$ 0.50
Emergency room	0.63 $\pm$ 1.27	0.67 $\pm$ 1.32	0.59 $\pm$ 1.19	0.061	0.65 $\pm$ 1.31
Unscheduled MD visit	0.98 $\pm$ 1.64	0.91 $\pm$ 1.58	1.03 $\pm$ 1.66	**0.032**	1.01 $\pm$ 1.74

Table 5. Comparison of outcome variables between ADMAPP adherent to non-adherent populations using logistic regression

	Crude Odds ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Disease Knowledge and Treatment		
Comfort with disease knowledge (Comfortable vs not comfortable)	**5.09 (3.49-7.41)**	**4.95 (3.24-7.57)**
Have read any part of BFRG (Yes vs No)	**6.42 (5.53-7.44)**	**6.44 (5.45-7.62)**
Use augmentation therapy (Yes vs No)	**2.05 (1.57-2.67)**	**2.08 (1.53-2.82)**
Exacerbating and Prophylactic Factors		
Still smoking (Yes vs No)	**0.40 (0.27-0.58)**	**0.47 (0.31-0.70)**
Drinker (Yes vs No)	**1.25 (1.09-1.43)**	1.12 (0.96-1.31)
Vaccinations		
Pneumonia in last 6 years (Yes vs No)	**1.29 (1.05-1.58)**	1.14 (0.90-1.44)
Flu vaccine in last year (Yes vs No)	**1.43 (1.17-1.75)**	**1.34 (1.08-1.68)**
Hepatitis A (Yes vs No)	**1.51 (1.30-1.74)**	**1.41 (1.20-1.66)**
Hepatitis B (Yes vs No)	**1.74 (1.50-2.02)**	**1.62 (1.37-1.91)**
Health and Health Perception		
Exercise (Yes vs No)	**2.21 (1.89-2.59)**	**2.07 (1.74-2.47)**
BMI		
(Normal vs Overweight/Obese)	1.11 (0.96-1.28)	1.04 (0.88-1.23)
(Normal vs Underweight)	1.06 (0.77-1.47)	0.99 (0.68-1.44)
Perceived weight		
(About Right vs Underweight)	1.14 (0.91-1.42)	1.03 (0.80-1.33)
(About Right vs Overweight)	1.17 (1.02-1.35)	1.12 (0.95-1.31)
Perceived fitness (Pretty fit/Getting fit/Very fit vs Out of Shape)	**1.68 (1.47-1.93)**	**1.66 (1.43-1.94)**
Perceived health (Good/Excellent vs Poor/Fair)	1.32 (1.15-1.51)	1.16 (0.98-1.36)
Health care provider visits		
Primary care ($\geq$ 1 visit vs 0 visits)	1.15 (0.91-1.46)	1.22 (0.94-1.60)
Lung specialist ($\geq$ 1 visit vs 0 visits)	1.01 (0.75-1.36)	1.07 (0.77-1.48)
Liver specialist ($\geq$ 1 visit vs 0 visits)	1.13 (0.88-1.45)	1.13 (0.85-1.50)
Other MD ($\geq$ 1 visit vs 0 visits)	**1.29 (1.12-1.47)**	**1.28 (1.10-1.50)**
Emergency services utilization over past year		
Hospital admittance (Yes vs No)	0.89 (0.78-1.03)	0.94 (0.80-1.11)
ICU admittance (Yes vs No)	1.06 (0.84-1.33)	1.15 (0.89-1.50)
ER (Yes vs No)	0.89 (0.77-1.03)	1.00 (0.84-1.18)
Unscheduled MD visit (Yes vs No)	**1.16 (1.01-1.33)**	**1.27 (1.08-1.48)**

Table 6. Results of testing for for missing ADMAPP adherence data

|	Have Information on ADMAPP Adherence n=3,526 # (%)	Missing Information on ADMAPP Adherence n=1,221 # (%)	P-value
Sex			0.428
Male	1,832 (51.96)	565 (46.27)	
Female	1,653 (46.88)	482 (39.48)	
Missing	41 (1.16)	174 (14.25)	
Marital status			0.705
Married	2,183 (61.91)	604 (49.47)	
Single	1,246 (35.34)	394 (32.27)	
Missing	97 (2.75)	253 (20.72)	
Race			0.550
White	3,388 (96.09)	1,011 (82.80)	
Non-White	85 (2.41)	22 (1.80)	
Missing	53 (1.50)	188 (15.40)	
Income			**0.013**
<$20,000	935 (26.52)	215 (17.61)	
$20,000-$40,000	775 (21.98)	135 (11.06)	
$40,000-$$60,000	501 (14.21)	71 (5.81)	
$60,000-$80,000	294 (8.34)	47 (3.85)	
$80,000-$100,000	159 (4.51)	32 (2.62)	
>$100,000	226 (6.41)	38 (3.11)	
Missing	636 (18.04)	683 (55.94)	
Comfort with disease knowledge			**<0.001**
Not comfortable	183 (5.19)	85 (6.96)	
Somewhat comfortable	1,534 (43.51)	575 (47.09)	
Comfortable	1,756 (49.80)	358 (29.32)	
Missing	53 (1.50)	203 (16.63)	
Read any part of BFRG			**0.001**
Yes	1,644 (46.63)	242 (19.82)	
No	1,822 (51.67)	358 (29.32)	
Missing	60 (1.70)	621 (50.86)	
Pneumonia vaccine in last 6 years			**0.011**
Yes	2,977 (84.43)	511 (41.85)	
No	429 (12.17)	100 (8.19)	
Missing	120 (3.40)	610 (49.96)	
Flu vaccine in last year			**0.003**
Yes	3,001 (85.11)	521 (42.67)	
No	461 (13.07)	113 (9.25)	
Missing	64 (1.82)	587 (48.08)	
Hepatitis A vaccine			**<0.001**
Yes	1,410 (39.99)	168 (13.76)	
No	1,484 (42.09)	351 (28.75)	
Missing	632 (17.92)	702 (57.49)	
Hepatitis B vaccine			**<0.001**
Yes	2,003 (56.81)	222 (18.18)	
No	1,108 (31.42)	322 (26.37)	
Missing	415 (11.77)	677 (55.45)	
Body mass index (BMI)			**0.022**
Underweight	167 (4.74)	45 (3.69)	
Normal	1,235 (35.03)	318 (26.04)	
Overweight	954 (27.06)	295 (24.16)	
Obese	771 (21.87)	263 (21.54)	
Missing	399 (11.32)	300 (24.57)	
Perceived weight			**0.036**
Underweight	409 (11.60)	73 (5.98)	
About right	1,381 (39.17)	224 (18.35)	
Overweight	1,666 (47.25)	343 (28.09)	
Missing	70 (1.99)	581 (47.58)	
Perceived fitness			**<0.001**
Out of shape	1,614 (45.77)	353 (28.91)	
Pretty fit	1,033 (29.30)	172 (14.09)	
Getting fit	674 (19.12)	107 (8.76)	
Very fit	106 (3.01)	9 (0.74)	
Missing	99 (2.81)	580 (47.50)	
Perceived Health			0.716
Poor	651 (18.46)	130 (10.65)	
Fair	1,472 (41.75)	273 (22.36)	
Good	1,190 (33.75)	217 (17.77)	
Excellent	132 (3.74)	20 (1.64)	
Missing	81 (2.30)	581 (47.58)	
Exercise Habits			**0.030**
Exercise	2,295 (65.09)	425 (34.81)	
Don't exercise	984 (27.91)	222 (18.18)	
Missing	247 (7.01)	574 (47.01)	

Additional Figures
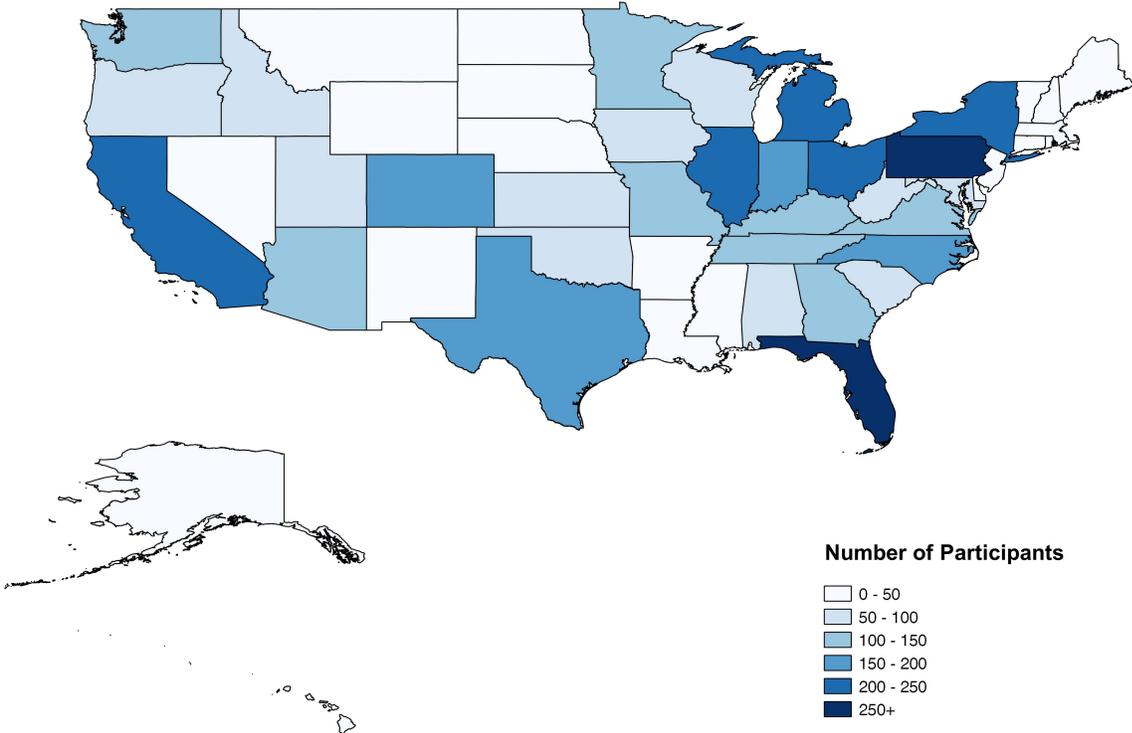
Figure 2. Choropleth map showing state of residence of study participants

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