Respiratory Medicine 143 (2018) 48–55

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Genotype is associated with smoking and other key health behaviors among individuals with alpha-1 antitrypsin deficiency-associated lung disease

Kristen E. Holm[a,b,*], David M. Mannino[c,d], Radmila Choate[c], Robert A. Sandhaus[a,b]

[a] Department of Medicine, National Jewish Health, United States
[b] AlphaNet, Inc., United States
[c] Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, United States
[d] GlaxoSmithKline Plc, United Kingdom

ARTICLE INFO

Keywords:
Augmentation therapy
Alpha-1 antitrypsin deficiency
Disease management
Genotype
Health behaviors
Lung disease

ABSTRACT

Objective: To examine the association of genotype with smoking and other key health behaviors among individuals with alpha-1 antitrypsin deficiency (AATD) associated lung disease.

Methods: Self-reported data were analyzed from 3506 individuals with AATD-associated lung disease. All data were collected upon enrollment in a disease management program designed for individuals who have been prescribed augmentation therapy. Multivariate logistic regression was utilized to examine the extent to which genotype was associated with smoking and other key health behaviors (i.e., getting a pneumonia vaccine, getting a flu vaccine, exercising, and maintaining a healthy weight). We hypothesized that MZs and SZs are more likely than ZZs to be current smokers, and that genotype is associated with additional health behaviors.

Results: MZs and SZs had higher odds of being a current smoker than ZZs (MZ versus ZZ OR = 2.73, $p < .001$; SZ versus ZZ OR = 4.34, $p < .001$). For every additional health behavior examined, MZs had higher odds of unhealthy behavior than ZZs (ORs ranged from 1.35 to 1.98, $p < .05$). SZs had higher odds of unhealthy behavior than ZZs with regard to lack of exercise (OR = 1.52, p = .003) and failure to maintain a healthy weight (underweight OR = 1.93, p = .028; overweight OR = 1.43, p = .015).

Conclusions: Among individuals who have been prescribed augmentation therapy for lung disease due to AATD, genotype is associated with smoking and additional health behaviors that are central to managing lung disease.

1. Introduction

Alpha-1 antitrypsin deficiency (AATD) is a genetic condition that increases the risk of developing lung disease [1]. The emphysema subtype of chronic obstructive pulmonary disease (COPD) is the most common health problem caused by AATD [2,3]. Various environmental exposures influence the risk of developing lung disease, but the primary factors that influence this risk are cigarette smoking and the severity of AATD [4–6].

The two most common deficient alleles are S and Z, with Z being more severely deficient [7]. The majority of identified patients with AATD-associated lung disease have the ZZ genotype [8]. The M allele is not deficient, and individuals with the MZ genotype are typically referred to as "carriers." Whether individuals with the MZ genotype are at increased risk of developing lung disease has been a controversy for decades [9]. Mounting evidence suggests that individuals with the MZ genotype are at an increased risk of developing lung disease, especially those who smoke [6,10–13]. However, the biological mechanisms that underlie the increased risk among individuals with the MZ genotype remain unknown, given that serum levels of alpha-1 antitrypsin are above the putative protective threshold in these individuals [14].

AATD-associated lung disease is currently incurable and typically has a gradually progressive course. The only specific drug therapy available for individuals with AATD-associated lung disease is augmentation therapy. Augmentation therapy involves infusions of plasma-derived alpha-1 antitrypsin, usually on a weekly basis, with the goal of slowing the rate of decline in lung function [15–21]. Guidelines for the management of AATD-associated lung disease provide specific recommendations regarding augmentation therapy, emphasize the importance of smoking cessation, and discuss additional behavioral recommendations such as vaccinations against pneumococcus and influenza, engagement in regular physical activity, and maintaining a healthy weight [18,22–24]. Disease management is an important component of treatment for AATD-associated lung disease [25,26]. A

* Corresponding author. National Jewish Health, 1400 Jackson Street, Denver, CO, 80206, United States.
E-mail address: holmk@njhealth.org (K.E. Holm).

https://doi.org/10.1016/j.rmed.2018.08.016
Received 20 June 2018; Received in revised form 21 August 2018; Accepted 31 August 2018
Available online 01 September 2018
0954-6111/

Abbreviation list

AATD	alpha-1 antitrypsin deficiency
BMI	body mass index
CCI	Charlson Comorbidity Index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
OR	odds ratio

major focus of disease management is the promotion of behavioral recommendations for optimal management of AATD-associated lung disease (e.g., smoking cessation, engagement in regular physical activity).

No research to date has systematically examined, among a sample of individuals with AATD-associated lung disease, the extent to which individuals with the MZ genotype (hereinafter MZs) and individuals with the SZ genotype (hereinafter SZs) differ from individuals with the ZZ genotype (hereinafter ZZs) with regard to health behaviors that are critical in managing lung disease. The aim of the current study was to examine the association of genotype with smoking and other key health behaviors among individuals with AATD-associated lung disease. We hypothesized that MZs and SZs are more likely than ZZs to be current smokers. We also hypothesized that genotype is associated more broadly with health behaviors that are recommended for individuals with AATD-associated lung disease (i.e., getting recommended vaccines, exercising, and maintaining a healthy weight). Individuals who did not know their genotype also were compared to ZZs. We hypothesized that these individuals have worse health behaviors than ZZs. The assumption underlying this hypothesis is that not knowing one's own genotype may indicate a low level of engagement in managing one's health condition, which would be demonstrated via limited participation in recommended health behaviors among these individuals. Data were collected by AlphaNet, a not-for-profit organization that provides a telephone-based disease self-management program designed for individuals with AATD-associated lung disease who are prescribed augmentation therapy [25]. AlphaNet follows the majority of individuals in the United States who are prescribed augmentation therapy for lung disease due to AATD. As such, these data provide an opportunity to examine correlates of health behaviors in a large sample of geographically diverse patients.

2. Methods

2.1. Sample and procedures

Analyses were conducted under a protocol that was approved by the Western Institutional Review Board (WIRB). This report utilizes cross-sectional data collected at baseline from patients who enrolled in AlphaNet between 1/1/08 and 12/31/15. The vast majority of patients enrolled in AlphaNet's disease management program have been prescribed augmentation therapy for lung disease due to AATD. A small percentage of the patients in this program are prescribed augmentation therapy for other health conditions due to AATD, such as panniculitis. All data were collected via structured interviews that were administered via telephone.

Between 1/1/08 and 12/31/15, 5522 adults enrolled in the disease management program. To improve our ability to assess the extent to which genotype is associated with health behaviors, we limited our sample to individuals with the most frequently-reported genotypes in AlphaNet's dataset. As such, we included individuals with an MZ, SZ, or

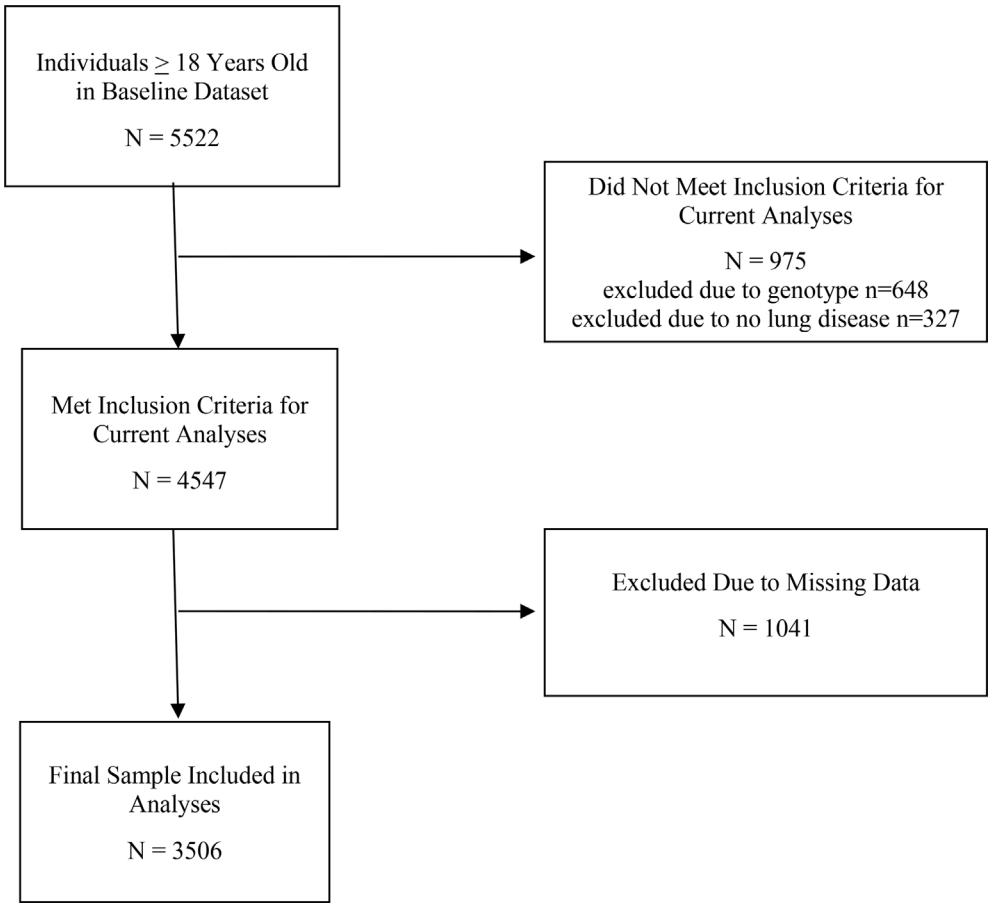

Fig. 1. Study flow diagram.

ZZ genotype, and patients who did not know their genotype. This resulted in excluding 648 individuals who reported other genotypes (e.g., ZNull, NullNull, MS, SS). We also excluded 327 individuals who did not self-report that they had lung disease. To be included in our final sample, individuals had to provide a valid response for all predictors that were used in the regression models and at least one of the health behaviors that were used as dependent variables in the regression models. This resulted in a final sample of 3506 (see Fig. 1).

2.2. Measures

2.2.1. Genotype

Each patient was asked what variant of alpha-1 they had. Response options in the structured interview were: ZZ, SZ, MZ, "I don't know," ZNull, NullNull, and "Other." The current analyses include the most frequently-reported responses, which were MZ, SZ, ZZ, and "I don't know."

2.2.2. Additional patient characteristics

The structured interview included questions regarding age, sex, and relationship status. We created three categories for age: 52 or younger, 53 to 64, and 65 or older. Age 53 was selected as a cut point because early-onset COPD has been defined as COPD that is diagnosed prior to age 53 [27]. Age 65 was selected as a cut point because this is the age at which individuals become eligible for Medicare.

Smoking status was assessed via a question that asked whether the individual had smoked more than one pack of cigarettes in their lifetime. Individuals who reported that they had smoked more than one pack of cigarettes in their lifetime were asked a follow-up question regarding whether they were currently smoking. Responses to these two questions were used to categorize each individual as a never smoker, an ex-smoker, or a current smoker.

The Charlson Comorbidity Index (CCI) was used to capture information regarding comorbid medical conditions [28]. The CCI uses categories of comorbidities that are assigned a weighted value based on the risk of mortality. A higher score indicates a higher mortality risk. The CCI has been used in prior COPD research [26,29–32]. Lung disease is assigned a value of 1, and therefore all individuals in this sample had a CCI score of 1 or higher. We treated the CCI score as a categorical variable with 4 categories: 1, 2, 3, and 4 or higher. Individuals with a CCI score of 1 were the reference group in our analyses, which allowed us to examine the extent to which additional health conditions—beyond AATD-associated lung disease—are associated with the health behaviors of interest.

Participants reported whether they regularly use oxygen, with yes/no response options. Oxygen use was considered to be a proxy for the severity of lung disease in our analyses. Participants also reported whether they had ever been evaluated at an organ transplant center, with yes/no response options. An evaluation at an organ transplant center indicates that the patient has experienced health problems associated with AATD that are severe enough to warrant consideration for a lung or liver transplant.

Comfort with knowledge regarding alpha-1 was assessed via the following question: "Do you feel comfortable with your current knowledge about alpha-1?" Response options were: "no; " "somewhat comfortable," and "yes, very comfortable." Reponses of "no" and "somewhat comfortable" were categorized as having low comfort with knowledge regarding alpha-1. A response of "yes, very comfortable" was categorized as having high comfort with knowledge regarding alpha-1.

2.2.3. Health behaviors

Current Smoking: Individuals who reported that they had smoked more than one pack of cigarettes in their lifetime were asked a follow-up question regarding whether they were currently smoking. Individuals who responded "yes" were categorized as current smokers. Individuals who indicated that they had never smoked or were not currently smoking were categorized as not a current smoker.

Recommended Vaccines: Individuals were asked whether they had received a pneumonia vaccine in the last 6 years. Individuals were also asked whether they had received a flu vaccine in the last year.

Exercise: Individuals were asked whether they exercised regularly, irregularly, or not at all. Individuals who indicated that they did not exercise at all were categorized as "does not exercise." Those who exercised irregularly or regularly were grouped together into a single category that captured engaging in some degree of exercise.

Maintaining a Healthy Weight: Individuals were asked to report their weight and height. This information was used to calculate body mass index (BMI). The standard weight status categories established by the Centers for Disease Control and Prevention were utilized to designate each participant as underweight (BMI $<$ 18.5), at a healthy weight (BMI $\geq$ 18.5 and $<$ 25.0), or overweight/obese (BMI $\geq$ 25.0) [33].

2.3. Analyses

Data were analyzed using SPSS Statistics Version 24. For all analyses, significance tests were two-sided with a significance level of 0.05.

2.3.1. Preliminary analyses to examine characteristics of participants

Characteristics of participants were summarized using number and percentage of participants. Given our focus on genotype, characteristics were summarized by genotype as well as for the full sample. Chi-square tests were used to examine whether characteristics of participants differ by genotype.

2.3.2. Analyses to examine the association of genotype with health behaviors

Multivariate logistic regression was used to examine the association of genotype with health behaviors while controlling for demographic and health characteristics. The same set of predictors was examined in each multivariate logistic regression model, and all variables were entered simultaneously. The primary predictor of interest was genotype. Covariates were selected to capture demographic and health characteristics that have been associated with health outcomes in prior research (i.e., age [31,34,35], sex [30,31,36], relationship status [29,34,37], smoking status [36,38–40], CCI score [28,29,41], and oxygen use [39,42]) and also to capture aspects of AATD-associated lung disease that are likely to be associated with health behaviors (i.e., evaluation at an organ transplant center, comfort with knowledge regarding alpha-1).

A binary multivariate logistic regression model was fit for each of the following health behaviors: current smoking, pneumonia vaccine, flu vaccine, and exercise. In each model, the dependent variable was coded such that a score of 0 indicated healthy behavior (e.g., not a current smoker), and a score of 1 indicated unhealthy behavior (e.g., is a current smoker). As such, in each model an odds ratio greater than 1 indicates increased odds of unhealthy behavior.

Binary logistic regression was not an appropriate method to examine correlates of maintaining a healthy weight due to the existence of three categories for this health behavior: underweight, healthy weight, and overweight/obese. Thus, a multinomial multivariate logistic regression model was fit. Worse health outcomes are associated with both extremes of BMI among patients with COPD (e.g., low BMI is associated with mortality [43–45] and worse quality of life [46,47] while high BMI is associated with healthcare utilization [48] and worse quality of life [47]). As such, the comparison group in this model was healthy weight (BMI $\geq$ 18 and $<$ 25). A single model was utilized to estimate the association of each predictor with being underweight (as compared to a healthy weight) as well as the association of each predictor with being overweight/obese (as compared to a healthy weight). As with the binary models, an odds ratio greater than 1 indicates increased odds of unhealthy behavior (i.e., being underweight or overweight).

2.3.3. Analyses to examine missing data

Individuals who were removed from the sample due to missing data were compared to individuals who were included in analyses via Chi-square tests. These analyses provide information regarding bias that may be introduced due to missing data.

3. Results

3.1. Characteristics of participants

Characteristics of the sample are in Table 1. Nearly one-third of the sample was under the age of 53 (32.3%). Less than a quarter of the sample had never smoked (24.1%). Genotype had a statistically significant association with every demographic and health characteristic examined. With regard to health behaviors, very few individuals were current smokers (4.2%) and only a minority of the sample had not gotten a pneumonia vaccine (12.1%) or a flu vaccine (13.6%). Nearly a third of the sample reported that they did not exercise (30.2%). Very few individuals were underweight (4.9%) and more than half of the sample was overweight/obese (56.1%). Genotype had a statistically significant association with all of the health behaviors.

3.2. The association of genotype with health behaviors

Tables 2 and 3 present results of the regression models. All regression models had adequate fit, as indicated by nonsignificant goodness-of-fit tests. The Hosmer-Lemeshow goodness-of-fit test was as follows for each binary logistic regression model: current smoker $\chi^2_{(df=8)} = 5.68$, p = .683; pneumonia vaccine $\chi^2_{(df=8)} = 4.84$, p = .774; flu vaccine $\chi^2_{(df=8)} = 5.42$, p = .712; and exercise $\chi^2_{(df=8)} = 8.24$, p = .411. The Pearson Goodness-of-Fit test for the multinomial logistic regression model for healthy weight was $\chi^2_{(df=2444)} = 2523.37$, p = .129.

As shown in Table 2, genotype was associated with current smoking while controlling for age, sex, relationship status, CCI score, oxygen use, organ transplant center evaluation, and comfort with knowledge regarding alpha-1. MZs had higher odds of being a current smoker than ZZs (OR = 2.73, 95% CI = 1.70–4.39, p < .001), as did SZs (OR = 4.34, 95% CI = 2.60–7.24, p < .001) and individuals who did not know their genotype (OR = 1.97, 95% CI = 1.25–3.09, p = .003).

Table 1
Characteristics of the sample.

	Full Sample (n = 3506)	Genotype Not Known by Patient (n = 662)	MZ (n = 464)	SZ (n = 266)	ZZ (n = 2114)	p
Demographic and Health Characteristics	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*	
Age						
52 or Younger	1132 (32.3%)	207 (31.3%)	117 (25.2%)	63 (23.7%)	745 (35.2%)	< .001
53 to 64	1440 (41.1%)	264 (39.9%)	203 (43.8%)	115 (43.2%)	858 (40.6%)	
65 or Older	934 (26.6%)	191 (28.9%)	144 (31.0%)	88 (33.1%)	511 (24.2%)	
Sex						
Male	1865 (53.2%)	367 (55.4%)	270 (58.2%)	140 (52.6%)	1088 (51.5%)	.036
Female	1641 (46.8%)	295 (44.6%)	194 (41.8%)	126 (47.4%)	1026 (48.5%)	
Relationship Status						
Single	1267 (36.1%)	290 (43.8%)	192 (41.4%)	97 (36.5%)	688 (32.5%)	< .001
Married/Civil Union	2239 (63.9%)	372 (56.2%)	272 (58.6%)	169 (63.5%)	1426 (67.5%)	
Smoking Status						
Never Smoker	844 (24.1%)	133 (20.1%)	92 (19.8%)	41 (15.4%)	578 (27.3%)	< .001
Ex-Smoker	2515 (71.7%)	493 (74.5%)	339 (73.1%)	198 (74.4%)	1485 (70.2%)	
Current Smoker	147 (4.2%)	36 (5.4%)	33 (7.1%)	27 (10.2%)	51 (2.4%)	
Charlson Comorbidity Index (CCI) Score						
1	1993 (56.8%)	352 (53.2%)	223 (48.1%)	126 (47.4%)	1292 (61.1%)	< .001
2	658 (18.8%)	124 (18.7%)	106 (22.8%)	57 (21.4%)	371 (17.5%)	
3	472 (13.5%)	85 (12.8%)	77 (16.6%)	43 (16.2%)	267 (12.6%)	
4 or higher	383 (10.9%)	101 (15.3%)	58 (12.5%)	40 (15.0%)	184 (8.7%)	
Oxygen Use						
No	1622 (46.3%)	271 (40.9%)	230 (49.6%)	137 (51.5%)	984 (46.5%)	.006
Yes	1884 (53.7%)	391 (59.1%)	234 (50.4%)	129 (48.5%)	1130 (53.5%)	
Organ Transplant Center Evaluation						
No	2958 (84.4%)	565 (85.3%)	430 (92.7%)	252 (94.7%)	1711 (80.9%)	< .001
Yes	548 (15.6%)	97 (14.7%)	34 (7.3%)	14 (5.3%)	403 (19.1%)	
Comfort with Knowledge Regarding Alpha-1						
Low	1804 (51.5%)	418 (63.1%)	311 (67.0%)	170 (63.9%)	905 (42.8%)	< .001
High	1702 (48.5%)	244 (36.9%)	153 (33.0%)	96 (36.1%)	1209 (57.2%)	
Health Behaviors	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*	
Current Smoker						
No	3359 (95.8%)	626 (94.6%)	431 (92.9%)	239 (89.8%)	2063 (97.6%)	< .001
Yes	147 (4.2%)	36 (5.4%)	33 (7.1%)	27 (10.2%)	51 (2.4%)	
Has Not Had Pneumonia Vaccine						
No	3009 (87.9%)	571 (88.3%)	365 (80.6%)	221 (86.0%)	1852 (89.6%)	< .001
Yes	414 (12.1%)	76 (11.7%)	88 (19.4%)	36 (14.0%)	214 (10.4%)	
Has Not Had Flu Vaccine						
No	2994 (86.4%)	564 (86.1%)	362 (79.0%)	223 (85.4%)	1845 (88.3%)	< .001
Yes	470 (13.6%)	91 (13.9%)	96 (21.0%)	38 (14.6%)	245 (11.7%)	
Does Not Exercise						
No	2432 (69.8%)	403 (61.6%)	296 (64.3%)	162 (61.1%)	1571 (74.6%)	< .001
Yes	1054 (30.2%)	251 (38.4%)	164 (35.7%)	103 (38.9%)	536 (25.4%)	
Maintain a Healthy Weight						
Underweight (BMI < 18.5)	171 (4.9%)	38 (5.7%)	25 (5.4%)	17 (6.4%)	91 (4.3%)	< .001
Healthy (BMI ≥ 18.5 and < 25)	1367 (39.0%)	256 (38.7%)	124 (26.7%)	87 (32.7%)	900 (42.7%)	
Overweight/Obese (BMI ≥ 25)	1963 (56.1%)	367 (55.5%)	315 (67.9%)	162 (60.9%)	1119 (53.0%)	

Table 2
Results of binary multivariate logistic regression models for smoking, vaccines, and exercise.

	Model 1 (n = 3506) Current Smoker	Model 2 (n = 3423) Has Not Had Pneumonia Vaccine	Model 3 (n = 3464) Has Not Had Flu Vaccine	Model 4 (n = 3486) Does Not Exercise
	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p
Age				
52 or Younger	4.78 (2.81–8.13), < .001	2.74 (2.02–3.73), < .001	2.41 (1.81–3.20), < .001	1.21 (0.98–1.49), .074
53 to 64	1.98 (1.14–3.42), .015	1.44 (1.06–1.95), .021	1.40 (1.06–1.86), .018	1.17 (0.92–1.35), .253
65 or Older	Ref	Ref	Ref	Ref
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.98 (0.69–1.38), .890	1.004 (0.81–1.24), .969	1.09 (0.89–1.33), .393	1.09 (0.94–1.26), .277
Relationship Status				
Single	Ref	Ref	Ref	Ref
Married/Civil Union	0.48 (0.34–0.68), < .001	0.89 (0.71–1.11), .295	0.79 (0.64–0.97), .024	0.78 (0.67–0.91), .002
Smoking Status				
Never Smoker		Ref	Ref	Ref
Ex-Smoker		0.72 (0.56–0.93), .012	0.84 (0.66–1.08), .169	1.17 (0.97–1.41), .110
Current Smoker	Not in Model[a]	1.20 (0.75–1.92), .454	1.53 (0.99–2.36), .058	3.10 (2.11–4.54), < .001
Charlson Comorbidity Index (CCI) Score				
1	Ref	Ref	Ref	Ref
2	1.47 (0.97–2.22), .071	1.16 (0.88–1.52), .285	1.45 (1.13–1.87), .003	1.20 (0.99–1.46), .071
3	0.77 (0.42–1.44), .415	0.80 (0.56–1.15), .226	0.88 (0.63–1.23), .445	1.24 (0.99–1.56), .061
4 or higher	1.51 (0.91–2.50), .115	0.95 (0.66–1.36), .756	1.24 (0.89–1.72), .201	1.70 (1.35–2.16), < .001
Oxygen Use				
No	Ref	Ref	Ref	Ref
Yes	1.45 (1.02–2.07), .040	0.57 (0.45–0.72), < .001	0.78 (0.63–0.97), .023	1.34 (1.14–1.57), < .001
Organ Transplant Center Evaluation				
No	Ref	Ref	Ref	Ref
Yes	0.22 (0.09–0.50), < .001	0.58 (0.40–0.85), .006	0.43 (0.30–0.63), < .001	0.74 (0.59–0.92), .007
Comfort with Knowledge Re: Alpha-1				
Low	Ref	Ref	Ref	Ref
High	0.56 (0.38–0.82), .003	0.57 (0.46–0.72), < .001	0.69 (0.56–0.85), < .001	0.75 (0.65–0.88), < .001
Genotype				
Not Known by Patient	1.97 (1.25–3.09), .003	1.11 (0.83–1.49), .478	1.11 (0.85–1.46), .443	1.55 (1.28–1.88), < .001
MZ	2.73 (1.70–4.39), < .001	1.91 (1.43–2.56), < .001	1.76 (1.33–2.32), < .001	1.35 (1.08–1.69), .009
SZ	4.34 (2.60–7.24), < .001	1.27 (0.85–1.90), .239	1.10 (0.75–1.62), .632	1.52 (1.15–2.01), .003
ZZ	Ref	Ref	Ref	Ref

[a] By definition, all current smokers are included in the "current smoker" group and therefore smoking status cannot be used as a predictor in this model.

MZs reported worse health behavior than ZZs for every additional health behavior examined, while controlling for age, sex, relationship status, smoking status, CCI score, oxygen use, organ transplant center evaluation, and comfort with knowledge regarding alpha-1 (see Tables 2 and 3). Odds ratios ranged from 1.35 (95% CI = 1.08 to 1.69, p = .009) for not exercising to 1.98 (95% CI = 1.20 to 3.26, p = .007) for being underweight. SZs reported worse health behavior than ZZs with regard to lack of exercise (OR = 1.52, 95% CI = 1.15–2.01, p = .003) and failure to maintain a healthy weight (underweight OR = 1.93, 95% CI = 1.07–3.45, p = .028; overweight OR = 1.43, 95% CI = 1.07–1.90, p = .015). Individuals who did not know their genotype reported worse health behavior than ZZs with regard to lack of exercise (OR = 1.55, 95% CI = 1.28–1.88, p < .001).

Post-Hoc Regression Models: Regression models were fit in which MZs were treated as the reference group. The only difference between the original models and the post-hoc models is that the reference group for genotype was changed from ZZ to MZ. These models allow us to compare SZs to MZs, and also to compare individuals who do not know their genotype to MZs. In the model for smoking, the odds of being a current smoker did not differ for SZs as compared to MZs (p = .100), or for individuals who did not know their genotype as compared to MZs (p = .205). In the remaining models, SZs differed from MZs only with regard to the flu vaccine. SZs had lower odds than MZs of reporting that they had not gotten the flu vaccine (OR = 0.63, 95% CI = 0.41–0.96, p = .030). Individuals who did not know their genotype differed from MZs with regard to three health behaviors. In all three instances, individuals who did not know their genotype had lower odds than MZs of reporting unhealthy behavior: no pneumonia vaccine (OR = 0.58, 95% CI = 0.41–0.82, p = .002), no flu vaccine (OR = 0.63, 95% CI = 0.46–0.88, p = .006), and being overweight (OR = 0.57, 95% CI = 0.44–0.74, p < .001).

3.3. Missing data analysis

Table 4 presents results of analyses that compare individuals who were included in analyses to individuals who were excluded from the sample due to missing data. The two groups did not differ with regard to sex or CCI score (p > .05). However, they differed with regard to every additional demographic and health characteristic examined. When the two groups were compared on each health behavior outcome, they did not differ with regard to BMI (p > .05). For all of the other health behavior outcomes, a higher percentage of the individuals who were removed from the sample reported unhealthy behavior.

4. Discussion

This is the first study to examine the extent to which MZs and SZs differ from ZZs with regard to health behaviors that are critical in managing lung disease. As hypothesized, MZs, SZs, and individuals who did not know their genotype were more likely than ZZs to be current smokers. SZs were also more likely than ZZs to exhibit unhealthy behavior with regard to exercise and maintaining a healthy weight. The most striking finding is that MZs reported worse health behavior than ZZs for every behavior examined.

Several different explanations could account for worse health behaviors among MZs who have developed lung disease. First, MZs may

Table 3
Results of multinomial multivariate logistic regression model for maintaining a healthy weight[a].

	Model 5 (n = 3501)	
	Underweight	Overweight
	OR (95% CI), p	OR (95% CI), p
Age		
52 or Younger	2.13 (1.37–3.32), .001	1.72 (1.41–2.09), < .001
53 to 64	1.29 (0.84–1.99), .244	1.55 (1.30–1.85), < .001
65 or Older	Ref	Ref
Sex		
Male	Ref	Ref
Female	1.60 (1.15–2.21), .005	0.94 (0.82–1.08), .401
Relationship Status		
Single	Ref	Ref
Married/Civil Union	0.65 (0.47–0.91), .012	1.08 (0.93–1.26), .319
Smoking Status		
Never Smoker	Ref	Ref
Ex-Smoker	0.99 (0.65–1.52), .960	1.03 (0.87–1.23), .708
Current Smoker	1.28 (0.62–2.65), .507	0.69 (0.47–1.02), .064
Charlson Comorbidity Index (CCI) Score		
1	Ref	Ref
2	0.75 (0.46–1.21), .239	1.49 (1.23–1.81), < .001
3	1.27 (0.80–2.01), .304	1.20 (0.97–1.49), .098
4 or higher	0.96 (0.54–1.70), .880	1.68 (1.32–2.13), < .001
Oxygen Use		
No	Ref	Ref
Yes	2.04 (1.42–2.92), < .001	1.03 (0.88–1.19), .723
Organ Transplant Center Evaluation		
No	Ref	Ref
Yes	0.71 (0.44–1.13), .147	0.70 (0.57–0.85), < .001
Comfort with Knowledge Re: Alpha-1		
Low	Ref	Ref
High	0.75 (0.54–1.06), .100	0.85 (0.73–0.98), .026
Genotype		
Not Known by Patient	1.33 (0.87–2.01), .186	1.10 (0.91–1.33), .321
MZ	1.98 (1.20–3.26), .007	1.94 (1.53–2.45), < .001
SZ	1.93 (1.07–3.45), .028	1.43 (1.07–1.90), .015
ZZ	Ref	Ref

[a] Healthy weight (BMI ≥ 18 and < 25) is the comparison group in this model.

Table 4
Comparison of patients included in analyses to patients excluded due to missing data.

	Included (n = 3506	Excluded (n = 1041	p
Demographic and Health Characteristics	*N (%)*	*N (%)*	
Age			< .001
52 or Younger	1132 (32.3%)	406 (39.0%)	
53 to 64	1440 (41.1%)	400 (38.4%)	
65 or Older	934 (26.6%)	235 (22.6%)	
Sex			.522
Male	1865 (53.2%)	542 (52.1%)	
Female	1641 (46.8%)	499 (47.9%)	
Relationship Status			.002
Single	1267 (36.1%)	380 (41.8%)	
Married/Civil Union	2239 (63.9%)	529 (58.2%)	
Smoking Status			.012
Never Smoker	844 (24.1%)	154 (26.5%)	
Ex-Smoker	2515 (71.7%)	389 (67.0%)	
Current Smoker	147 (4.2%)	38 (6.5%)	
Charlson Comorbidity Index (CCI) Score			.106
1	1993 (56.8%)	296 (54.0%)	
2	658 (18.8%)	93 (17.0%)	
3	472 (13.5%)	83 (15.1%)	
4 or higher	383 (10.9%)	76 (13.9%)	
Oxygen Use			< .001
No	1622 (46.3%)	297 (56.4%)	
Yes	1884 (53.7%)	230 (43.6%)	
Organ Transplant Center Evaluation			< .001
No	2958 (84.4%)	549 (91.7%)	
Yes	548 (15.6%)	50 (8.3%)	
Comfort with Knowledge Regarding Alpha-1			< .001
Low	1804 (51.5%)	610 (62.6%)	
High	1702 (48.5%)	365 (37.4%)	
Genotype			< .001
Not Known by Patient	662 (18.9%)	172 (16.5%)	
MZ	464 (13.2%)	238 (22.9%)	
SZ	266 (7.6%)	104 (10.0%)	
ZZ	2114 (60.3%)	527 (50.6%)	
Health Behaviors	*N (%)*	*N (%)*	
Current Smoker			.012
No	3359 (95.8%)	543 (93.5%)	
Yes	147 (4.2%)	38 (6.5%)	
Has Not Had Pneumonia Vaccine			< .001
No	3009 (87.9%)	435 (80.7%)	
Yes	414 (12.1%)	104 (19.3%)	
Has Not Had Flu Vaccine			< .001
No	2994 (86.4%)	461 (80.2%)	
Yes	470 (13.6%)	114 (19.8%)	
Does Not Exercise			.001
No	2432 (69.8%)	382 (62.7%)	
Yes	1054 (30.2%)	227 (37.3%)	
Maintain a Healthy Weight			.789
Underweight (BMI < 18.5)	171 (4.9%)	52 (5.1%)	
Healthy Weight (BMI ≥ 18.5 and < 25)	1367 (39.0%)	385 (37.9%)	
Overweight/Obese (BMI ≥ 25)	1963 (56.1%)	579 (57.0%)	

have worse health behavior prior to developing lung disease. MZs would be expected to have more smoking exposure than ZZs prior to developing lung disease, given that MZs have a less severe genetic component of their lung disease. MZs may have a broader pattern of unhealthy behavior prior to the development of lung disease, for example—poor exercise habits in addition to smoking. This pattern of unhealthy behavior may persist after lung disease is diagnosed and thereby account for our findings.

A second explanation is that an individual's knowledge of their genotype may influence their health behavior. This explanation is consistent with research among individuals with AATD who are at risk for, but have not yet developed, lung disease [49,50]. One study that focused exclusively on ZZs found that individuals who were identified as ZZ at birth have a lower rate of smoking as adolescents than demographically matched controls who did not have AATD [50]. Another study focused on changes in smoking behavior among adult smokers after they learned results of genetic testing for AATD. This study found that MZs were less likely than SZs and ZZs to engage in a range of cessation-related behaviors, including seeking information on smoking cessation, using pharmacotherapy for smoking cessation, reducing the amount of cigarettes smoked per day, and making a 24-h quit attempt [49]. In our sample of individuals with lung disease, knowledge of genotype may similarly influence health behavior. If so, this could account for our finding that MZs reported worse health behaviors than ZZs.

A third explanation is that MZs exhibit worse health behavior as a result of inconsistent messages about the extent to which information regarding AATD is applicable to them. A concrete example of an inconsistency is the fact that all of the MZs in the current analyses have been prescribed augmentation therapy, despite the fact that current guidelines do not recommend the use of augmentation therapy for individuals with the MZ genotype due to lack of evidence of benefit [18]. There is ongoing debate regarding whether MZs are at increased risk of developing lung disease [6,9], and the biological mechanisms that underlie increased risk among MZs remain unknown [14]. This lack of clarity may make it difficult for MZs to know which information regarding the treatment of AATD-associated lung disease is applicable to

them. Of note, our analyses adjusted for the patient's level of comfort with their knowledge regarding alpha-1, which was associated with all of the health behaviors except being underweight. MZs reported worse health behavior even after adjusting for comfort with knowledge regarding alpha-1. While our question regarding comfort with knowledge likely does not fully capture the patient experience of inconsistent messages, our results suggest that unclear/inconsistent messages may not completely account for worse health behaviors among MZs.

These three explanations are not mutually exclusive. All three explanations may account, to some degree, for our findings. Additional research is needed to replicate our findings, especially among individuals with AATD-associated lung disease for whom augmentation therapy is not prescribed. Additional research also is needed to better understand why genotype, and the MZ genotype in particular, is associated with health behaviors among individuals with AATD-associated lung disease. If these findings are replicated, results would suggest that MZs (and also SZs) may need targeted educational materials and additional interventions that are tailored to their unique needs.

The 4.2% smoking rate in our sample is low in comparison to estimated rates for the general United States population (which range from 15.1% to 31.4% [51–54]) and for individuals with non-AATD COPD (which range from 27.2% to 38.0% [55,56]). In addition, the percentage of individuals in our sample who had not gotten a pneumonia or flu vaccine (12.1% and 13.6%, respectively) also is low in comparison to estimated rates for the general population (which range from 32.2% to 57.8% [57–59]) and for individuals with non-AATD COPD (which range from 47.0% to 51.5% [60,61]). Fifty-six percent of our sample had a BMI $\geq$25, in comparison to 66.4% in the general population [53] and rates of 70% or higher among individuals with non-AATD COPD [62,63]. Thirty percent of our sample indicated that they do not exercise at all, as compared to 26.3% in the general population [51]. While it may be surprising that our sample contains current smokers and individuals with the MZ genotype, it is worth noting that the Clinical Practice Guidelines published in 2016 [18] were the first guidelines in the United States to explicitly state that augmentation therapy is not recommended for individuals who continue to smoke or for individuals with the MZ genotype.

Findings of this study should be interpreted in light of a few limitations. The primary limitation is that our sample only included individuals who are prescribed augmentation therapy. Among individuals with lung disease, MZs and SZs are less likely than ZZs to be identified. Once identified, they are less likely than ZZs to be prescribed augmentation therapy. Thus, the individuals who are included in our sample likely reflect some degree of bias due to the method of ascertainment. This bias may differ by genotype. MZs who are prescribed augmentation therapy may differ from other MZs with regard to their health behavior, or may differ from other genotypes with regard to the validity of their self-reported health behavior. Missing data are a second source of bias. The individuals who were removed from our sample due to missing data differed from those who were included with regard to several demographic and health characteristics, and were more likely to report unhealthy behavior. An additional limitation is that objective measures of the severity of lung disease were not included because all data were collected via self-report. Oxygen use was included in all models as a proxy for severity of lung disease, but use of oxygen provides only a rough approximation of the severity of lung disease. As a second means of measuring severity, analyses also included a variable that captures whether the patient had ever been evaluated at an organ transplant center. This variable captures health problems due to AATD that are severe enough to warrant consideration for a lung or liver transplant. We acknowledge that these two variables are not accepted measures for the severity of lung disease. A further limitation is that analyses are based on cross-sectional data. Finally, it must be acknowledged that only a small number of individuals in this sample reported being current smokers (n = 147) or being underweight (n = 171). This may influence our statistical power to detect factors that are associated with current smoking and being underweight, and it will be especially important to replicate our findings with regard to correlates of these health behaviors.

One should exercise caution when extrapolating these findings to the broader population of individuals with AATD-associated lung disease, as findings may not generalize to patients for whom augmentation therapy has not been prescribed. The extent to which our sample differs from this broader population can be examined by comparing characteristics of our sample (e.g., age, sex, smoking status) to samples described in other studies. Two studies were utilized for this comparison: 1) a study that included 1619 individuals with AATD-associated lung disease from the WebMD Lung Health Check Database [55], and 2) a study that included 578 individuals with AATD-associated lung disease who were recruited from the Alpha-1 Foundation Research Registry [37]. With regard to sex, our sample was 46.8% female as compared to 54.7% in the WebMD Database [55] and 50.2% in the Alpha-1 Registry [37]. The percentage of our sample that was 65 or older was similar to the WebMD Database (26.6% as compared to 26.7%) [55]. With regard to relationship status, 36.1% of our sample was single as compared to 22.8% in the Alpha-1 Registry [37]. Oxygen use was 53.7% in our sample as compared to 51.4% in the Alpha-1 Registry [37]. Among our sample, 24.1% had never smoked, as compared to 21.3% in the WebMD Database [55] and 31.7% in the Alpha-1 Registry [37]. The percentage of current smokers in our sample was notably lower than in the WebMD Database: 4.2% as compared to 21.6% [55]. We would expect the percentage of current smokers in our sample to be lower than in the broader population of individuals with AATD-associated lung disease, given that our sample is comprised exclusively of individuals who are prescribed augmentation therapy.

The current study also has several strengths. It is the first to examine whether health behaviors differ systematically by genotype among individuals with AATD-associated lung disease. Multiple health behaviors were examined, making it possible to assess consistency of findings across health behaviors. The use of data collected by AlphaNet provided access to a large, geographically diverse sample. The findings are novel, and suggest that individuals with a less severe genetic predisposition to develop disease may have additional needs with regard to education and intervention to promote optimal health behavior following the diagnosis of lung disease.

Conflicts of interest

KEH has received consulting income from AlphaNet. DMM is a full-time employee of GlaxoSmithKline plc and owns stock of GlaxoSmithKline plc. He also has received royalties from Up-to-Date, is on the Board of Directors of the COPD Foundation, and has been compensated as a medical expert in legal cases. RC has received research support from AlphaNet. RAS has served on advisory boards and/or as a speaker for Grifols, CSL Behring, Shire, and AstraZeneca. He is on the Board of Directors of AlphaNet and The Alpha-1 Project, is on the Medical and Scientific Advisory Committee of the COPD Foundation, and serves as the Medical Director of AlphaNet.

Acknowledgments

This work was funded by AlphaNet, Inc., United States.

References

[1] R.A. Sandhaus, alpha1-Antitrypsin deficiency. 6: new and emerging treatments for alpha1-antitrypsin deficiency, Thorax 59 (10) (2004) 904–909.
[2] O.C. Ioachimescu, J.K. Stoller, A review of alpha-1 antitrypsin deficiency, COPD 2 (2) (2005) 263–275.
[3] N.A. Molfino, Genetics of COPD, Chest 125 (5) (2004) 1929–1940.
[4] A.S. Mayer, et al., Risk factors for symptom onset in PI*Z alpha-1 antitrypsin deficiency, Int. J. Chronic Obstr. Pulm. Dis. 1 (4) (2006) 485–492.
[5] G.M. Turino, et al., Clinical features of individuals with PI*SZ phenotype of alpha 1-

antitrypsin deficiency. Alpha 1-Antitrypsin Deficiency Registry Study Group, Am. J. Respir. Crit. Care Med. 154 (6 Pt 1) (1996) 1718–1725.
[6] K. Molloy, et al., Clarification of the risk of chronic obstructive pulmonary disease in alpha1-antitrypsin deficiency PiMZ heterozygotes, Am. J. Respir. Crit. Care Med. 189 (4) (2014) 419–427.
[7] F.J. de Serres, I. Blanco, Prevalence of alpha1-antitrypsin deficiency alleles PI*S and PI*Z worldwide and effective screening for each of the five phenotypic classes PI*MS, PI*MZ, PI*SS, PI*SZ, and PI*ZZ: a comprehensive review, Ther. Adv. Respir. Dis. 6 (5) (2012) 277–295.
[8] F.J. de Serres, Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys, Chest 122 (5) (2002) 1818–1829.
[9] C. Mittman, The PiMZ phenotype: is it a significant risk factor for the development of chronic obstructive lung disease? Am. Rev. Respir. Dis. 118 (4) (1978) 649–652.
[10] J. Lieberman, B. Winter, A. Sastre, Alpha 1-antitrypsin pi-types in 965 COPD patients, Chest 89 (3) (1986) 370–373.
[11] M.G. Foreman, et al., Alpha-1 antitrypsin PiMZ genotype is associated with chronic obstructive pulmonary disease in two racial groups, Ann. Am. Thorac. Soc. 14 (8) (2017) 1280–1287.
[12] C.P. Hersh, et al., Chronic obstructive pulmonary disease in alpha1-antitrypsin PI MZ heterozygotes: a meta-analysis, Thorax 59 (10) (2004) 843–849.
[13] I.C. Sorheim, et al., Alpha(1)-antitrypsin protease inhibitor MZ heterozygosity is associated with airflow obstruction in two large cohorts, Chest 138 (5) (2010) 1125–1132.
[14] C.P. Hersh, Diagnosing alpha-1 antitrypsin deficiency: the first step in precision medicine, F1000Res 6 (2017) 2049.
[15] M. Wencker, et al., Longitudinal follow-up of patients with alpha(1)-protease inhibitor deficiency before and during therapy with IV alpha(1)-protease inhibitor, Chest 119 (3) (2001) 737–744.
[16] R.A. Sandhaus, Alpha 1-antitrypsin augmentation therapy, Agents Actions Suppl. 42 (1993) 97–102.
[17] R.A. Sandhaus, Augmentation therapy in alpha-1 antitrypsin deficiency, COPD 6 (3) (2009) 147–148.
[18] R.A. Sandhaus, et al., The diagnosis and management of alpha-1 antitrypsin deficiency in the adult, Chronic Obstr. Pulm. Dis. 3 (3) (2016) 668–682.
[19] K.R. Chapman, et al., Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial, Lancet 386 (9991) (2015) 360–368.
[20] N.G. McElvaney, et al., Long-term efficacy and safety of alpha1 proteinase inhibitor treatment for emphysema caused by severe alpha1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE), Lancet Respir. Med. 5 (1) (2017) 51–60.
[21] R.A. Sandhaus, Randomized, placebo-controlled trials in alpha-1 antitrypsin deficiency, Ann. Am. Thorac. Soc. 13 (Suppl 4) (2016) S370–S373.
[22] American Thoracic Society/European Respiratory Society, American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency, Am. J. Respir. Crit. Care Med. 168 (7) (2003) 818–900.
[23] D.D. Marciniuk, et al., Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline, Can. Respir. J. 19 (2) (2012) 109–116.
[24] M. Miravitlles, et al., European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha1-antitrypsin deficiency, Eur. Respir. J. 50 (5) (2017).
[25] M.A. Campos, et al., Effects of a disease management program in individuals with alpha-1 antitrypsin deficiency, COPD 6 (1) (2009) 31–40.
[26] J.T. Perkins, et al., Benefits among patients with alpha-1 antitrypsin deficiency enrolled in a disease management and prevention program, Chronic Obstr. Pulm. Dis. 4 (1) (2016) 56–64.
[27] E.K. Silverman, et al., Gender-related differences in severe, early-onset chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 162 (6) (2000) 2152–2158.
[28] M.E. Charlson, et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (5) (1987) 373–383.
[29] P. Almagro, et al., Mortality after hospitalization for COPD, Chest 121 (5) (2002) 1441–1448.
[30] J.P. de Torres, et al., Gender and COPD in patients attending a pulmonary clinic, Chest 128 (4) (2005) 2012–2016.
[31] R. Ferrari, et al., Gender differences in predictors of health status in patients with COPD, J. Bras. Pneumol. 36 (1) (2010) 37–43.
[32] J.H. Jennings, et al., The association between depressive symptoms and acute exacerbations of COPD, Lung 187 (2) (2009) 128–135.
[33] Centers for Disease Control and Prevention (CDC), About adult BMI, https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html , Accessed date: 7 May 2018.
[34] K.E. Holm, et al., The impact of age on outcomes in chronic obstructive pulmonary disease differs by relationship status, J. Behav. Med. 37 (4) (2014) 654–663.
[35] C.H. Martinez, et al., Age-related differences in health-related quality of life in COPD: an analysis of the COPDGene and SPIROMICS cohorts, Chest 149 (4) (2016) 927–935.
[36] J.E. Connett, et al., Changes in smoking status affect women more than men: results of the Lung Health Study, Am. J. Epidemiol. 157 (11) (2003) 973–979.
[37] K.E. Holm, et al., Differences in adjustment between individuals with alpha-1 antitrypsin deficiency (AATD)-associated COPD and non-AATD COPD, COPD 10 (2) (2013) 226–234.
[38] M.A. Campos, et al., Exacerbations in subjects with alpha-1 antitrypsin deficiency receiving augmentation therapy, Respir. Med. 103 (10) (2009) 1532–1539.
[39] J. Garcia-Aymerich, et al., Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study, Am. J. Respir. Crit. Care Med. 164 (6) (2001) 1002–1007.
[40] R.E. Kanner, et al., Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study, Am. J. Med. 106 (4) (1999) 410–416.
[41] K.E. Covinsky, et al., Depressive symptoms and 3-year mortality in older hospitalized medical patients, Ann. Intern. Med. 130 (7) (1999) 563–569.
[42] M.L. Moy, et al., Multivariate models of determinants of health-related quality of life in severe chronic obstructive pulmonary disease, J. Rehabil. Res. Dev. 46 (5) (2009) 643–654.
[43] B.R. Celli, et al., The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease, N. Engl. J. Med. 350 (10) (2004) 1005–1012.
[44] A.F. Connors Jr.et al., Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments), Am. J. Respir. Crit. Care Med. 154 (4 Pt 1) (1996) 959–967.
[45] A. Domingo-Salvany, et al., Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 166 (5) (2002) 680–685.
[46] H. Katsura, K. Yamada, K. Kida, Both generic and disease specific health-related quality of life are deteriorated in patients with underweight COPD, Respir. Med. 99 (5) (2005) 624–630.
[47] E.P. Rutten, et al., Changes in body composition in patients with chronic obstructive pulmonary disease: do they influence patient-related outcomes? Ann. Nutr. Metab. 63 (3) (2013) 239–247.
[48] N.T. Vozoris, D.E. O'Donnell, Prevalence, risk factors, activity limitation and health care utilization of an obese, population-based sample with chronic obstructive pulmonary disease, Can. Respir. J. 19 (3) (2012) e18–24.
[49] M.J. Carpenter, et al., Does genetic testing result in behavioral health change? Changes in smoking behavior following testing for alpha-1 antitrypsin deficiency, Ann. Behav. Med. 33 (1) (2007) 22–28.
[50] T. Thelin, T. Sveger, T.F. McNeil, Primary prevention in a high-risk group: smoking habits in adolescents with homozygous alpha-1-antitrypsin deficiency (ATD), Acta Paediatr. 85 (10) (1996) 1207–1212.
[51] M.L. Adams, et al., Linear association between number of modifiable risk factors and multiple chronic conditions: results from the Behavioral Risk Factor Surveillance System, Prev. Med. 105 (2017) 169–175.
[52] A. Jamal, et al., Current cigarette smoking among adults - United States, 2005-2015, MMWR Morb. Mortal. Wkly. Rep. 65 (44) (2016) 1205–1211.
[53] V. Pernenkil, T. Wyatt, T. Akinyemiju, Trends in smoking and obesity among US adults before, during, and after the great recession and Affordable Care Act roll-out, Prev. Med. 102 (2017) 86–92.
[54] G.K. Singh, et al., Social determinants of health in the United States: addressing major health inequality trends for the nation, 1935-2016, Int. J. MCH AIDS 6 (2) (2017) 139–164.
[55] T. McGrady, et al., Characteristics of chronic obstructive pulmonary disease (COPD) patients reporting alpha-1 antitrypsin deficiency in the WebMD Lung Health Check database, Chronic Obstr. Pulm. Dis. 2 (2) (2015) 141–151.
[56] A.G. Wheaton, et al., Employment and activity limitations among adults with chronic obstructive pulmonary disease–United States, 2013, MMWR Morb. Mortal. Wkly. Rep. 64 (11) (2015) 289–295.
[57] G.C. Farmer, et al., Does primary language influence the receipt of influenza and pneumococcal immunizations among community-dwelling older adults? J. Aging Health 22 (8) (2010) 1158–1183.
[58] J. Santaularia, et al., Prevalence of influenza vaccination and its association with health conditions and risk factors among Kansas adults in 2013: a cross-sectional study, BMC Publ. Health 16 (2016) 185.
[59] J.A. Singleton, T.A. Santibanez, P.M. Wortley, Influenza and pneumococcal vaccination of adults aged > or = 65: racial/ethnic differences, Am. J. Prev. Med. 29 (5) (2005) 412–420.
[60] R.M. Arabyat, D.W. Raisch, L. Bakhireva, Influenza vaccination for patients with chronic obstructive pulmonary disease: implications for pharmacists, Res. Soc. Adm. Pharm. 14 (2) (2018) 162–169.
[61] D.J. Hsu, et al., Identification of barriers to influenza vaccination in patients with chronic obstructive pulmonary disease: analysis of the 2012 Behavioral Risk Factors Surveillance System, Chronic Obstr. Pulm. Dis. 3 (3) (2016) 620–627.
[62] M.D. Eisner, et al., Body composition and functional limitation in COPD, Respir. Res. 8 (2007) 7.
[63] Y. Liu, et al., Body mass index, respiratory conditions, asthma, and chronic obstructive pulmonary disease, Respir. Med. 109 (7) (2015) 851–859.