HHS Public Access

Author manuscript

Respirology. Author manuscript; available in PMC 2015 April 30.

Published in final edited form as:

Respirology. 2015 January ; 20(1): 108–114. doi:10.1111/resp.12421.

Menthol cigarette smoking in the COPDGene cohort: Relationship with COPD, comorbidities and CT metrics

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Abstract

Background and objective—Menthol cigarettes contain higher levels of menthol to produce a characteristic mint flavour and cooling sensation. Compared with non-menthol cigarettes, little information exists on the effects of menthol cigarette smoking on clinical and radiological characteristics of chronic obstructive pulmonary disease (COPD). The main objective of the present study was to examine associations between menthol cigarette use and the risk of COPD and its characteristics, such as exacerbation, comorbidities and computed tomography (CT) abnormalities.

Methods—We analysed the data from 5699 current smokers in the COPDGene cohort to evaluate whether lung function, comorbidities, exacerbations and CT parameters were different between menthol and non-menthol cigarette smokers.

Results—There were 3758 (65.9%) who reported use of menthol cigarettes. Multivariable regression analysis revealed that younger age, female gender and African-American ethnicity were significantly associated with smoking of menthol cigarettes. No significant associations were found between menthol cigarette use and COPD, major CT findings or comorbidities, such as cardiovascular disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension, diabetes, gastro-oesophageal reflux and osteoporosis; however, menthol cigarette smokers were more likely to experience a severe exacerbation of COPD during

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longitudinal follow-up (odds ratio 1.29; 95% confidence interval: 1.01–1.54) compared with the non-menthol cigarette smokers.

Conclusions—These results confirm that menthol cigarettes are not safer than traditional cigarettes and suggest that menthol cigarette smokers may have more frequent severe exacerbations than non-menthol cigarette smokers.

Keywords

chronic obstructive pulmonary disease; computed tomography; exacerbation; menthol; smoking

INTRODUCTION

Menthol cigarettes were created in the 1920s, but came into widespread use in the mid-1950s, accounting for 25–30% of all cigarettes sold in the United States since the 1970s.[1] Because mentholation improves the taste of cigarettes and masks the irritant effects of smoking, such as throat pain, burning and cough, this additive may provide the user physical relief and psychological assurance against concerns on the health dangers of smoking.[2–5] Therefore, menthol in cigarettes may facilitate initiation of smoking, increase dependency or lessen the motivation to quit,[5–7] although some studies have suggested that this might not be the case.[4,8,9] Nonetheless, it is likely that initiation and cigarette dependency are very complex and multifaceted and cannot be ascribed to the presence of a single cigarette additive.[4] Mentholation may increase the hazards of smoking by increasing exposure to known toxic smoke constituents and affect smoking behaviour, such as puff number and volume.[4] This phenomenon may contribute to the risk of disease related with smoking between menthol and non-menthol cigarette smokers.

There are strong ethnic differences in the use of menthol cigarettes; African-American smokers are more likely to smoke menthol cigarettes than Whites.[1,10] Menthol use has been suggested as an explanation for higher incidence rates of lung cancer in African-American males compared with White males.[1,2] However, many epidemiological studies do not support the hypothesis that mentholation increases the risk of lung cancer in smokers.[1,2,4,11] Menthol cigarettes may impact the risk of non-cancerous diseases related with smoking, but there is little information about potential adverse health effects of mentholation.[3] There is no doubt that cigarette smoking is the primary risk factor for lung function impairment and chronic obstructive pulmonary disease (COPD), and certain comorbidities like cardiovascular diseases can be attributed to smoking.[12–14] However, the relative risk of menthol cigarettes on COPD and its comorbidities is sparse.

In the present study, we evaluate whether lung function, computed tomography (CT) parameters and comorbidities are different between current menthol and non-menthol cigarette smokers in the COPDGene cohort.

METHODS

Study population

COPDGene is a multicentre study to examine the genetic epidemiology of smoking-related lung disease.[15] The study enrolled 10 300 non-Hispanic Whites or African-Americans aged 45–80 years, with a 10 or greater pack-year history of cigarette smoking, from 21 clinical centres in the United States. Subjects were enrolled after providing written informed consent. The research protocol was approved by ethics and review boards of the participating centres.

On enrolment, subjects were asked whether they currently smoked. If the subject answered yes, they were asked 'Do you now smoke or did you smoke menthol cigarettes?' Of 5699 current smokers, 2829 (49.7%) subjects were African-Americans. Subjects were placed in the group of menthol cigarette smokers if they answered yes and in the group of non-menthol cigarette smokers if they answered no. Of these patients, 3772 (66%) participated in a longitudinal follow-up study with a mean time of 1.49 years (range 0.08–3.42 years) to prospectively track their clinical course, including the development of exacerbations, using a telecommunication system that employed automated telephone contact or web-based questionnaire.[16]

Data collection and measurement

Demographic data and respiratory and medical history were collected via interview or self-administered questionnaires.[15] Dyspnoea was assessed using the modified Medical Research Council (mMRC) scale, and health-related quality of life was determined by the St George's Respiratory Questionnaire. Participants underwent spirometry before and after the administration of albuterol. Subjects with COPD were those who met the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria for stage 1 or higher fixed airflow obstruction with a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio lower than 0.7. Comorbid disease status was ascertained through the question 'Have you ever been told by a physician that you have [disease]?' Cardiovascular disease was defined by an affirmative response to at least one of heart attack, coronary artery disease, angioplasty or coronary artery bypass surgery. Cerebrovascular disease status was determined by an affirmative response to transient ischaemic attack or stroke. Subjects performed the standardized 6-min walk test (6MWT) and chest CT, and the BODE (body mass index (BMI), airflow obstruction, dyspnoea, exercise capacity) index score was determined.

Total exacerbations of COPD during the follow-up period were self-reported and quantified by the sum of episodes of emergency room visits, hospitalizations, and treatment with antibiotics or systemic glucocorticoids for lung problems since the last visit using the COPDGene longitudinal follow-up dataset. Additionally, the frequency of severe exacerbations during the follow-up period was calculated using the number of emergency room visits or hospitalizations. We analysed the data from 5699 smokers in this study, and the results regarding exacerbation frequency were collected from the 3722 subjects who participated in the longitudinal follow-up study.

Quantitative computed tomography analysis

In the COPDGene study, analysis of the lung parenchyma and airways was performed on whole lung volumetric multi-detector CT scans of the chest obtained without the administration of contrast material as previously described.[15] Quantitative analysis of lung density was performed with the Slicer software package (http://www.Slicer.org). Emphysema was defined as a lung attenuation value of less than −950 Hounsfield units on inspiratory scans, and gas trapping was defined as that of less than −856 Hounsfield units on expiratory scans. Automated airway analysis, including airway wall area percentage and square root of the luminal perimeter of a standardized airway of 10-mm diameter (Pi10), was performed with the use of Volumetric Information Display and Analysis Pulmonary Workstation 2 software (http://www.vidadiagnostics.com) as previously described.[15,17]

Statistical analysis

A chi-square test for categorical variables and a Mann–Whitney test for continuous variables were used to evaluate the differences between the groups. To determine the predictors of menthol cigarette use in the COPDGene, we constructed a logistic regression model, with smoking of menthol cigarettes as the dependent variable, and age, gender, race, pack-years of smoking, age smoked first cigarette and BMI as the independent variables. Multivariable logistic regression was applied to determine the association between menthol cigarette use and the presence of respiratory symptoms or comorbidities, adjusted for age, gender, race, pack-years and BMI. Correlations between menthol cigarette exposure and spirometry were determined using multivariate linear regression models, adjusted for age, gender, race, pack-years and BMI. Model adjustment was also done for the type of CT scanner used. A negative binomial regression model, adjusted for age, gender, race, pack-years, BMI, FEV_1 (% of predicted value) and follow-up duration (year), was used to model exacerbation frequency, given its skewed distribution. Statistical analyses were conducted with SPSS software (version 19.0; IBM, Armonk, NY, USA), and *P*-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Subject characteristics

Of 5699 subjects recruited in the COPDGene study and analysed, 3758 (65.9%) reported use of menthol cigarettes. Demographic comparisons between menthol and non-menthol cigarette smokers are summarized in Table 1. Compared with non-menthol smokers, menthol cigarette smokers were younger in age (54.4 ± 6.9 vs 58.2 ± 8.0 years, $P < 0.001$). Menthol cigarette smokers were more frequently African-American (66.3 vs 17.4%, $P < 0.001$) and had a fewer pack-year history of smoking (41.1 ± 22.3 vs 46.5 ± 24.7 years, $P < 0.001$). Menthol cigarette users smoked their first cigarette at a younger age and had higher BMI than non-menthol cigarette smokers. Menthol cigarette smokers exhibited better lung function (FEV_1, FVC and FEV_1/FVC) and a lower percentage of COPD defined by spirometry, but tended to have shorter 6MWT distance and greater mMRC scores. The proportions of subjects with chronic cough, chronic sputum production or current use of respiratory medications were significantly less for menthol than for non-menthol cigarette smokers.

The multivariable analysis to determine the predictors for menthol cigarette use is displayed in Table 2. In the models comparing menthol to non-menthol cigarette smokers, younger age, female gender and African-American race were significant predictors of use of menthol cigarettes.

Exacerbation, comorbidity and computed tomography parameters

During a mean follow-up time of 1.49 years (range 0.08–3.42 years), menthol cigarette smokers experienced more frequent severe exacerbation annually compared with non-menthol smokers (0.22 ± 0.99 vs 0.18 ± 0.98 per year, $P = 0.008$), although there was no significant difference between subjects with and without menthol exposure in annual exacerbation (Table 3). We assessed differences in comorbidity prevalence based upon the use of menthol cigarettes. Compared with non-menthol, menthol cigarette smokers reported less frequently physician-determined diagnoses of cardiovascular diseases, peripheral vascular diseases, gastro-oesophageal reflux and osteoporosis. However, there were no significant differences in cerebrovascular disease, hypertension and diabetes.

Menthol cigarette smokers exhibited significantly less emphysema and gas trapping on chest CT than non-menthol cigarette smokers (3.1 ± 5.9 vs 4.2 ± 7.2, $P < 0.001$; and 15.5 ± 15.6 vs 19.0 ± 17.7, $P < 0.001$). However, the segmental wall area percentage and Pi10 were not significantly different between menthol and non-menthol cigarette smokers.

Regression models

To further examine the role of menthol cigarette use, multivariable regression models were performed. In COPDGene study, there were no significant differences between menthol and non-menthol cigarette smokers in lung function measured with spirometry (FEV_1, FVC and FEV_1/FVC ratio), clinical measures of exercise capacity and dyspnoea (6MWT distance and mMRC score), or the presence of respiratory symptoms (Table 4). Logistic models did not detect statistically significant differences between subjects with and without menthol cigarette exposure in risk for COPD and various comorbidities, such as cardiovascular disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension, diabetes, gastro-oesophageal reflux and osteoporosis. Among CT metrics, no differences from menthol cigarette exposure were found in emphysema percentage, gas trapping percentage and segmental wall area, but Pi10 demonstrated a significant negative correlation with menthol cigarette use, after adjustment for age, race, pack-years, BMI and type of CT scanner used.

In a negative binomial regression model, the odds ratio of severe exacerbation during the follow-up period was 1.29 (95% confidence interval: 1.01–1.54) for the menthol cigarette group as compared with the non-menthol group (Table 5).

DISCUSSION

To our knowledge, this is the first large, well-characterized cohort study that examines the effects of menthol cigarette smoking on the risk of COPD and its characteristics, such as exacerbation, comorbidities and CT metrics. We found that subjects who smoked menthol versus non-menthol cigarettes were equally likely to have COPD and comorbidities, such as

cardiovascular disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension, diabetes, gastro-oesophageal reflux and osteoporosis, in multivariable regression models. However, the risk of developing the first severe exacerbation during the follow-up period was higher for menthol compared with non-menthol cigarettes smokers. In addition, although Pi10 demonstrated a significant negative correlation with menthol cigarette use, we found no differences from menthol cigarette smokers in other CT measurements, such as emphysema and gas trapping. These results suggest that although mentholation of cigarettes does not affect the occurrence of COPD and comorbidities or major CT findings, menthol cigarette smokers have more frequent severe exacerbations than non-mentholated cigarette smokers.

Consistent with previously published studies,[1,2,10,18] our data showed that preference for mentholated cigarettes was much greater in African-Americans than Whites. As 49.7% of the current smokers enrolled in the COPDGene study were African-Americans, menthol cigarettes smokers were more numerous than non-menthol cigarettes smokers in the current study. In addition, younger age and female gender were also identified as significant predictors of menthol smokers in multivariable analysis. A previous study reported that young smokers aged 18–25 years are more likely to smoke menthol cigarettes than older smokers (aged 26 years or older), supporting that younger individuals favour menthol cigarettes compared with older smokers.[16] Several studies, including analyses performed using National Survey on Drug Use and Health (2004–2008) data, have shown that female smokers are more likely to smoke menthol cigarettes than male smokers.[18–21] In this study, there were more male than female in the participants reporting use of menthol cigarettes, but female gender was one predictor of menthol cigarette use in multivariable analysis, suggesting that female smokers prefer menthol cigarettes compared with male smokers.

An important finding in our study is that there is no effect of mentholation on the risk of COPD based on post-bronchodilator spirometry. Menthol cigarette smokers showed lower percentage of COPD in univariate comparisons, but there were no significant differences between menthol and non-menthol cigarette smokers in the risk of COPD in multivariable models. A previous study demonstrated that menthol cigarette smoking does not affect the rate of decline in lung function in 1 year, or between 1 year and 5 years.[22] Moreover, a study by Vozoris reported that there is no significant association between mentholated cigarette smoking and self-reported COPD,[3] providing support for our results. The present study showed that there was no effect of menthol smoking on the occurrences of comorbidities, such as cardiovascular disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension, diabetes, gastro-oesophageal reflux and osteoporosis. These findings broaden previous observations showing no association between menthol cigarettes, and hypertension, myocardial infarction and congestive heart failure.[3] Interestingly, using longitudinal data, we demonstrate that the risk of developing the first severe exacerbation was significantly higher for the menthol group, although annual exacerbations did not differ. The reason for the effect of menthol cigarette exposure on severe exacerbation is not completely clear. One possibility is that mentholation of cigarettes may impair host defence mechanism. Menthol is associated with reduced ciliary beat frequency in human ciliated respiratory cells, thereby potentially reducing the capacity of lung to clear the airways.[6,23] Another possible explanation is that the local anaesthetic effect

of menthol may delay treatment of exacerbations, as menthol produces topical anaesthesia by direct interaction with peripheral nerve endings.[24] Even though potential links cannot be established and further studies are necessary, the association between menthol cigarettes and severe exacerbation of COPD is noteworthy, given that these findings are based on large population data and independent of multiple demographic and smoking status variables.

In this study, menthol cigarettes smokers had significantly less emphysema and gas trapping on chest CT than non-menthol cigarettes smokers, but these differences were not statistically significant in multivariable regression models. However, we found that Pi10 was inversely associated with menthol cigarette exposure. Pi10 is used as the parameter for airway wall thickness[25,26] and related to symptoms of dyspnoea, chronic cough and wheezing attacks in subjects with COPD.[27,28] In the current study, menthol cigarette smokers had a trend towards lower risk for chronic cough, chronic sputum production and current use of respiratory medication than non-menthol cigarette smokers. Whether less airway wall thickness determined by Pi10 in menthol cigarette users represents a differential effect of menthol on radiological measures of airway abnormality is unknown, and there are no other studies reporting airway wall thickness in individuals who smoke menthol versus non-menthol cigarettes. Furthermore, our results showed that airway measures on CT currently in use did not behave identically in multivariable regression models, as no significant difference from menthol exposure was found in segmental wall area. No gold standard method in CT-based metrics of airway disease has been identified.[29] As airway measures on CT scan have significantly different derivation, they each provide different information. For instance, airway wall area percentage reflects wall thickness relative to airway size, and thus it will not be changed if both elements increase.[29] Therefore, significant negative correlation of Pi10 with menthol cigarette use with no significant association between segmental wall area percentage and menthol use in multivariate analysis must be carefully interpreted. Taken together, further research is needed to determine the radiological characteristics of menthol cigarette smokers.

This paper has several strengths. First, it includes large numbers of well-characterized smokers, which allows for evaluation of various characteristics and extensive adjustment for important confounding factors. In addition, COPD is not self-reported but defined by post-bronchodilator spirometry. Furthermore, subjects were followed longitudinally every 6 months; thus, prospective exacerbation risk for a history of menthol cigarette use can be evaluated. Although our cohort included many subjects who were elderly and chronically ill, there was acceptance of both the web-based and telephony systems due to increased familiarity with electronic communications and the efficiency of the system.[16] However, there is a potential limitation in the accuracy of data, as a subject who did not understand a question would accidentally input or give the wrong answer.[16] Limitations of the current study include lack of details on menthol cigarette use. For instance, the amount and duration of cigarette smoking were known, but the proportion of menthol use was not. In addition, we did not have the menthol cigarette data for former smokers because the question about menthol cigarette use was asked for only current smokers in the COPDGene study. Furthermore, the COPDGene study has a higher representation of severe and very severe COPD compared with most populations. The subset of African-Americans amounted to 49.7% of the current smokers in the COPDGene study, which over-represented their

proportion in the United States, causing potential selection bias. There is also a concern that the duration of follow-up was variable and for some participants was less than 1 year, which can lead to erroneous data in exacerbation frequency secondary to the seasonal effect on exacerbations. In addition, the rate of COPD exacerbations might be overestimated because underdiagnosed diseases like heart failure or coronary disorders could aggravate symptoms, since comorbidities of COPD were self-reported. Finally, although the COPDGene study has a large sample size, further studies with more detailed data about menthol cigarette smoking will be required to confirm our observations.

In summary, we demonstrate that menthol cigarette smoking does not affect the risk of COPD or various comorbidities. However, mentholated cigarette smokers have more frequent severe exacerbations during longitudinal follow-up compared with the non-menthol cigarette smokers. These results suggest that menthol cigarettes are not safer than traditional cigarettes, although they have no direct effect on the risk of COPD and comorbidities or major CT findings. Further studies should be in design and should explore whether menthol cigarettes induce any clinical or radiological changes in smokers.

Acknowledgments

This paper was supported by the research funds of Chonbuk National University in 2012 and a fund of Biomedical Research Institute, Chonbuk National University Hospital.

Abbreviations

6MWT	6-min walk test
BMI	body mass index
BODE	BMI, airflow obstruction, dyspnoea, exercise capacity
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
mMRC	modified Medical Research Council
OR	odds eratio
Pi10	square root of the luminal perimeter of a standardized airway of 10-mm diameter
SGRQ	St George’s Respiratory Questionnaire

References

1. Brooks DR, Palmer JR, Strom BL, Rosenberg L. Menthol cigarettes and risk of lung cancer. Am J Epidemiol. 2003; 158:609–16. [PubMed: 14507595]

2. Lee PN. Systematic review of the epidemiological evidence comparing lung cancer risk in smokers of mentholated and unmentholated cigarettes. BMC Pulm Med. 2011; 11:18. [PubMed: 21501470]
3. Vozoris NT. Mentholated cigarettes and cardiovascular and pulmonary diseases: a population-based study. Arch Intern Med. 2012; 172:590–1. [PubMed: 22493467]
4. Werley MS, Coggins CR, Lee PN. Possible effects on smokers of cigarette mentholation: a review of the evidence relating to key research questions. Regul Toxicol Pharmacol. 2007; 47:189–203. [PubMed: 17097785]
5. Anderson SJ. Menthol cigarettes and smoking cessation behaviour: a review of tobacco industry documents. Tob Control. 2011; 20:ii49–56. [PubMed: 21504932]
6. Murray RP, Connett JE, Skeans MA, Tashkin DP. Menthol cigarettes and health risks in Lung Health Study data. Nicotine Tob Res. 2007; 9:101–7. [PubMed: 17365741]
7. Giovino GA, Sidney S, Gfroerer JC, O'Malley PM, Allen JA, Richter PA, Cummings KM. Epidemiology of menthol cigarette use. Nicotine Tob Res. 2004; 6:S67–81. [PubMed: 14982710]
8. Hyland A, Garten S, Giovino GA, Cummings KM. Mentholated cigarettes and smoking cessation: findings from COMMIT. Community Intervention Trial for Smoking Cessation. Tob Control. 2002; 11:135–9. [PubMed: 12035007]
9. Delnevo CD, Gundersen DA, Hrywna M, Echeverria SE, Steinberg MB. Smoking-cessation prevalence among U.S. smokers of menthol versus non-menthol cigarettes. Am J Prev Med. 2011; 41:357–65. [PubMed: 21961462]
10. Lawrence D, Rose A, Fagan P, Moolchan ET, Gibson JT, Backinger CL. National patterns and correlates of mentholated cigarette use in the United States. Addiction. 2010; 105:13–31. [PubMed: 21059133]
11. Kabat GC, Shivappa N, Hébert JR. Mentholated cigarettes and smoking-related cancers revisited: an ecologic examination. Regul Toxicol Pharmacol. 2012; 63:132–9. [PubMed: 22429780]
12. Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. Chest. 2011; 139:165–73. [PubMed: 21208876]
13. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. Eur Respir J. 2007; 30:616–22. [PubMed: 17906084]
14. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009; 33:1165–85. [PubMed: 19407051]
15. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010; 7:32–43. [PubMed: 20214461]
16. Stewart JI, Moyle S, Criner GJ, Wilson C, Tanner R, Bowler RP, Crapo JD, Zeldin RK, Make BJ, Regan EA. For The COPDGene Investigators. Automated telecommunication to obtain longitudinal follow-up in a multicenter cross-sectional COPD study. COPD. 2012; 9:466–72. [PubMed: 22676387]
17. Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, Criner GJ, Kim V, Bowler RP, Hanania NA, et al. COPDGene investigators. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. Radiology. 2011; 261:274–82. [PubMed: 21788524]
18. Caraballo RS, Asman K. Epidemiology of menthol cigarette use in the United States. Tob Induc Dis. 2011; 9:S1. [PubMed: 21624147]
19. Allen B, Unger JB. Sociocultural correlates of menthol cigarette smoking among adult African Americans in Los Angeles. Nicotine Tob Res. 2007; 9:447–51. [PubMed: 17454699]
20. Clemmey P, Brooner R, Chutuape MA, Kidorf M, Stitzer M. Smoking habits and attitudes in a methadone maintenance treatment population. Drug Alcohol Depend. 1997; 44:123–32. [PubMed: 9088784]
21. Rosenbloom J, Rees VW, Reid K, Wong J, Kinnunen T. A cross-sectional study on tobacco use and dependence among women: does menthol matter? Tob Induc Dis. 2012; 10:19. [PubMed: 23181980]
22. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, Tashkin DP. Lung Health Study Research Group. Smoking cessation and lung function in mild-to-moderate chronic

obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med. 2000; 161:381–90. [PubMed: 10673175]

23. Riechelmann H, Brommer C, Hinni M, Martin C. Response of human ciliated respiratory cells to a mixture of menthol, eucalyptus oil and pine needle oil. Arzneimittelforschung. 1997; 47:1035–9. [PubMed: 9342418]
24. Ahijevych K, Garrett BE. Menthol pharmacology and its potential impact on cigarette smoking behavior. Nicotine Tob Res. 2004; 6:S17–28. [PubMed: 14982706]
25. Patel BD, Coxson HO, Pillai SG, Agustí AG, Calverley PM, Donner CF, Make BJ, Müller NL, Rennard SI, Vestbo J, et al. International COPD Genetics Network. Airway wall thickening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008; 178:500–5. [PubMed: 18565956]
26. Mets OM, Schmidt M, Buckens CF, Gondrie MJ, Isgum I, Oudkerk M, Vliegenthart R, de Koning HJ, van der Aalst CM, Prokop M, et al. Diagnosis of chronic obstructive pulmonary disease in lung cancer screening computed tomography scans: independent contribution of emphysema, air trapping and bronchial wall thickening. Respir Res. 2013; 14:59–66. [PubMed: 23711184]
27. Grydeland TB, Dirksen A, Coxson HO, Eagan TM, Thorsen E, Pillai SG, Sharma S, Eide GE, Gulsvik A, Bakke PS. Quantitative computed tomography measures of emphysema and airway wall thickness are related to respiratory symptoms. Am J Respir Crit Care Med. 2010; 181:353–9. [PubMed: 19926869]
28. Lynch DA, Al-Qaisi MA. Quantitative computed tomography in chronic obstructive pulmonary disease. J Thorac Imaging. 2013; 28:284–90. [PubMed: 23748651]
29. Martinez CH, Chen YH, Westgate PM, Liu LX, Murray S, Curtis JL, Make BJ, Kazerooni EA, Lynch DA, Marchetti N, et al. Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease. Thorax. 2012; 67:399–406. [PubMed: 22514236]

SUMMARY AT A GLANCE

Little information exists on the effects of menthol cigarette smoking on clinical and radiological characteristics of chronic obstructive pulmonary disease (COPD). Our results confirm that menthol cigarettes are not safer than traditional cigarettes and suggest that menthol cigarette smokers may have more frequent severe exacerbations than non-menthol cigarette smokers.

Table 1

Subject characteristics

Characteristics	Menthol	Non-menthol	*P*-value
Number	3758	1941	—
General characteristics			
Age (year)	54.4 ± 6.9	58.2 ± 8.0	<0.001
Gender			0.281
Male (%)	54.7	56.2	
Female (%)	45.3	43.8	
Race			<0.001
White (%)	33.7	82.6	
African-American (%)	66.3	17.4	
Smoking history (pack-years)	41.1 ± 22.3	46.5 ± 24.7	<0.001
Age smoked first cigarette	16.7 ± 5.2	17.0 ± 4.9	<0.001
BMI (kg/m^2)	28.7 ± 6.5	27.9 ± 5.8	<0.001
Pulmonary variables			
FEV_1 (% of predicted value)	82.5 ± 21.8	77.1 ± 23.4	<0.001
FVC (% of predicted value)	89.8 ± 17.6	87.5 ± 17.8	<0.001
FEV_1/FVC (%)	0.72 ± 0.13	0.67 ± 0.14	<0.001
COPD defined by spirometry (%)	32.1	45.8	<0.001
6MWT (ft)	1325.7 ± 369.2	1389.2 ± 379.0	<0.001
mMRC score	1.4 ± 1.5	1.3 ± 1.4	0.012
SGRQ total score	28.2 ± 22.7	27.8 ± 23.2	0.303
BODE index	1.3 ± 1.6	1.3 ± 1.7	0.181
Respiratory symptoms			
Chronic cough (%)	39.5	46.3	<0.001
Chronic sputum (%)	35.5	40.1	<0.001
Current medication use (%)	30.6	34.5	0.011

Data are presented as mean ± standard deviation or %.

BMI, body mass index; BODE, BMI, airflow obstruction, dyspnoea, exercise capacity; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWT, 6-min walk test.

Table 2

Multivariate logistic regression for predictors of menthol cigarette use in the COPDGene study

	OR	95% CI	*P*-value
Age (per year)	0.97	0.96–0.97	<0.001
Female gender	1.15	1.01–1.30	0.034
African-American race	8.35	7.26–9.60	<0.001
Smoking history (pack-years)	1.00	1.00–1.01	0.092
BMI	1.01	1.00–1.02	0.073

Additional variable tested but not retained in the final model was age smoked first cigarette.

BMI, body mass index; CI, confidence interval; OR, odds ratio.

Table 3

Prevalence of exacerbations and comorbidities and radiological measurements

Characteristics	Menthol	Non-menthol	*P*-value
Exacerbations			
Exacerbations per annum	0.47 ± 1.97	0.49 ± 1.66	0.245
Severe exacerbations per annum	0.22 ± 0.99	0.18 ± 0.98	0.008
Comorbidity			
Cardiovascular disease	6.5	10.4	<0.001
Congestive heart failure	2.2	2.9	0.106
Peripheral vascular disease	1.5	2.5	0.007
Cerebrovascular disease	3.7	3.8	0.866
Hypertension	38.9	36.9	0.148
Diabetes	12.4	11.5	0.304
Gastro-oesophageal reflux	17.6	22.8	<0.001
Osteoporosis	4.6	8.6	<0.001
CT measurements			
Emphysema percentage	3.1 ± 5.9	4.2 ± 7.2	<0.001
Gas trapping percentage	15.5 ± 15.6	19.0 ± 17.7	<0.001
Segmental wall area (%)	61.7 ± 3.3	61.7 ± 3.4	0.551
Pi10	3.7 ± 0.1	3.7 ± 0.1	0.252

Data are presented as mean ± standard deviation or %.

CT, computed tomography; Pi10, square root of the luminal perimeter of a standardized airway of 10-mm diameter.

Table 4

Associations of menthol cigarette use and pulmonary variables, comorbidities or CT metrics

Parameters	OR or β	95% CI or SE	*P*-value
Pulmonary variables			
FEV_1 (% of predicted value)	0.46	0.68	0.501
FVC (% of predicted value)	0.42	0.55	0.439
FEV_1/FVC (%)	0.003	0.004	0.453
COPD defined by spirometry	1.03	0.90–1.18	0.714
6MWT (ft)	−20.02	11.10	0.072
mMRC score	0.02	0.04	0.664
Chronic cough	1.10	0.97–1.26	0.140
Chronic sputum	1.13	0.99–1.29	0.072
Comorbidity			
Cardiovascular disease	0.93	0.74–1.17	0.529
Congestive heart failure	0.71	0.48–1.05	0.089
Peripheral vascular disease	1.05	0.68–1.61	0.835
Cerebrovascular disease	1.18	0.85–1.64	0.322
Hypertension	1.02	0.89–1.16	0.807
Diabetes	1.00	0.82–1.22	0.995
Gastro-oesophageal reflux	1.01	0.87–1.18	0.891
Osteoporosis	0.98	0.76–1.26	0.849
CT variable			
Emphysema percentage	−0.06	0.20	0.778
Gas trapping percentage	−0.06	0.51	0.912
Segmental wall area (%)	−0.05	0.11	0.662
Pi10	−0.01	0.004	0.019

6MWT, 6-min walk test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council; OR, odds ratio; Pi10, square root of the luminal perimeter of a standardized airway of 10-mm diameter; SE, standard error.

Table 5

Adjusted odds ratios of exacerbations during the follow-up period

	Exacerbation			Severe exacerbation		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Menthol	1.10	0.97–1.25	0.130	1.29	1.01–1.54	0.007
Non-menthol	1.00			1.00		

CI, confidence interval; OR, odds ratio.