Relationship Between Pulmonary Airflow (FEV1) and Use of Menthol vs Non-Menthol Cigarettes in the COPDGene® Population

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Abstract

Chronic Obstructive Pulmonary disease (COPD) is the fourth leading causes of death in the United States and a major public health issue. The relationship between smoking and COPD is well known as smoking is the primary risk factor for development of COPD. However, whether smoking mentholated versus non-mentholated cigarettes is associated with an increased risk of developing COPD is unclear. For this project, I analyzed data on pulmonary function (as measured by forced expiratory volume, percent predicted FEV1, ppFEV1) on 2858 European Americans (EA) and 2790 African Americans (AA), a total of 5648 participants who had a smoking history greater than 10 pack years, from the COPDGene® multicenter observational study. Men comprised 55.1% of the population and 44.9% were women. EA participants were significantly older than AA participants (57.8 versus 53.5 years, respectively, $p<0.00001$), had smoked substantially more pack-years (47.6 versus 38.1 pack-years, respectively, $p<0.00001$), and had lower ppFEV1 (76.4% predicted versus 84.9% predicted, respectively, $p< 0.0001$). Overall, significantly more European Americans smoked non-menthol cigarettes than menthol cigarettes, 55.8% versus 44.3%, respectively (p-value < 0.00001), whereas significantly more African Americans smoked menthol cigarettes than non-menthol cigarettes, 88.2% versus 11.8%, respectively p-value < 0.00001). An analysis of the effects of age, pack-years, race, and menthol cigarette smoking on (adjusted) ppFEV1 revealed that ppFEV1 significantly decreased with

increasing age and pack-years, and also was significantly higher in AA versus EA participants ($p<0.000001$ for all). Menthol versus non-menthol cigarettes smoking was not associated with ppFEV1, when race was included, although interactions among the variables was not explored. These results confirm previous relationships regarding the effects of age, race, and pack-years on ppFEV1, but identified no independent effects of menthol versus non-menthol cigarette smoking. However, the relationship between ppFEV1 and age, pack-years, menthol cigarette smoking, race, and sex was not straightforward and additional analyses need to be done. My results indicate that the relationships between ppFEV1, age, pack-years and menthol cigarette smoking differ by sex and between races, thus, different public health interventions to facilitate smoking cessation and reduce COPD will need to be targeted to specific groups.

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1.0 Background

1.1 Definition and Public Health Relevance

Chronic obstructive pulmonary disease, otherwise known as COPD, is a serious pulmonary disease that severely limits pulmonary airflow and presents as a chronic cough, wheezing, shortness of breath, and sputum production. The severe airflow limitation results from a combination of two lung conditions, emphysema and chronic bronchitis. The chronic cough is due to chronic bronchitis that results from inflammation. The shortness of breath is due to emphysema that results from damage to the alveoli.

COPD is a major public health concern, it is the fourth leading cause of death in the United States, after heart disease, cancer and accidents (Xu 2018). In 2018 16.4 million people reported a COPD diagnosis of whom,156,979 Americans die each year (National Vital Statistics System – Mortality Data (2019) via CDC WONDER). Overall, in 2014, the mortality rate for COPD was higher in men than women, 44.3 per 100,000 versus 35.6 per 100,000 (National Vital Statistics System – Mortality Data (2019) via CDC WONDER).

Prevalence and mortality of COPD also differs between European Americans and African Americans. Gillum and colleagues (1990) analyzed data on 76,559 individuals from the National Center for Health Statistics. They reported that in 1986, the prevalence of COPD was lower among African Americans than among European Americans (African American to European ratio 0.80). Furthermore, European American men had the highest mortality rates (approximately 30 deaths per 100,000), followed by African American men (approximately 20 deaths per 100,000),

European American women (approximately 15 deaths per 100,000), and finally African American women (approximately 8 deaths per 100,000).

The costs of COPD for individuals and society are substantial. Life expectancy for individuals who have COPD and currently smoke with COPD is shorter than that for individuals who have COPD and are former smokers or never smokers. Specifically, Shavelle and colleagues reported that the life expectancy of current smokers with more severe disease is 5.8 years less, former smokers with more severe disease is 5.6 years less, and individuals who have never smoked with more severe disease lose 1.3 years. In addition to the reduction in lifespan, in 2003 COPD incurred a $32.1 billion loss in the United States alone du e to medical costs. These costs have been paid mostly by Medicare, Medicaid and private insurance. (Petty 2006) In 2013, Torabipour et al conducted a cost analysis of hospitalized patients with COPD. This analysis consisted of 165 subjects that have been diagnosed with COPD, at Imam Khomeini hospital in Iran. Data was obtained retrospectively from billing data. They reported that the mean costs per patient increased from $423.3 in 2011 to $2,436.20 in 2013. Ford et al performed an analysis using data from 2006-2010 Medical Expenditure Panel Survey, the 2004 National Nursing Home Survey, and the 2010 Centers for Medicare and Medicaid Services to find that the mean medical costs including hospitalizations and medications per patient was 5.7 times higher in 2013 than 2011.

Although the prevalence of COPD and its associated costs are high, the burden of disease varies by geographic regions. Using data from the Burden of Obstructive Lung Disease (BOLD) study, a study that collected data from multiple countries to identify risk factors and to quantify prevalence of obstructive lung disease, Buist et al. estimated global prevalence of COPD to be 10.1% in 2007 and ranged from 6% in Germany to 19% in Cape Town, South Africa. The overall estimated prevalence of COPD in United States is 10.1%, (Buist 2007), but it varies substantially.

As can be seen in figure 1 (derived from BFRSS 2019 data), the prevalence of COPD is highest along the Mississippi and Ohio rivers.

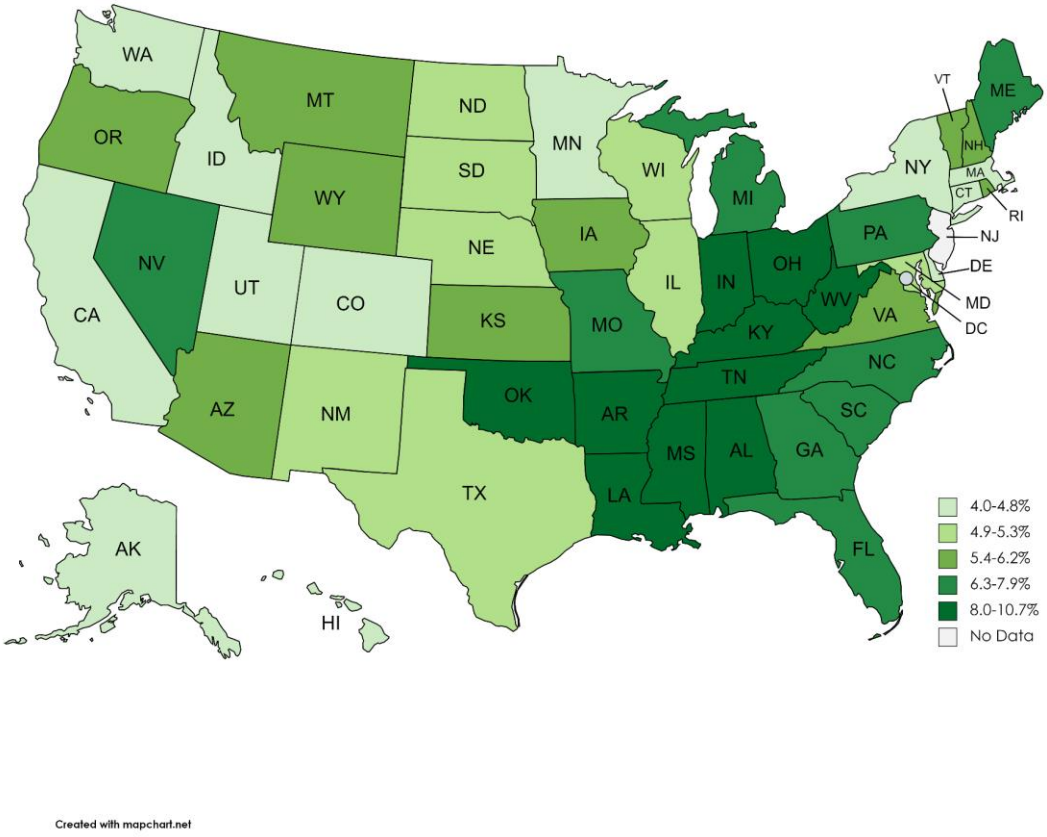

Figure 1. COPD Prevalance in the United States

As a result of the high prevalence of COPD overall and its impact on the health individuals and society, as well as differences in COPD prevalence by geographic regions and among ethnic/racial groups, researchers have been studying the environmental and genetic factors that affect the development of COPD since 1959(Ciba 1959).

1.2 Forced Expiratory Volume (FEV) as a Measure of Pulmonary Airflow

As described above, COPD can severely limit pulmonary airflow. Forced Expiratory Volume (FEV), as assessed by spirometry, is a common measure of pulmonary airflow and is used in the diagnosis of COPD (Pierce 2005). Specifically, FEV1 is the volume of air that an individual can forcibly expire from their lungs within 1 second after inhaling deeply. The higher the volume of air that individuals can force from their lungs, the better the lung function (Spirometry Testing Dec 2013). Instead of FEV1, clinicians and researchers who study COPD often analyze "percent predicted FEV1" which is the ratio of the individual's measured FEV1 to the mean FEV1 predicted for an individual's age, weight, and sex. This ratio is expressed as a percent.

Because of the ubiquity of the use of FEV1 for precent predicted FEV1, I will also refer to "precent predicted FEV1" as FEV1 throughout this essay.

Among individuals without COPD, FEV1 ranges 80% or higher, and most individuals with normal pulmonary function have percent predicted FEV1 between 80 – 120%. (Spirometry Testing Dec 2013).

Pulmonary airflow as measured by FEV1 is one of the components of the GOLD stages I-IV that are used clinically to categorize severity of COPD (GOLD 2021 Report). COPD patients with very mild disease (Stage 1) have FEV1≥80%. Patients with Stage 2 moderate disease have ppFEV1 measures between 50% and 80%. Stage 3 patients have severe disease with a FEV1 between 30% and 50%. Stage 4 is a very severe disease with a FEV1<30% (GOLD 2021 Report).

1.3 Environmental Risk Factors

Numerous environmental elements have been reported as risk factors for the development of COPD, including smoking, second hand smoke, dust, fumes and chemicals, air pollution both indoor and outdoor, and childhood respiratory infections such as childhood pneumonia (Hayden 2015). As an example of indoor air pollution, in countries in which the mean income of the population is low, individuals may be exposed to fumes from cooking indoors with traditional open-fire cookstoves. The fuel used to heat the stoves is usually animal dung and crop scraps (Gorlick 2012). These stoves do not have chimneys resulting in poor ventilation within the home and the family members breathing in the polluted air. (Gorlick 2012) Paulin and colleagues (2019) assessed the relationship between outdoor air pollution, such as increased ozone levels and FEV1 values. They analyzed data from the SPIROMICS Air Pollution Study from November 2011 to July 2018. This study was a multicenter cross-sectional study of 1874 current or former smokers from seven urban centers across the United States. These investigators reported that long term ozone exposure was associated with reduced FEV1 (Paulin et al, 2017).

Hayden and colleagues analyzed data from the COPDGene® cohort (described in Section 2.1 below) to evaluate a relationship between childhood pneumonia and COPD. In this cohort, 854 individuals (8.4% of the population) reported having childhood pneumonia. Individuals with childhood asthma were at increased risk of developing COPD (odds-ratio = 1.4), and FEV1 among these individuals was 69.1% when a value of 77.1% was expected (Hayden 2015).

1.4 Tobacco Use

Tobacco use is the primary risk factor for development of COPD (Hylkema 2007) Although numerous tobacco products exist, including pipes, cigars and smokeless tobacco, cigarettes are the most frequently used. Cigarettes were introduced in the United States in the early 19th century and were initially rolled by hand. After the invention of the cigarette rolling machine, cigarettes became easily accessible to the overall population and lead to more individuals smoking (Cross 2014).

Based on analyses conducted by The American Lung Society (ALS 2020) of data from the 2015 National Health Interview Survey conducted by the Centers for Disease Control and Prevention, smoking rates differ among racial and ethnic populations. Overall, 16.6% of African Americans smoke, which is similar to that or non-Hispanic white (16.6%), and higher than that for Hispanics (10.1%) and Asian Americans (7%.). Indigenous Americans (including Alaskan Natives,) have the highest rates (21.9%). Overall, women smoke less than men but the proportions differ by sex. For example, 20% of African American men versus 13.5% or women smoke, whereas the proportions of men and women smokers are more similar among non-Hispanic whites, 17.3% of men and 16.0% of women. Substantially fewer women than men smoke among Hispanics (7.1 versus 13.1%, respectively) and among Asian Americans (2.6% versus 12.0%, respectively). In contrast, more American Indians/Alaskan Native Indian women smoke (24%, compared to men (19%).

1.4.1 Menthol cigarettes

Menthol cigarettes were introduced by Lloyd Hughes (Reid 1993). Hughes had asthma and carried a small container of menthol crystals from which he would breathe vapors for asthma relief. He discovered that cigarettes stored in the same container with the menthol crystals absorbed the menthol flavoring and had a cool taste (Reid 1993). The menthol flavored cigarettes were not as harsh as non-menthol cigarettes and thus were more palatable, and marketable, to a larger swath of the population including women, youth, and African Americans (Sutton 2004).

Currently, all cigarettes contain approximately 600 chemicals, inclusive of added menthol (either natural or synthetic), even cigarettes marketed as non-menthol cigarettes (Tobacco Products Scientific Advisory Committee 2011). The difference between menthol and non-menthol cigarettes is that more menthol, 2.9 to 19.6 mg/cigarette, is added to cigarettes classified as menthol in the United States. Cigarettes classified as non-menthol contain 0.002 to 0.07mg/cigarette of menthol (Ai J 2018).

Menthol versus non-menthol cigarette smoking differs among racial and ethnic populations. Villanti and colleagues (2016) analyzed tobacco use data from the 2004-2014 National Surveys on Drug Use and Health, a nationally representative survey of the US civilians who are greater than 12yo and non-institutionalized. Across this time-period, they reported that the percentages of individuals who smoked menthol cigarettes ranged from a low of 25-29% among European Americans, to 30-38% among non-Hispanic Asian Americans, to 37-47% of Hispanic Americans, and a high of 84.6-86% of non-Hispanic African Americans.

Because menthol masks the harshness of cigarettes, researchers have hypothesized that high levels of menthol in cigarettes may reduce an individual's ability to quit smoking. Recently, results from a few studies support this hypothesis. In 2014, Smith and colleagues reported results

of their clinical trial of 1504 adult smokers with a smoking history of at least 10 cigarettes per day within the past 6 months (Smith 2014) who had also expressed an interest in quitting smoking. The study group was comprised of 814 white non-menthol and 439 menthol cigarette smokers, as well as 186 African American menthol smokers. The number of African American non-menthol smokers (n= 16) was too low to provide meaningful results and were excluded from the analyses. Smoking status was collected at 4, 8 and 26 weeks after the adults ceased smoking. The researchers reported that menthol cigarette smokers were less likely to have smoking cessation success (OR=0.72; C.I = 0.60 to 0.87). Menthol cigarette smokers also had a higher nicotine dependence, fewer prior attempts to quit, and less confidence in being able to quit smoking. The researcher's model also predicted that the probability of continued smoking abstinence for non-menthol versus menthol cigarette smokers was 45% vs. 37%, respectively (Smith 2014).

In addition to the results on smoking cessation among menthol versus non-menthol cigarette smokers, Smith and colleagues reported that African American women had a higher risk of failure compared to white women OR=2.63 (C.I = 1.75, 3.96) However, no differences were observed between smoking cessation frequency in white versus African American men OR=1.01 (C.I. = 0.59, 1.74) (Smith 2014).

1.5 Rationale for Current Study and Gaps in Knowledge

Because the primary risk factor for COPD is smoking, knowledge of variables that increase smoking would enable the development of targeted interventions to reduce smoking and thus may prevent many cases of COPD. The addition of menthol to cigarettes masks the harshness of cigarette smoke. Furthermore, a few studies have indicated that individuals who smoke menthol

cigarettes are less likely to be able to quit smoking. The effect of smoking menthol versus non-menthol cigarettes on FEV1 and the possible development of COPD is unclear. In the current study, I assessed the effects of several risk factors, including age, pack-years, race, and menthol versus non-menthol cigarettes, on FEV1 and categories of FEV1 that correspond to the GOLD stages for COPD.

1.6 Hypothesis and Specific Aims

The overall goals of the current study are to assess (1) whether smoking menthol versus non-menthol cigarettes is an independent risk factor for decreased FEV1, and (2) whether the effects of this possible risk factor differ between European Americans and African Americans.

To achieve this goal, I performed the following specific aims using data from the COPDGene® study:

(1) Assess whether measures of FEV1 and a variety of risk factors (including age, pack-years, sex, smoking behaviors) differed between European Americans and African Americans.

(2) Assess whether measures of FEV1 and a variety of risk factors (including age, pack-years, sex, smoking behaviors) differed between menthol versus non-menthol cigarette smokers within the European Americans and African Americans, separately.

(3) Assess whether age, pack-years, race, and menthol versus non-menthol cigarette smoking are independent risk factors for FEV1 proportion.

2.0 Methods

2.1 COPDGene® Study

COPDGene® is an observational study with a primary objective to identify genetic factors that contribute to COPD (Regan et al 2010). This multicenter study has enrolled over 10,000 patients from 21 sites in the Unites States. Non-Hispanic European American men and women, and African American men and women between the ages of 45 and 80 were recruited through radio ads, health fairs, and identified from registry databases in research offices for participation in this study. The four subject groups in this study are: (1) COPD participants who have a diagnosis of COPD Gold Stage 1-4, (2) participants with FEV1 less than 80% who do not have a Gold Stage diagnosis (e.g., Gold Stage Unclassified), (3) smokers without COPD (and no Gold Stage diagnosis) with FEV1 greater than 80%, and (4) non-smoking controls. As described in section 1.2, the 4 Gold Stages are used to indicate the severity of diagnosed COPD (GOLD 2021 Report). All groups, except the non-smoking controls had a smoking history greater than 10 pack years (1 pack of cigarettes per day for 10 years). To be included in COPDGene® the non-smoking controls had to have smoked less than 101 cigarettes over their lifetime. Exclusion criteria for the COPDGene® study included: a lung disease other than COPD, chronic bronchitis, or emphysema. Participants were also excluded if they had previous lung surgery to remove one lobe or more of the lung. All participants were able to complete spirometry and all participants self-assigned to one racial category.

2.2 Measurements

Participants of the COPDGene® trial consented to multiple procedures and data collection activities. Data on pack years (packs per day/years smoked), and whether the participant currently smokes or previously smoked menthol cigarettes was self-reported by the participant completing questionnaires and medical history forms. All participants completed (1) pre- and post-bronchodilator spirometry tests to measure airflow obstruction, (2) blood collection to test for the alpha 1 antitrypsin deficiency and other proteins associated with COPD, (3) a 6-minute walk test to measure exercise capacity, and (4) a chest CT scan to measure emphysema and any airway disease.

2.2.1 Measurement of Airflow

For each participant, pulmonary airflow was measured by spirometry, specifically using Forced Expiratory Volume (FEV). FEV1 is the measurement of how much air you can forcibly move from your lungs in 1 second. The higher volume of air that can be forced from the lungs the better the lung function. Variability of spirometry results are minimized by performing the spirometry procedure once without a bronchodilator, administering a bronchodilator and, waiting until optimal absorption level is achieved and then administering the spirometry procedure again. For the current study, I used percent predicted FEV1 percent, that is, the ratio of the measured FEV1 to the FEV1 predicted based on the individuals age, sex, and weight cohort (see section 1.2). In addition to analyzing FEV1 as a quantitative trait, I also divided the participants into categories of pulmonary airflow based on their FEV1 results: high (FEV1≥80%, medium (FEV1 between

50% and 80%, low (FEV1 between 30% and 50%) and very low FEV1<30%. These categories correspond to Gold Stages I-IV described in section 1.2.

For this project I only included participants who answered the question on the medical history questionnaire “Do you now smoke or did you smoke menthol cigarettes?”

2.3 Statistical Methods

I first tested for differences for a variety of traits between European Americans and African Americans. Differences between the two groups were assessed using chi-squared tests for categorical data (such as sex) (Using the chi-square calculator from Social Science Statistics) and t-tests for quantitative measures (using the data analytics toolpak add-in from excel), such as FEV1. Because I was interested in the possible relationships between these traits and participants who smoked menthol versus non-menthol cigarettes, I next performed analyses between menthol and non-menthol cigarette smokers within European American and African American groups separately. Finally, I used general regression analysis (Using excel data analytics toolpak add-in from excel) to assess the effects of age, pack-years, race, and menthol versus non-menthol cigarette use on FEV1 measures.

3.0 Results

3.1 Characteristic of the Study Population

Data on a total of 5648 participants was available for the current study of possible relationships between menthol versus non-menthol cigarette smokers on FEV1 and COPD-related risk factors (such as age, sex, and pack-years). The total number of European American participants was similar to the number of African American participants, n=2858 versus 2790, respectively (Table 1). More males than females were recruited, 55.1% versus 44.9%, overall, and the proportion of African American male participants was higher than the proportion of European American participants, 56.3% versus 53.8%, respectively, although these differences were not statistically significant (p=0.056). Participants ranged in age from 39 to 85 years old and mean age of the total population was 55.7 years. European Americans were 4.3 years older than African Americans (57.8 versus 53.5 years, respectively) and this difference was significant (p-value = 6.36×10^{-111}; Table 1).

Table 1. Population Characteristics

	Total	European American	African American	Test statistic (χ^2 or t-test) and p-value
n	5648	2858	2790	
Sex				χ^2_1 = 3.65, p=0.055974
Male (%)	3110 (55.1%)	1538 (53.8%)	1572 (56.3%)	
Female (%)	2538 (44.9%)	1320 (46.2%)	1218 (43.7%)	
Age at visit, years (Mean ± sd, range)	55.67 ± 7.52; range: 39 - 85	57.84 ± 7.98	53.46 ± 6.28	t=22.89, **p-value = 6.36×10^{-111}**
Smoking				
Current Vs Former				X^2_1 = 34.443, **p-value <0.00001**
Current (%)	5333 (94.4%)	2648 (92.7%)	2685 (96.2%)	
Former (%)	315 (5.6%)	210 (7.3%)	105 (3.8%)	
Pack years. (Mean ± sd; range)	42.91 ± 23.29; range 10 - 237.2	47.62 ± 24.10	38.08 ± 21.38	t= 15.74, **p-value = 1.24×10^{-54}**
Cigarette type				χ^2_1= 1217, **p-value <0.00001**
Menthol. (%)	3722 (65.9%)	1262 (44.2%)	2460 (88.2%)	
Non-menthol. (%)	1926 (34.1%)	1596 (55.8%)	330 (11.8%)	
FEV1				
FEV1 ratio, %) (Mean ± SD; range)	80.61 ± 22.46; range: 10.3 - 159.9	76.41 ± 22.66	84.91 ± 21.41	t=-14.49, **p-value =9.67×10^{-47}**

Table 1 (continued)

FEV1 Category				χ^2_5= 148.69, **p-value <0.00001**
FEV1>80.1%	3166 (56.1%)	1405 (49.2%)	1761 (63.1%)	
FEV1 50.1%-80%	1863 (33%)	1026 (35.9%)	837 (30%)	
FEV1 30.1%-50%	459 (8.1%)	311 (10.9%)	148 (5.3%)	
FEV1 <30%	160 (2.8%)	116 (4%)	44 (1.6%)	

With respect to smoking behaviors, most of the participants were current smokers, only 5.6% self-reported as former smokers. Although the proportions were low, more European Americans were former smokers than were African Americans (7.3% versus 3.8%, respectively; p-value < 0.00001). The number of pack-years of cigarettes smoked ranged widely, from a low of 10 pack-years to a maximum of 237.2 pack-years. European American participants smoked an average of 9.5 pack years more than African American participants (47.6 versus 38.1 pack-years, respectively), this difference was highly significant ($p = 1.24x10^{-54}$ (Table 1). The proportions of non-menthol versus menthol cigarette smokers varied substantially between European and African American participants. European Americans smoked more non-menthol cigarettes versus menthol cigarettes (55.8% versus 44.3%, respectively), whereas African Americans smoked more menthol cigarettes than non-menthol cigarettes (88.2% versus 11.8%, respectively), and these differences were highly significant (p-value < 0.00001).

Overall, mean pulmonary function, as measured by FEV1, ranged from a low of 10.3% to a high of 159.9%. FEV1 was significantly higher among African Americans than among European Americans, mean FEV1was 84.9% versus 76.4%, respectively; p-value = 9.67×10^{-42}. As can be seen in Table 1, this overall difference in FEV1 is also reflected in the proportion of participants within each of the FEV1 categories. A higher proportion of African Americans (63.1%) had pulmonary function greater than 80.1%, whereas slightly less than one-half (49.2%) of European

Americans were in the high function category. Similarly, approximately half as many African Americans as European Americans had poor (FEV1 from 30.1-50%) or severely poor (FEV1 < 30%) pulmonary function. For example, 1.6% of African Americans were in the severely poor category versus 4% of European Americans. These differences in frequencies among the FEV1 categories were highly significant (p-value < 0.00001).

Table 2. Study Population

	European American	European American	European American Test statistic (X^2 or t-test) and p-value	African American	African American	African American Test statistic (X^2 or t-test) and p-value
	Menthol	Non-Menthol		Menthol	Non-Menthol	
	1262	1596		2460	330	
Sex			X^2=1.8767, p-value is .1707			$X^{2=}$3.61, p-value = 0.0576
Male (%)	661 (52.4%)	877 (55%)		1370 (56%)	202 (61.2%)	
Female (%)	601 (47.6%)	719 (45%)		1090 (44%)	128 (38.8%)	
Age at visit (Mean ± sd)	56.9±7.78	58.58±8.06	t=-5.62, **p-value = $2.09x10^{-8}$**	53.11±5.99	56.04±7.59	t=-8.06, **p-value = $1.11x10^{-15}$**
Smoking			x^2=5.16, **p-value = .023**			$x^{2=}$20.17, **p<0.00001**
Current (%)	1185 (94%)	1463 (91.7%)		2382 (96.8%)	303 (91.8%)	
Former (%)	77 (6%)	133 (8.3%)		78 (3.2%)	27 (8.2%)	
Pack years. (Mean ± sd)	47.08±23.62	48.05±24.48	t=-1.07, p-value = 0.29	37.96±20.94	39.95±24.42	t=-0.79, p-value = 0.43
FEV1 (Mean ± sd)	77.30±22.30	75.7±22.93	t=1.88, p-value = 0.059	85.08±20.96	83.63±24.46	t=1.16, p-value = 0.25
FEV1 Range			x^2=16.11, **p-value = 0.0011**			$x^{2=}$14.94, **p-value = 0.0018**
FEV1>80.1%	655(51.9%)	750(47%)		1551(63%)	210(63.6%)	
FEV1 50.1%-80%	424(33.6%)	602(37.7%)		754(30.7%)	83(25.2%)	
FEV1 30.1%-50%	147(11.6%)	164(10.3%)		122(5%)	26(7.9%)	
FEV1 <30%	36(2.9%)	80(5%)		33(1.3%)	11(3.3%)	

I next assessed the relationships between participants who smoked menthol versus non-menthol cigarettes within the European American and African Americans populations separately (Table 2). As noted in Table 1, more European American participants smoked non-menthol cigarettes, whereas more African Americans smoked menthol cigarettes. The proportions of European American men (and women) who smoked menthol versus non-menthol cigarettes were similar. For example, men comprised 52.4% of menthol cigarette smokers and 55% of non-menthol cigarette smokers and this difference was not significant (p-value = 0.17). Among African American participants, men comprised 56% of the menthol cigarette smokers and 61.2% of the non-menthol cigarette smokers, but this difference was not significant ($p < 0.058$),

Menthol cigarette smokers were significantly younger than non-menthol cigarette smokers for both European American and African American participants. European American menthol cigarette smokers were 1.7 years younger on average than non-menthol cigarette smokers (age = 56.9 versus 58.6 years, respectively; p-value = 2.09×10^{-8}). African American menthol cigarette smokers were 2.9 years younger than non-menthol cigarette smokers (age = 53.1 versus 56.0 years, respectively; p-value = 1.11×10^{-15}). Overall, the numbers of former smokers comprised only 5.6% of the total population (Table 1). However, the proportion of non-menthol cigarette smokers who were former smokers was significantly higher than the proportion of menthol cigarette smokers who were former smokers among both European and African American participants (p-values = 0.023 and < 0.0001, respectively) (Table 2).

For both European Americans and African Americans, the number of pack-years were 1-2 years lower, respectively, among menthol versus non-menthol cigarette smokers, but these differences were not significant (Table 2). Similarly, although FEV1 was 1.4 - 1.6% higher for menthol versus non-menthol cigarette smokers among both European and African American

participants, these differences were not significant (see Table 2 and Figure 2). In contrast, the relative proportions of participants in the 4 different FEV1 categories differed significantly between menthol versus non-menthol smokers among both European and African American participants (p-values < 0.001 for both). In general, menthol cigarette smokers had better pulmonary function than non-menthol cigarette smokers. Among European Americans, a lower proportion of non-menthol smokers than menthol smokers had FEV1<30% (2.9% versus 5%, respectively). Also, a higher proportion of menthol smokers versus non-menthol smokers had mild or no disease, FEV1>80.1%) (51.9 versus 47%, respectively), Among African Americans, a similar proportion of menthol versus non-menthol cigarette smokers had FEV1 > 80.1% (63% versus 63.6%, respectively). However, lower proportions of menthol cigarette smokers compared to non-menthol cigarette smokers had poor FEV1 outcomes; 6.3% of menthol cigarette smokers versus 11.2% of non-menthol cigarette smokers had FEV1 <50%.

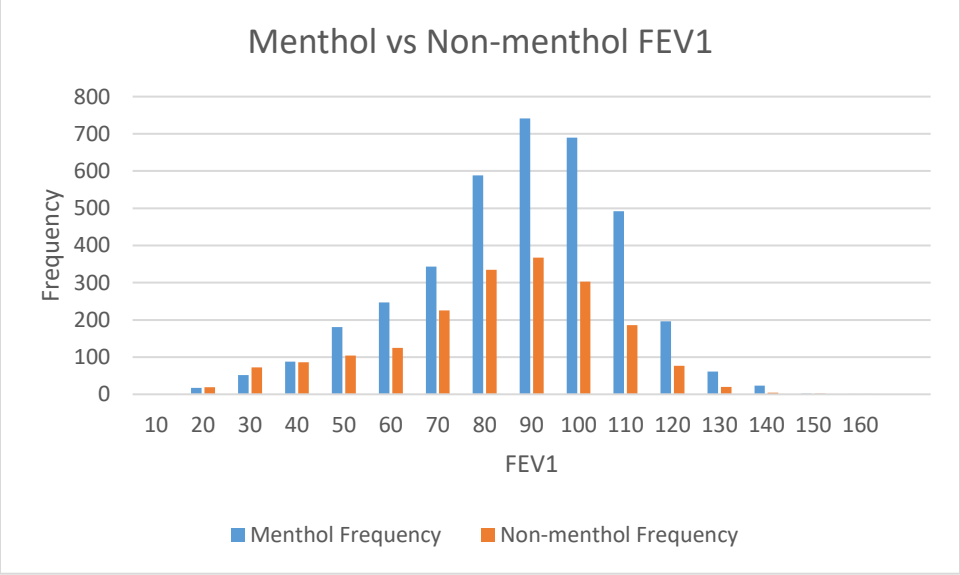

Figure 2. Menthol Vs Non-menthol FEVI Frequency Histogram

Finally, I performed a general linear model (GLM) analysis and assessed the simultaneous effects of age, pack-years, race, and menthol/non-menthol cigarette use on FEV1; the results are presented in Table 3. Overall, these variables accounted for 9.9% of the total variation FEV1 (r2 = 0.0987, p-value = $1.4x10^{-125}$). As can be seen in Table 3 (and Appendix A; Figures 1- 4), FEV1 significantly decreased with both increasing age (β = -0.51; p-value = 4.2x10-^{34}) and increasing number of pack years (β = -0.145; p-value = 2.3x10-^{28}). Furthermore, FEV1 was significantly higher among African American participants than among European American participants (β = 4.72; p-value = $9.3x10^{-13}$). Menthol versus non-menthol cigarette use was not significantly associated with FEV1 after inclusion of age, pack-years, and race.

Table 3. Estimate of Effects of Age, Pack Years, Race and Menthol Cigarettes on FEVI

	Coefficients ± Standard Error	t Stat	P-Value
Age at Visit	-0.510± 0.042	-12.2	$4.21x10^{-34}$
Pack-years	-0.145± 0.013	-11.1	$2.30x10^{-28}$
Race (EA = 0, AA=1)	4.72 ± 0.66	7.15	$9.38x10^{-13}$
Menthol/Non-menthol	0.38 ± 0.68	0.55	0.58
r^2	0.0987		$1.14 x10^{-125}$

4.0 Discussion

Based on an analysis of the Center for Disease Control and Prevention's National Health Interview Survey data from 1965-2018, the American Lung Associations states that the prevalence of current cigarette smoking among U.S. adults declined from 42.4% in 1965 to 13.9% in 2017 (ALA Overall Tobacco Trends) Between 1997 and 2015, the overall prevalence of smoking in the US decreased almost 10% between 1997 and 2015; prevalence was 25.7% in 1997 and 15.1% in 2015. (Ward et al., 2016) This overall reduction in smoking was primarily due to a decrease in the proportion of non-menthol cigarette smokers versus menthol cigarette smokers. For example, among individuals aged 26+ years, the prevalence of non-menthol cigarette smokers was 17.4% in 2004 and 13.4% in 2014 (Villanti et al., 2016). In contrast, among menthol cigarette smokers of the same age and time frame, the prevalence increased between from 7.1 to 7.8% respectively (Villanti et al., 2016). Furthermore, as described in the Introduction, and also in a review by Villanti and colleagues (2017), menthol cigarette smokers are less successful at quitting cigarettes than non-menthol cigarette smokers across multiple ethnic and racial groups, despite their increased number of quit attempts. Thus, menthol cigarette smokers may be at increased risk of developing COPD.

As described in the Introduction, cigarette smoking, increased age, and number of pack-years are strongly associated with increased risk of COPD. Given the higher prevalence of menthol cigarette smokers in African Americans and reports that menthol cigarette smokers are less successful at long-term smoking cessation, African Americans may have poorer measures of FEV1 and thus have an increased risk of developing COPD. In this project, I assessed the relationship between FEV1 (a surrogate for COPD risk) and risk factors for poor pulmonary function using data on 5648 participants who were current or former smokers from the COPDGene® study.

By design, the number of European American (n=2858) and African American (n=2790) recruited into the COPDGene® study were similar. Consistent with the observation that males have a higher prevalence of COPD, more males (55.1%) than females (44.9%) were present in the study, although the relative proportions of males versus females did not differ significantly between European Americans and African Americans (Table 1). Consistent with previous reports (Villanti et al., 2016), women were more likely to smoke menthol cigarettes versus non-menthol cigarettes than were men. In European Americans 45.5% of women versus 42.9% of men smoked menthol cigarettes, whereas in African Americans 89.5% of women and 87.1% of men smoked menthol cigarettes, although these differences were not statistically significant (Table 2). Although women currently have a lower prevalence of COPD than men, given that individuals who smoke menthol cigarettes have more difficulty quitting smoking, COPD prevalence may increase among women smokers in the future.

African American participants were significantly more likely to smoke menthol cigarettes than European Americans (88.2% versus 44.2%, respectively). Although these proportions are higher than those reported by the CDC, 76.8% in non-Hispanic blacks and 24.6% of white adults, the relative proportions are similar.(CDC, 2020 Menthol and Cigarettes) Overall, African American participants were 4.3 years younger than European American participants and menthol cigarette smokers were significantly younger than non-menthol cigarette smokers among both European American and African American participants, 1.7 and 2.9 years, respectively (Table 2). These results are also consistent with previous reports that menthol cigarette smokers were younger than non-menthol cigarette smokers (Rath et. al., 2016) and that the proportion of adolescents who smoked menthol cigarettes were more likely to progress to becoming a long-term smoker (reviewed by Villanti et al., 2017).

In the current study, African Americans smoked significantly fewer pack years than European Americans (38.1 versus 47.6 pack-years). Furthermore, the number of pack-years was

1-2 years lower among menthol versus non-menthol cigarette smokers in European and African Americans, although this difference was not significant. These results are similar to other reports that African Americans smoke fewer cigarettes than European Americans, (CDC, 2020, African Americans and Tobacco Use). Differences in the ages and pack years between the two groups may be due to the difference in price of menthol versus non-menthol cigarettes. Because the proportion of African Americans smoking menthol cigarettes is higher than that of European Americans, and menthol cigarettes are more expensive, African Americans may smoke fewer cigarettes (Mills et al 2015). Mills et. al. also reported that a few menthol brands offer promotional prices in predominately black neighborhoods, thus resulting in more African Americans smoking menthol cigarettes. In addition, the additives in menthol cigarettes might reduce the number of cigarettes needed to obtain the same effects. Tauros et al also reported that African Americans are more likely to smoke menthol cigarettes and fewer cigarettes, than are European Americans. Tauros also reports that menthol and non-menthol cigarettes are not considered substitutes for each other. Thus, even if the price of menthol cigarettes went up, the smoker would not be inclined to start smoking non-menthol nonmenthol cigarettes instead. Pulmonary function (as measured by FEV1) was significantly better among the African American (84.9%) compared to the European American participants (76.4%). Although mean FEV1 was ~1.5% higher in menthol cigarette smokers than non-menthol cigarette smokers, this difference was not significant. However, the proportion of menthol versus non-menthol smokers who fell into each FEV1 category was significantly different among both European and African Americans. These results are consistent with the observations that African American participants and menthol cigarette smokers were younger and smoked fewer pack-years.

Finally, I assessed whether age, pack-years, race, and menthol cigarette smoking were independently associated with FEV1. As expected from the univariate results and the literature reports, age, pack-years, and race were significantly, and independently associated with FEV1, Appendix Table A2. In contrast, menthol cigarette smoking was not a significant independent risk factor for FEV1, although it was positively associated with increased FEV1 (Table 3).

4.1 Limitations of the Current Study

In comparison with reports in the literature, the current study is relatively small, that is ~5,600 individuals versus >57,000 individuals from the large CDC data sets. Although menthol cigarette smoking was not an independent risk factor for FEV1, it may interact with other risk factors. For example, when race was not included in the regression model, menthol (versus non-menthol) cigarette smoking was significantly associated with increased FEV1 ($\beta = 2.44$, p-value $= 7.9 \times 10^{-5}$; Appendix Table A1.

Furthermore, although the age difference between European and African American participants was 4.4 years, the number of pack years differed by 9.6 years, indicating a possible interaction among the age, pack-years, race, and menthol smoking variables. Finally, the possible effects of sex could be included in a multivariable regression analysis. These analyses were beyond the scope of my current project, although they may lead to additional insights.

4.2 Conclusions

Similar to results in the literature, my results indicate that decreased FEV1, as a measure of poorer pulmonary function, and a marker for COPD, is significantly associated with increasing age, increasing number of pack-years, and European American (versus African American) status. Menthol versus non-menthol cigarette smoking did not have any significant effects on FEV1 percent. However, the relationships between FEV1, age, sex, pack-years, race, and menthol versus non-menthol cigarette smoking were not straightforward, indicating the presence of possible interactions among these variables. Future directions may include studies of possible interactions between race, menthol, pack years, FEV1 and age. In addition, studies of the effect of menthol cigarette smoking on the likelihood of quitting smoking are needed.

Appendix A

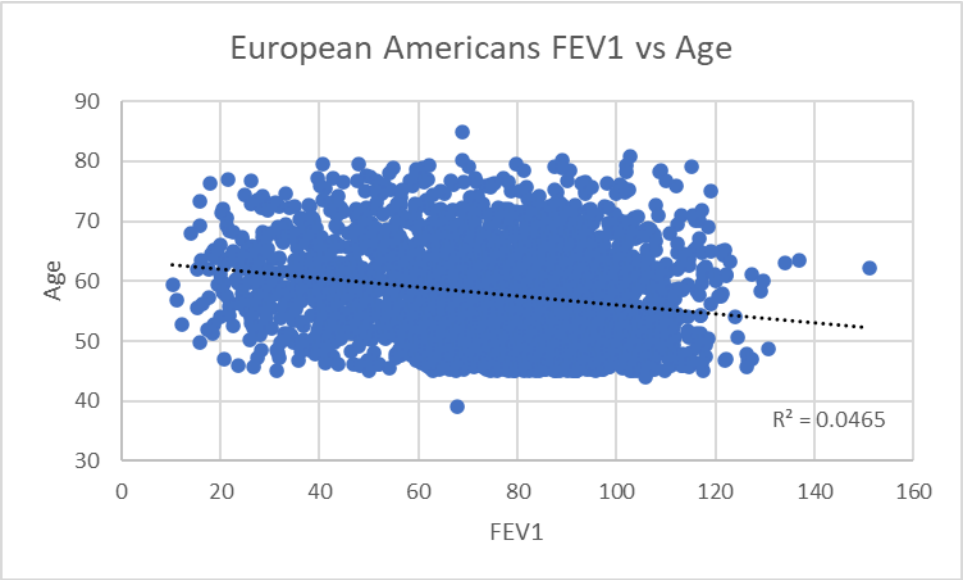

Figure A 1. European Americans FEVI vs Age

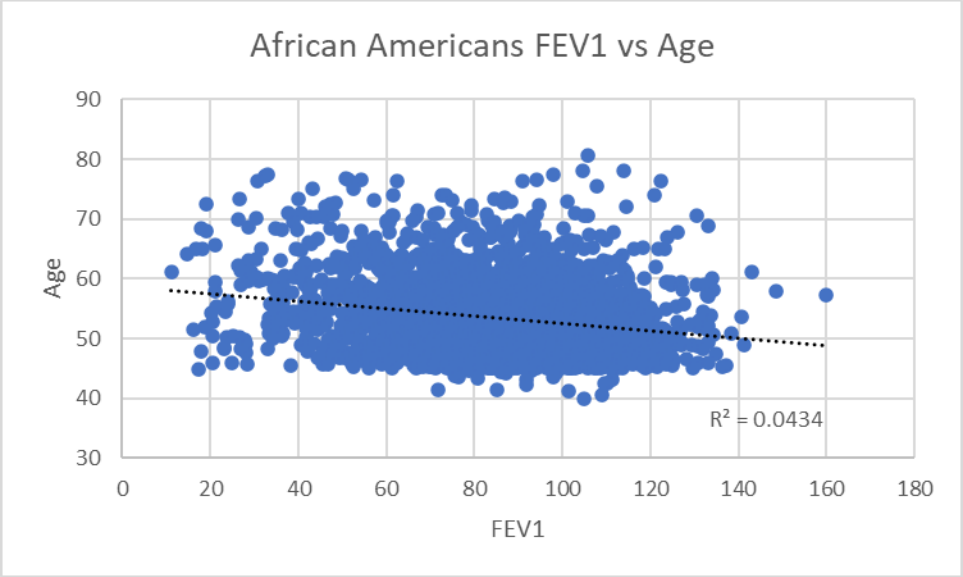

Figure A 2. African American FEVI vs Age

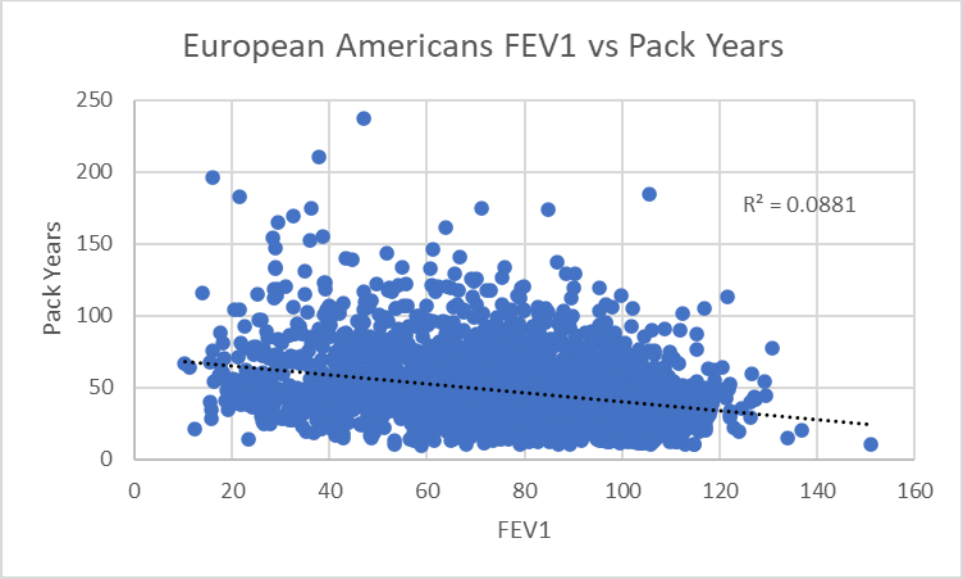

Figure A 3. European Americans FEVI vs Pack Years

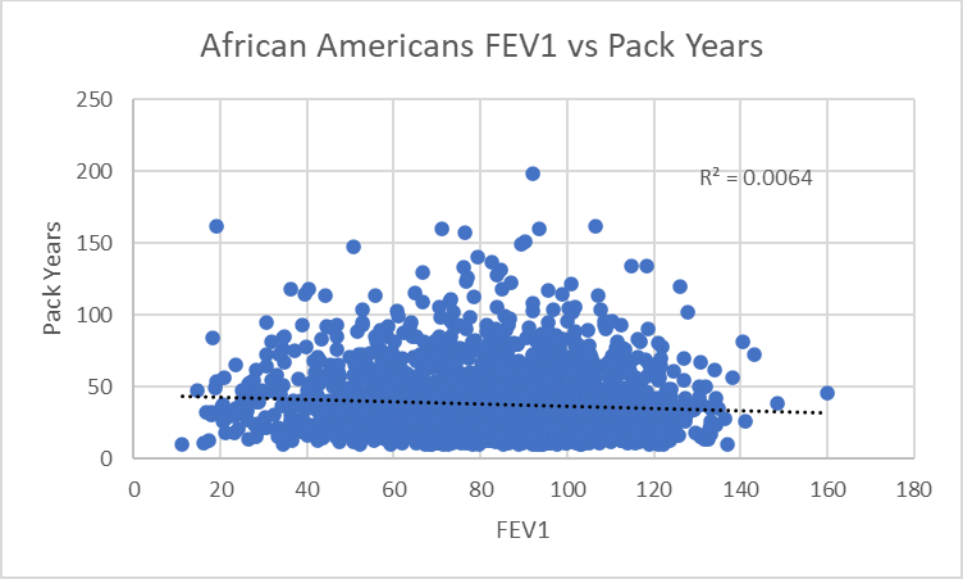

Figure A 4. African American FEVI vs Pack Years

Table A 1. Estimate of Effects of Age, Pack Years, and Menthol Cigarettes on FEVI

	Coefficients ± Standard Error	t Stat	P-Value
Age at Visit	-0.56± 0.04	-13.56	3.00×10^{-41}
Pack-years	-0.16± 0.01	-11.96	1.50×10^{-32}
Menthol/Non-menthol	2.44 ± 0.62	3.95	7.96×10^{-5}
r^2	0.09		8.27×10^{-116}

Table A 2. Estimate of Effects of Age, Race, and Pack Years on FEVI

	Coefficients ± Standard Error	t Stat	P-Value
Age at Visit	-0.51± 0.04	-12.40	7.32×10^{-35}
Race	4.88± 0.60	8.16	3.99×10^{-16}
Pack Years	-0.14 ± 0.01	-11.10	2.50×10^{-28}
r^2	0.099		8.54×10^{-127}

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