

PREDICTORS, INDICATORS, AND VALIDATED MEASURES OF DEPENDENCE IN MENTHOL SMOKERS

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This article presents a comprehensive review of the menthol cigarette dependence-related literature and results from an original analysis of the Total Exposure Study (TES), which included 1,100 menthol and 2,400 nonmenthol adult smokers. The substantial scientific evidence available related to age of first cigarette, age of regular use, single-item dependence indicators (smoking frequency, cigarettes per day, time to first cigarette, night waking to smoke), smoking duration, numerous validated and widely accepted measures of nicotine/cigarette dependence, and our analysis of the TES do not support that menthol smokers are more dependent than nonmenthol smokers or that menthol increases dependence.

KEYWORDS. Menthol, smoking, dependence, addiction, FTND, CPD, TTFC

INTRODUCTION

A decade ago, concerns were raised that the addition of menthol to cigarettes may enhance addiction to smoking.¹ In 2009, Congress passed the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which gave the Food and Drug Administration (FDA) authority to regulate tobacco products based on a public health standard. The FSPTCA directed the FDA to refer “the issue of the impact of the use of menthol in cigarettes on the public health” to the Tobacco Products Scientific Advisory Committee (TPSAC).² The TPSAC provided its report to the FDA in March 2011.³ Since that time, the FDA has published its own Preliminary Scientific Assessment of Menthol in cigarettes.⁴ Regarding the impact of menthol on dependence, both reports make conclusions suggesting that menthol is associated with increased dependence. Both reports relied heavily on unpublished and unadjusted analyses. The TPSAC report has not been updated

since 2011 and much of the relevant dependence literature, including studies with validated dependence measures and menthol comparisons, is not included in the FDA preliminary report or reference addendum. We believe a thorough assessment of the scientific evidence demonstrates that menthol does not increase cigarette dependence. Our analysis of data from the Total Exposure Study (TES) further supports that menthol smokers are not more dependent on smoking compared with nonmenthol smokers.

In our assessment of the topic, we rely on the peer-reviewed published scientific evidence.⁴ Studies that included dependence predictors, indicators, and validated dependence measures, which are widely accepted in the scientific community, are included in our review. We also considered the type of statistical testing, whether adjustments were made to control for differences between groups, whether results were statistically significant, and whether there was sufficient detail provided to be able to

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reproduce the study or analysis. For completeness, we included all identified dependence-related menthol literature results. Those with nonvalidated measures and incomplete descriptions are included in the discussion.

In this article, we also present original results from an analysis of data collected as part of the TES. The TES included 3,585 adult smokers from 31 states across the United States. The TES data were used to estimate exposure to tobacco smoke constituents,⁶ examine differences in exposure by machine-derived tar yield categories and menthol status,^{7,8} and compare biomarkers of potential harm in adult smokers and nonsmokers.⁹ This specific analysis examines Fagerström Test for Nicotine Dependence (FTND) scores, FTND questions, and the Heaviness of Smoking Index (HSI) among 1,104 menthol and 2,481 nonmenthol adult smokers.

Predictor of Cigarette Dependence

The relationship between age of smoking initiation and dependence has been well studied. Early onset of smoking is associated with greater likelihood of developing dependence.¹⁰ Hu et al.¹¹ reported that “early age of smoking onset [was] . . . significantly correlated with daily smoking and lifetime nicotine dependence.” Breslau et al.¹² found that after “controlling for sex and race, persons who smoked their first cigarette at 14 to 16 years of age were 1.6 times more likely to become dependent than those who initiated smoking at an older age ($P = 0.03$).” The relationship between early onset of smoking and dependence was also examined in the National Cancer Institute’s (NCI) Monograph 20, which reported that “In terms of smoking trajectories, early smoking onset has been associated with steeper acceleration in smoking rate, greater persistence over time, and greater likelihood of developing dependence.”^{10,13–15} In a large study examining the presence of dependence among smokers, Donny and Dieker¹⁶ found that “non-dependent smokers initiated smoking and daily smoking at a later age.” More recently, Kendler et al.¹⁶ concluded that “controlling for genetic and familial-environmental effects, age at onset

of regular smoking predicted level of nicotine dependence.” Later smoking initiation is associated with lower cigarette consumption (frequency and cigarettes per day [CPD]), higher rates of smoking cessation, shorter smoking duration, and lower dependence.^{10,13,18–25} Therefore, comparisons of age of first cigarette and age of daily smoking between menthol and nonmenthol smokers could be useful as a predictor of differences in dependence.

Indicators of Cigarette Dependence

Commonly used single-item dependence indicators include frequency of smoking, CPD, and time to first cigarette (TTFC). More recently, night waking to smoke has been identified as a dependence indicator. Smoking daily, smoking more cigarettes per day, smoking within 30 minutes, and night waking to smoke are listed as the “associated features” of tobacco use disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-IV).²⁶ Non-daily or intermittent smokers often do not meet established dependence criteria. According to the DSM-IV, approximately 50% of daily smokers met DSM-IV criteria for nicotine dependence.²⁶ CPD and TTFC are the 2 main factors that drive FTND scores and together comprise the HSI.²⁷ TTFC is also associated with cigarette consumption, and CPD is associated with night waking to smoke.²⁸ CPD has been described as a proxy for dependence and scientists have evaluated “the importance of phenotype definition (i.e., CPD versus FTCD score as a measure of nicotine dependence) on genome-wide association studies of nicotine dependence.”²⁹ Rice et al.²⁹ concluded that “daily cigarette consumption and the Fagerström Test for Cigarette Dependence show different associations with polymorphisms in genetic loci” associated with nicotine dependence.

The authors who analyzed the National Health Interview Survey (NHIS)³⁰ reported that “In 2011, an estimated 19.0% (43.8 million) of U.S. adults were current cigarette smokers. Of these, 77.8% (34.1 million) smoked every day, and 22.2% (9.7 million) smoked some days.”

Recent estimates from the National Survey on Drug Use and Health (NSDUH)³¹ suggest that among current cigarette smokers aged 12 years or older in 2011, 60.7% were daily smokers. Non-daily smokers often do not meet established dependence criteria, and studies have reported lower scores for intermittent smokers on multiple dependence measures.^{32,33}

Smoking frequency, CPD, TTFC, and night waking to smoke have all been reported as significant predictors of cessation outcomes but are not always consistent across studies.^{25,28,34,35} For example, the Baker et al.³⁵ analysis reported TTFC predicted cessation, but TTFC was not a significant predictor of cessation in other studies.^{28,36} Smoking duration has also been associated with cessation outcomes and dependence.^{10,37,38} Researchers have used other dependence-related statements, questions, and nonvalidated scales to compare menthol and nonmenthol smokers. However, in the current review, we focus on widely accepted and validated indicators and measures.

Validated and Widely Accepted Measures of Cigarette Dependence

Widely used and validated measures of dependence have been described and reviewed by authoritative sources including the U.S. Surgeon General's Report,³⁷ the NCI's Monograph 20,¹⁰ and the World Health Organization's International Agency for Research on Cancer³⁹ report. These measures include the following: FTND,⁴⁰ Fagerström Tolerance Questionnaire,^{41,42} Cigarette Dependence Scale (CDS-12 and CDS-5),⁴³⁻⁴⁵ HSI,⁴⁶ Nicotine Dependence Syndrome Scale,^{47,48} Hooked on Nicotine Checklist,⁴⁹ Wisconsin Inventory of Smoking Dependence Motives,⁵⁰ DSM-IV,⁵¹ and the International Classification of Diseases.⁵²

The FTND has been one of the most widely used extensively studied measures of dependence. The FTND and DSM-IV have been described as the "two gold standard measures for nicotine dependence."¹⁰ The FTND includes 6-items: number of cigarettes smoked per day, time to first cigarette, difficulty refraining from smoking when forbidden, smoking

when ill in bed most of the day, which cigarette would hate most to give up, and smoking frequency.^{40,42} Based on the score, nicotine dependence has been classified as very low (0–2), low (3–4), medium (5), high (6–7), or very high (8–10).⁵³ Other researchers have used different classifications in their analysis, such as low/medium (0–5) vs. high (6–10) and low (0–3), medium (4–5), and high (6–10).⁵⁴ Recently, Dr. Fagerström has proposed that the FTND be renamed to the Fagerström Test for Cigarette Dependence (FTCD).⁵⁵ We use the FTND when results were reported as such. The HSI, which includes the FTND categories of TTFC and CPD,⁴⁶ is the shortest widely accepted and validated measure of dependence.

LITERATURE REVIEW METHODS

Identifying Menthol and Dependence Related Scientific Literature

In early 2010 and 2011, we conducted two detailed searches of PubMed and Scopus for any publication with the words "menthol" and "cigarettes" or "smoking." Since 2011, we have continued to search the literature on a quarterly basis. This review is inclusive of publications that were available in English, either online or in print, prior to January 2014. We have attempted to be inclusive of all articles and all results relevant to nicotine/cigarette dependence in menthol and nonmenthol smokers. Dependence measures and indicators are often reported as part of the sample characteristics in articles not focused on dependence.

LITERATURE REVIEW

Cigarette Dependence Predictor Results

Age of Initiation and Progression among Menthol and Nonmenthol Smokers We identified 16 articles that compared the age of initiation or progression to regular smoking among menthol and nonmenthol smokers. These studies reported the mean age of first cigarette, mean age at first regular smoking, or compared

the percentage of menthol and nonmenthol smokers in age categories for these two outcomes. Among the 9 studies we identified that examined age of first cigarette use among menthol and nonmenthol smokers, 7 reported no difference in mean age overall and among various subgroups^{56–62} and 2 reported later age of first cigarette among menthol smokers.^{62,63}

In terms of age of regular smoking, we identified 9 studies. Seven reported no difference in the age of onset of regular smoking between menthol and nonmenthol smokers^{57,60,65–69} and 3 reported a later average age of regular smoking for menthol smokers.^{67,70,71} Overall, these studies consistently reported that menthol smokers have the same or later mean age of first use and the same or later mean age of regular smoking.

Cigarette Dependence Indicator Results

In this section, the menthol literature which includes commonly used single-item dependence indicators include frequency of smoking, CPD, TTFC, night waking to smoke, and smoking duration is reviewed.

Smoking Frequency (Daily vs. Non-daily)

We identified 8 publications that included information on daily and non-daily smoking among menthol and nonmenthol smokers. Five studies reported that menthol smokers are less likely to be daily smokers.^{67,70,72–74} Three other large scale analyses reported no difference in daily vs. non-daily smoking among menthol and nonmenthol smokers.^{63,71,75}

Cigarettes per Day We identified 30 studies and dozens of analyses within these manuscripts that provide information on CPD among menthol and nonmenthol smokers. With the exception of 1 publication,⁷⁶ these authors consistently report that menthol smokers smoke the same or fewer CPD compared with nonmenthol smokers.

Dozens of analyses have reported no difference in CPD for menthol versus nonmenthol smokers among daily and non-daily smokers⁷⁷ by race/ethnicity;⁶⁵ within specific racial/ethnic groups, including African American/

Black,^{62,67,78,79} White,^{58,62,67} Hispanic,^{67,78,79} American Indian/Alaskan Native,⁶⁷ and Asian/Pacific Islander smokers;⁶⁷ among both men and women;^{65,80} and overall.^{54,57,60,62,68,80–84}

Other studies and analyses found that menthol smokers reported statistically significantly fewer CPD compared with nonmenthol smokers. These analyses have reported fewer CPD among menthol versus nonmenthol smokers at baseline;⁶⁶ within specific racial/ethnic groups of smokers, including African American/Black,^{58,85,86} Hispanic,^{58,86} and White smokers;^{78,79,85,86} among both men and women;⁸⁷ among White women, African American women, and African American men;⁸⁸ among former smokers and current smokers;^{69,78} and overall.^{36,58,61,63,64,67,70,79,89–91}

The one analysis that reported higher cigarette consumption among menthol smokers may have had an error in the coding/analysis. Muilenburg and Legge⁷⁶ reported that menthol cigarette smokers, and specifically that African American underage menthol cigarette smokers, had the highest rates of cigarette consumption. However, the authors also reported that 81% of the African American smokers in the analysis reported smoking nonmenthol cigarettes. Such a high percentage of nonmenthol use among African American smokers is inconsistent with all other published analyses of the sociodemographic patterns of menthol cigarette use.

Time to First Cigarette (TTFC) We identified 19 publications and dozens of analyses of TTFC among menthol and nonmenthol smokers. For ease in comparing findings of the various studies, the results of the analyses are reviewed in sections on the first 30 minutes versus later, FTND TTFC categories, mean TTFC, and then other TTFC categorizations.

TTFC Within First 30 Minutes vs. after 30 Minutes of Waking. With the exception of one published unadjusted analysis among African Americans⁸¹ and one unadjusted analysis among non-daily smokers,⁷⁷ all other published studies report no difference for menthol versus nonmenthol smoking for TTFC within the first 30 minutes versus after

30 minutes of waking. Nine studies, which included studies with large diverse samples and multivariate analyses, report no difference in TTFC ≤ 30 minutes versus >30 minutes for menthol and nonmenthol smokers.^{36,54,57,67,70,77,84,92,93}

TTFC FTND categories (≤ 5 , 6–30, 31–60, and >60 Minutes). Two studies reported the percentage of menthol and nonmenthol smokers in the original FTND TTFC categories. In one unadjusted analysis, Collins and Moolchan⁸² reported a higher percentage of menthol smokers in the TTFC ≤ 5 minutes category, but no significant differences in the percentage of menthol and nonmenthol in the 6–30, 31–60, or >60 minutes TTFC groups.⁸² The TTFC ≤ 5 minutes comparison was based on 12 nonmenthol smokers. The study was limited by an unequal sample size, small overall number of nonmenthol smokers ($n = 41$), and the lack of adjustment for differences between groups. Jones et al.⁶³ reported 4,603 adults, aged 20+ years who participated in the NHANES 1999–2010. The authors reported no statistically significant difference in the weighted percentage of menthol and nonmenthol smokers in the TTFC ≤ 5 , 6–30, 31–60, and >60 minutes categories.⁶³

Mean TTFC. Two small studies and one large study reported mean TTFC among menthol and nonmenthol smokers. In a sample of 95 women, menthol smokers had a shorter mean TTFC.⁹⁴ Another study analyzed data from 127 adult smokers (60 menthol smokers and 67 nonmenthol smokers) and found no significant difference.⁹⁵ In an analysis of data from 46,273 current adult smokers, White menthol smokers had statistically significantly longer mean TTFC compared with White nonmenthol smokers (21 vs. 20 minutes), African American menthol smokers had statistically significantly shorter mean TTFC compared with African American nonmenthol smokers (21 vs. 25 minutes), and no other statistically significant differences were found for any other race/ethnicity groups.⁷⁰

Other TTFC categorizations. Five additional studies reported various other TTFC

categorizations. These studies generally report findings that are mixed, with some results suggesting shorter TTFC, some longer TTFC, and some with no difference in TTFC for menthol versus nonmenthol smokers.^{62,96,97}

One publication included a cohort of 13,268 adult smokers with 5 years follow-up and found baseline menthol use was associated with smoking >60 minutes after waking and menthol smokers were statistically significantly less likely to report smoking within 10 minutes of waking at follow-up.⁶⁶ An analysis of 46,273 current smokers aged 18 years and older found no overall difference in the percentage of menthol vs. nonmenthol smokers who smoked in the first 5 minutes (22.27 vs. 22.17, respectively), in 6–10 minutes (9.11 vs. 9.51, respectively), 11–15 minutes (7.03 vs. 7.50, respectively), or 16+ minutes (59.09 vs. 58.52, respectively).⁷⁰ Of the nine CPD TTFC comparisons, only one was significant by menthol status, which was TTFC ≤ 5 minutes for those who smoked 6–10 CPD.⁷⁰

Night Waking to Smoke Two studies reported on night waking to smoke among menthol and nonmenthol smokers. Bover et al.²⁸ report that “Night-smoking status was determined by an answer of ‘yes’ to the question ‘Do you sometimes awaken at night to have a cigarette or use tobacco?’” In their multivariate analysis of predictors, menthol smokers had an increased Adjusted Odds Ratio (AOR) for night waking to smoke compared with nonmenthol (AOR, 1.497 [95% confidence interval [CI], 1.195–1.874]); however, menthol was specifically tested and was not a significant predictor of 26-week cessation outcomes.²⁸ An unadjusted analysis from another study reported that a higher percentage of menthol smokers reported sometimes waking at night to smoke.⁵⁸

Smoking Duration As mentioned in the introduction, smoking duration is associated with nicotine dependence and cessation outcomes.^{10,36,38} Twelve studies were identified that included smoking duration comparisons by menthol status. Three studies reported no difference,^{62,84,98} one study reported no

difference and shorter duration for two different groups of menthol smokers,⁸³ and the other 8 studies reported shorter smoking duration among menthol versus nonmenthol smokers.^{57,70,80,85,87,89,90,99}

Validated and Widely Accepted Measures of Cigarette Dependence Results

We identified 23 articles in our review.^{32,56,57,60,68,73,74,80–84,89,92,95,97,98,100–105} Seventeen published studies included validated measures and a menthol comparison, 1 analysis included partial FTND scores, and 5 studies compared validated dependence measures among smokers in racial/ethnic groups with disproportionately high and low menthol use. These studies are summarized in Table 1.

Whereas the percentage of menthol smokers is higher, studies have reported that African American adolescent smokers have lower FTND scores and DSM-IV dependence compared with Whites.^{38,100,101} Among adults as well, African American smokers were reported to have lower FTND scores and DSM-IV dependence compared with White smokers.^{38,92}

Among adolescents, studies have found no difference by menthol status on the Hooked on Nicotine Checklist,^{73,74,102} and lower Hooked on Nicotine Checklist scores for adolescent preferring only menthol vs. only nonmenthol and compared to those who smoked both.⁷³ No difference by menthol status on the FTND was reported in another study of adolescents.⁸²

Other studies have reported no significant effect of menthol on partial FTND scores among adult men and women,⁸⁰ no difference by menthol status by race and gender in Fagerström Tolerance Questionnaire scores,⁸⁸ and no difference by menthol status on the Nicotine Dependence Syndrome Scale among adults.^{68,103} Menthol smokers are also reported to score the same or lower on the HSI.^{97,103} Nine studies among adults have found no difference by menthol status on the FTND.^{54,56,57,60,81,83,84,95,105}

TES METHODS

Study Design and Conduct

The TES was a cross-sectional, multi-center, ambulatory study conducted at 39 clinical sites across the United States. Details about the design of the study have been reported elsewhere.^{6,7,106} Covance Clinical Research Unit Inc. managed the recruitment of participants and study conduct. Healthy men and women who were aged at least 21 years at study entry were screened for enrollment. Adult smokers must have reported smoking at least one manufactured cigarette per day for at least the past year. They could not have used any other nicotine-containing products and must not have changed brands or have reported smoking more than 10% of their daily cigarette consumption outside their regular brand's tar yield category for the 3 months preceding visit 1. Participants were not eligible for inclusion if they were pregnant or nursing. Good Clinical Practice and the principles of the Declaration of Helsinki¹⁰⁷ were followed in all aspects of the TES. The study was Institutional Review Board-approved and informed consent was documented prior to participation.

Statistical Methods for FTND and HSI Scores between Menthol and Nonmenthol Smokers

Logistic regression models were used to examine the relationships between menthol smoking status and the FTND. The response variables were measures of nicotine dependence (FTND) for Model A and menthol smoking status for Model B. Model B was used to compare the results with previous publications in the literature. The explanatory factors included in the models were age (21–34 years, 35–49 years, 50+ years), gender (male or female), race (African American/Black or White), education level (<high school graduate, high school graduate, college graduate), annual household income (<\$20,000, \$20,000–\$49,999, \$50,000+) and machine-measured tar yield category (T1: ≤ 2.9; T2: 3.0–6.9; T3: 7.0–12.9; T4: ≥ 13.0 mg).

TABLE 1. Studies with Validated and Widely Accepted Measures of Nicotine/Cigarette Dependence

Study Authors	Population/Sample	Findings Related to Validated and Widely Accepted Measures of Nicotine/Cigarette Dependence
Allen & Unger ⁵⁶	432 adult AA smokers	No significant difference by menthol status in odds of higher score on FTND for both women and men.
Benowitz et al. ⁹⁵ Brody et al. ¹⁰⁵	127 adult smokers 63 adult smokers	No significant difference by menthol status in FTND scores. No statistically significant difference in FTND scores for menthol (mean, 4.1; SD±2.1) and nonmenthol (mean, 3.9; SD±2.4) smokers.
Collins & Moolchan ⁸²	572 adolescent smokers (531 smoked menthol)	No difference in FTND scores.
DiFranza et al. ¹⁰² Duncan et al. ¹⁰¹	237 adolescents 1,376 adolescents and young adults (12–33 years), 768 AA (56%) and 610 White	No difference between menthol and nonmenthol on the HONC . Among ever smokers, AA were statistically significantly less likely to be DSM-IV dependent as compared to White (19.82 vs. 32.81, respectively, $p < 0.001$).
Faseru et al. ⁵⁷	540 AA light smokers (≤ 10 cigarettes per day) in a clinical trial for smoking cessation	No significant difference between menthol and nonmenthol smokers on numerous measures, including FTND .
Hooper et al. ¹⁰³	3,396 current smokers from the Florida 2007 BRFSS	Menthol smokers had statistically significantly lower mean scores on the NDSS in the unadjusted analysis. No significant difference between menthol and nonmenthol smokers in AOR of dependence (NDSS) in the multivariate analysis.
Kandel & Chen ³⁸	12,550 White, 4,903 AA, 4,839 Hispanic current smokers (ages 12 and older) from the NHSDA	Despite higher percentage of menthol, minorities smoked significantly fewer CPD compared with Whites. Whites more likely than African-Americans to be DSM-IV dependent even controlling for CPD.
Li et al. ⁷⁴	14 and 15 year olds in New Zealand. 2,387 menthol and 11,071 nonmenthol.	The authors reported that the “multiple linear regression model did not find a significant result linking reported HONC score to menthol preference (coef. = $-.21$, $P = .165$).”
Luo et al. ⁹²	2,925 White and AA adult smokers (not menthol specific)	African-American smokers had lower FTND scores compared with Whites.
Marsh et al. ⁷³	New Zealand youth surveys from 2004 (N = 564), 2006 (N = 334), and 2008 (N = 325)	The authors found, “there was no evidence of an association between use of menthol and HONC scores.” Authors state “However, those preferring menthol-only had lower HONC scores than those preferring only nonmenthol.” Lower HONC scores among menthol-only as compared to those who smoke both types of cigarettes.
Moolchan et al. ¹⁰⁰	115 treatment seeking adolescents	African American adolescents had significantly lower FTND scores as compared with those who were not African-Americans.
Frost-Pineda et al. reported here	3,585 adult smokers (1,104 menthol and 2,481 nonmenthol)	No significant increased odds of menthol use for any of the FTND questions. Menthol cigarette smoking did not increase the odds of higher FTND scores regardless of how scores were categorized. Higher FTND scores were not associated with increased odds of smoking menthol cigarettes.
Muscat et al. ⁹⁷	525 adult smokers	No significant increased odds of high FTND scores vs. low/medium FTND scores among menthol as compared to nonmenthol smokers (OR, 1.1, 95% CI, 0.6, 2.1).
Murray et al. ⁸⁰	5,887 adult smokers	Among males and among females, respectively, there was no significant effect of menthol on partial FTND scores.
Mustonen et al. ⁸⁸	307 White and AA adult smokers in a clinical study of NRT. Smoked at least 10 CPD	No difference in FTQ scores between White males, White females, African-American males or African-American females.
Okuyemi et al. ⁸¹	600 AA smokers in a bupropion trial	No significant difference in FTND scores for menthol compared to nonmenthol.
Okuyemi et al. ⁶⁰	480 adult AA smokers at an inner-city health center	No significant difference in FTND scores between menthol and nonmenthol cigarette smokers.
Okuyemi et al. ⁶⁸	755 AA smokers in smoking cessation trial	No significant difference between menthol and nonmenthol on the NDSS or MNWS (a withdrawal scale).
Reitzel et al. ¹⁰⁴		

(Continued on next page)

TABLE 1. Studies with Validated and Widely Accepted Measures of Nicotine/Cigarette Dependence (Continued)

Study Authors	Population/Sample	Findings Related to Validated and Widely Accepted Measures of Nicotine/Cigarette Dependence
Reitzel et al. ⁹⁸	183 adult smokers (83 menthol and 100 nonmenthol) 1,067 adult smokers	There was no statistically significant difference in mean HSI score between menthol (3.60) and nonmenthol (3.73) smokers. Menthol smokers had statistically significantly lower mean dependence scores as measured by the HSI ($p = .01$).
Rojewski et al. ⁸⁴	166 adult smokers	No significant difference between menthol and nonmenthol smokers in mean FTND scores.
Winhusen et al. ⁸³	510 adult smokers	No statistically significant difference in FTND scores by menthol status.

AA = African American; AI = American Indian; AN = Alaska Native; AOR = adjusted odds ratio; BRFSS = Behavioral Risk Factor Surveillance System; CPD = cigarettes per day; FTND = Fagerström Test for Nicotine Dependence; FTQ = Fagerström Tolerance Questionnaire; HONC, Hooked on Nicotine Checklist; HSI = Heaviness of Smoking Index; MNWS = Minnesota Nicotine Withdrawal Scale; NDSS = Nicotine Dependence Syndrome Scale; NHIS = National Health Interview Survey; NHSDA = National Household Survey on Drug Abuse; NRT = nicotine replacement therapy; PI = Pacific Islander; TTFC = time to first cigarette; TUS CPS = Tobacco Use Supplements to the Current Population Surveys

In Model A, in addition to using the conventional FTND levels as the response variable, several other FTND categories were used. In addition, the interaction term menthol status by race was included in Model A with the other mentioned explanatory factors. Each question of the FTND was also analyzed individually. In Model B, the probability of being a menthol smoker was modeled. In a separate model, TTFC was compared between menthol and nonmenthol smokers. In another model, the effect of menthol status on the HSI was tested.

The SAS PROC LOGISTICS procedure was used to run the logistic regression models. Statistical significance was evaluated at $P < .05$. Missing values for any of the variables required for a specific analysis resulted in the observation being excluded from the analysis. SAS version 9.1.3 software was used to perform the statistical analysis.

TES Results

In the TES study, 30% of adult smokers reported they smoked menthol cigarettes. Twenty-two percent of White smokers and 73% of African American smokers smoked menthol cigarettes. Descriptive statistics for sociodemographic characteristics and smoking-related variables of menthol and nonmenthol smokers is presented in Table 2. Results are reported for African

American and White smokers as there were few respondents from other Racial groups.

Results for FTND and HSI Analysis

Mean FTND scores were similar for menthol (4.5 [SD, 2.13]) and nonmenthol adult smokers (4.6 [SD, 2.14]). A histogram of the FTND scores is presented in Figure 1. After adjusting for covariates, the following factors were associated with higher odds of smoking menthol cigarettes in the logistic regression model: women compared with men; African Americans compared with Whites; smoking a cigarette ≥ 13 mg tar yield compared with cigarettes ≤ 2.9 mg tar yield and being aged 34–49 years versus aged 21–31 years (Table 3). No significant increased odds of menthol use for any of the FTND questions were found (Table 3).

- Menthol cigarette smoking did not increase the odds of higher FTND scores regardless of how the FTND scores were categorized (i.e., in 5 categories, 3 or 2 categories [Table 4]). The interaction term menthol smoking status (i.e., menthol or nonmenthol) by race (i.e., African American/Black or White) was not statistically significant in Model A. This indicates that there is no evidence that menthol smoking status affects FTND scores differently in African Americans/Blacks and Whites.

TABLE 2. Descriptive Statistics for Demographics and Smoking History

Characteristic	Menthol (n = 1044)	Nonmenthol (n = 2297)
Age (years)		
Mean (SD)	41.8 (12.1)	42.0 (13.0)
Range (min, max)	(21, 76)	(21, 80)
Gender, No. (%)		
Female	664 (63.6)	1258 (54.8)
Male	380 (36.4)	1039 (45.2)
Race, No. (%)		
African American	448 (42.9)	166 (7.2)
White	596 (57.1)	2131 (92.8)
BMI (kg/m ²)		
Mean (SD)	28.57 (7.33)	27.31 (6.29)
Range (min, max)	(16.0, 66.7)	(15.0, 70.0)
Annual Household Income, No. (%)		
<\$20,000	374 (36.0)	604 (26.4)
\$20,000-\$49,999	451 (43.4)	1083 (47.3)
≥\$50,000	214 (20.6)	603 (26.3)
Number missing	5	7
Education, No. (%)		
<High school graduate	114 (11.0)	163 (7.1)
High school graduate	756 (72.8)	1745 (76.4)
College graduate	168 (16.2)	375 (16.4)
Number missing	6	14
Region, No. (%)		
Midwest	203 (19.4)	525 (22.9)
Northeast	179 (17.1)	251 (10.9)
South	471 (45.1)	745 (32.4)
West	191 (18.3)	776 (33.8)
Cigarettes smoked per day, Mean (SD) and No. (%)		
Mean (SD)	15.0 (8.7)	16.8 (9.0)
Range (min, max)	(1, 54)	(1, 84)
1–10 CPD	374 (35.8)	594 (25.9)
11–20 CPD	442 (42.3)	1054 (45.9)
21–30 CPD	168 (16.1)	479 (20.9)
>30 CPD	59 (5.7)	165 (7.2)
Number missing	1	5
Tar category, No. (%)		
≤2.9 mg	154 (14.8)	326 (14.2)
3.0–6.9 mg	198 (19.0)	694 (30.2)
7.0–12.9 mg	239 (22.9)	753 (32.8)
≥13.0 mg	453 (43.4)	524 (22.8)

- Higher FTND scores were not associated with increased odds of smoking menthol cigarettes (Table 5).

Menthol smokers have about the same odds of smoking their first cigarette more than 30 minutes after they wake up as nonmenthol smokers when adjusted for the other factors (Tables 4 and 5). In addition, the interaction term, menthol smoking status (i.e., menthol or nonmenthol) by race (i.e., African-American/Black or White) was not statistically significant

in Model A. No statistically significant effect of menthol was observed on HSI scores (Table 6).

DISCUSSION

Our review of the scientific evidence included widely accepted predictors, indicators, and validated measures of nicotine/cigarette dependence that have been published in the peer-reviewed literature. We are aware of 4 other menthol analyses in the literature that include incomplete descriptions and measures that are not listed among validated measures.^{10,37,39} These publications include three analyses of the National Youth Tobacco Survey by Wackowski and Delnevo¹⁰⁷ and Hersey et al.^{109,110} and a report by Nonnemaker et al.¹¹¹ Mixed findings were reported in the odds of endorsing three¹¹⁰ or four¹⁰⁸ dependence-related statements. It is problematic that although the models in both of these publications did not adjust for socioeconomic status, both did adjust their dependence-related statement analyses for frequency of smoking in the past 30 days and CPD, both of which are dependence indicators. Hersey et al.¹⁰⁹ reported that menthol smokers had a significantly higher odds of being above the median on a nicotine dependence scale for adolescents but no details about the scores (medians, means, SD or 95% CI) are provided. Nonnemaker et al.¹¹¹ reported a statistically significant association between menthol and higher levels of dependence in the third wave of the survey ($\beta = 1.25$; 95% CI, 0.10–2.4). However, it is not clear from the data presented whether this is a meaningful difference in scores. The analyses included a scale that was not validated, scores for menthol and nonmenthol smokers were not provided, and no adjustment was made for socioeconomic status.¹¹¹ Mean scores on the questionnaire were similar for White and African American adolescent smokers despite the difference in the proportion who reported menthol.¹¹⁰

We note there are several instances where validated dependence measure comparisons between menthol and nonmenthol smokers have been made and presented to the FDA and TPSAC at public meetings, but the results

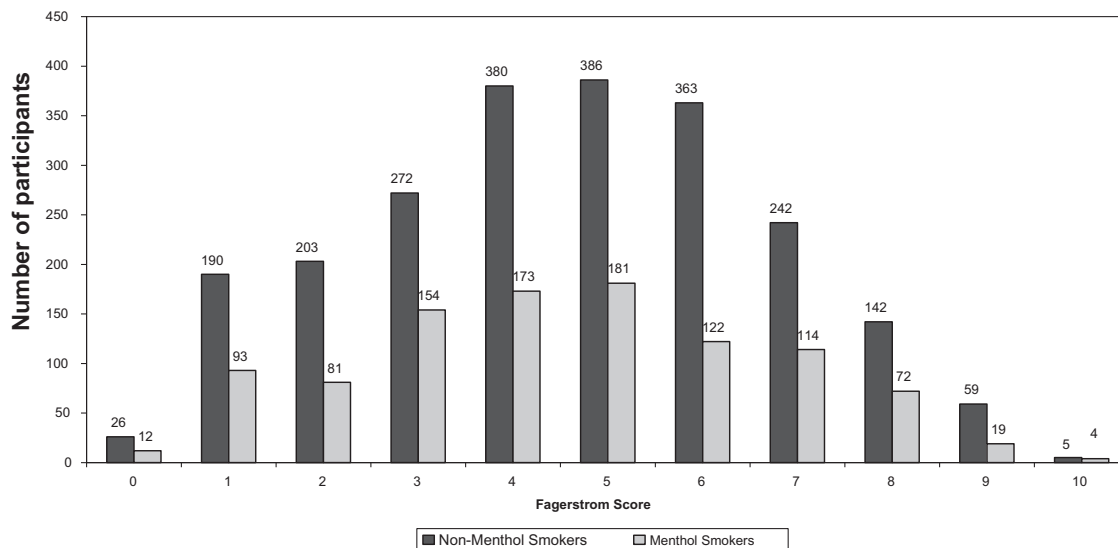


FIGURE 1. Histogram of FTND scores for menthol and nonmenthol smokers.

are not included in subsequent publications. For example, Reitzel^{112–114} presented analyses from 3 studies with 3 different populations to the TPSAC and the FDA Center for Tobacco Products showing that menthol smokers were not more dependent as measured by the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68) and that there was no statistically significant difference on any of the 13 WISDM subscales in their multivariate analyses. These results are available online and are referenced in the TPSAC's report to the FDA Center for Tobacco Products,³ but are not mentioned in the subsequent publications.^{98,104,115}

In the current study, we reviewed dependence-related predictors, indicators, and validated dependence measures in menthol versus nonmenthol smokers. We note that menthol cigarette smokers are not a homogenous population. There are notable sociodemographic differences between menthol smokers and nonmenthol smokers, and these differences (and differences in subgroups of menthol and nonmenthol cigarette smokers), if not controlled for, could affect measures of disease risk and behavioral outcomes. Analyses of national surveys report that menthol smokers are "mainly female, aged 45–64, non-Hispanic white, married, blue-collar workers, smokers who lived in the South and metropolitan areas

and who reported having attained a high school diploma or GED."⁷⁰

Based on the 2006/2007 Tobacco Use Supplement to the Current Population Survey, approximately 27% of current adult smokers in the United States report smoking menthol cigarettes.¹¹⁵ The percentage of menthol use within each sociodemographic group varies. Specifically, the percentage of adult smokers who smoke menthol cigarettes is higher (>27% and non-overlapping 95% CI with other groups) among the following:

- Women compared with men.
- Those between ages 18–24 and 45–64 years compared with those who are aged 24–44 years and those who are 65+ years.
- African Americans compared with every other race/ethnicity group.
- Those who have a family income of <\$25,000 per year compared with all other income groups.
- Those with some high school education compared with those in other educational attainment groups.
- Service workers compared with blue- and white-collar workers.
- The unemployed compared with those who are employed and those who are not in the labor force.

TABLE 3. Odds of Menthol Use in the Total Exposure Study

Characteristic	No.	Percentage menthol	OR for menthol*	95% CI
Gender				
Male	1419	26.8	1.00	Reference
Female	1922	34.6	2.13	1.78 to 2.56
Age				
21–34 years	1041	29.3	1.00	Reference
35–49 years	1328	35.8	1.31	1.07 to 1.62
50+ years	972	27.2	1.13	0.90 to 1.42
Race				
White	2727	21.9	1.00	Reference
African American	614	73	9.53	7.52 to 12.09
Education				
<High school graduate	277	41.2	1.00	Reference
High school graduate	2501	30.2	0.85	0.62 to 1.16
College graduate	543	30.9	1.25	0.86 to 1.82
Income				
<\$20,000	978	38.2	1.00	Reference
\$20,000–\$49,999	1534	29.4	1.04	0.84 to 1.27
≥\$50,000	817	26.2	1.08	0.84 to 1.39
Tar Yield Category				
≤2.9 mg	480	32.1	1.00	Reference
3.0–6.9 mg	892	22.2	0.98	0.73 to 1.30
7.0–12.9 mg	992	24.1	1.26	0.95 to 1.66
≥13.0 mg	977	46.4	2.25	1.72 to 2.96
Time until first cigarette				
≤5 minutes	997	33.8	0.88	0.62 to 1.25
6–30 minutes	1421	31.3	0.90	0.66 to 1.23
30–60 minutes	486	24.5	0.70	0.50 to 0.98
≥60 minutes	428	32.2	1.00	Reference
Hate most to give up				
First in the morning	1592	34.2	1.10	0.91 to 1.32
All other	1736	27.9	1.00	Reference
How many smoked/day				
10 or less	740	40	1.00	Reference
11–20	1624	29.9	0.97	0.76 to 1.24
21–30	725	25.7	1.04	0.76 to 1.41
31 or more	230	30.4	1.40	0.93 to 2.10
↑ during 1 h waking/rest of day				
No	1917	30.9	1.00	Reference
Yes	1405	31.3	0.94	0.78 to 1.14
Refrain forbidden places				
No	2480	30.8	1.00	Reference
Yes	844	32.4	1.08	0.88 to 1.32
Ill in bed most of the day				
No	2010	30	1.00	Reference
Yes	1317	32.8	1.11	0.92 to 1.34

*Odds ratio from logistic regression model adjusting for all other factors listed in the Table.

CI = confidence interval; OR = odds ratio.

Studies that adjust for these differences between menthol and nonmenthol smokers are better able to assess the impact of menthol on outcomes.

Numerous publications have reported the different patterns of menthol use in various groups (by gender, race/ethnicity, age, etc.),^{65,67,70,71,72} provided reasons for

different patterns of use,^{56,59,117,118} and commented on initiation among menthol and nonmenthol smokers.^{102,111} Although this literature is important to understanding the overall public health implications of menthol versus nonmenthol smoking, it is beyond the scope of this review, which is focused on dependence.

TABLE 4. Effect of Menthol Status on FTND Scores and Time to First Cigarette (Model A)

Menthol status	Odds ratio	95% CI
Fagerström's categorization of the scores ^a		
Menthol	1.05	0.91 to 1.22
Nonmenthol	1	Reference
Low/Medium (0-5) vs. high (6-10) scores		
Menthol	0.94	0.79 to 1.13
Nonmenthol	1	Reference
Low (0-3), medium (4-5), and high (6-10) scores		
Menthol	0.97	0.83 to 1.13
Nonmenthol	1	Reference
Time to first cigarette: >30 minutes, ≤ 30 minutes		
Menthol	0.88	0.72 to 1.05
Nonmenthol	1	Reference

^a5 categories: very low: 0–2 points, low: 3–4 points, medium: 5 points, high: 6–7 points, very high: 8–10 points.

Note: Adjusted for age, race, gender, education and tar yield category.

No statistically significant difference was observed.

CI = confidence interval.

Because measures of dependence are often associated with measures of cessation, a comprehensive review of the cessation-related menthol literature would also be useful for the scientific community and regulatory agencies. Briefly, we recognize that there are numerous studies with cessation-related indicators and outcomes, such as quit intentions, thinking about quitting, confidence in quitting, motivation to quit, desire to quit, reasons for not

TABLE 6. Effect of Menthol Status on Heaviness of Smoking Index (HSI) Score

Menthol status	Odds ratio	95% CI
HSI score		
Menthol	1	Reference
Nonmenthol	1.13	0.95 to 1.34

Note: Adjusted for age, race, gender, education, income and tar yield category.

No statistically significant difference was observed.

CI = confidence interval.

quitting, quit attempts, relapse, length of abstinence, and short- and long-term cessation outcomes by menthol status that are also informative. A review of studies with long-term cessation outcomes (6 months to >5 years) also supports the conclusion that menthol does not increase dependence. Many studies have reported that there is no difference in cessation and no effect of menthol on various long-term cessation outcomes overall^{28,61,66,68,80,81,85,96,104,115,119–123} or in specific subgroups, such as among White and Hispanic smokers⁵⁸ and among those who received placebo gum or motivational interview.⁶⁸ Fu et al.³⁵ reported that menthol smokers who received an intervention had increased odds of cessation as compared to nonmenthol smokers. The Hyland et al.⁶⁶

TABLE 5. Effect of the FTND Scores and Time to First Cigarette on Menthol Status (Model B)

Measure	Nonmenthol	Menthol	Odds Ratio	95% CI
5 categories: very low: 0–2 points, low: 3–4 points, medium: 5 points, high: 6–7 points, very high: 8–10 points				
Very Low FTND	419	186	0.84	0.64 to 1.12
Low FTND	652	327	0.96	0.75 to 1.24
Medium FTND	386	181	1	Reference
High FTND	605	236	0.89	0.69 to 1.16
Very High FTND	206	95	1.32	0.95 to 1.83
2 categories: low/medium (0–5) and high (6–10) scores				
Low/Medium FTND	1457	694	1	Reference
High FTND	811	331	1.05	0.88 to 1.26
3 categories: low (0–3), medium (4–5) and high (6–10) scores				
Low FTND	691	340	1	Reference
Medium FTND	766	354	1.01	0.82 to 1.24
High FTND	811	331	1.06	0.86 to 1.31
Time to First Cigarette (TTFC)				
TTFC > 30 minutes	657	257	1	Reference
TTFC ≤ 30 minutes	1636	782	1.17	0.96 to 1.42

Note: Adjusted for age, race, gender, education and tar yield category. No statistical significance was observed at a *P* value < .05.

CI = confidence interval; FTND = Fagerström Test for Nicotine Dependence

and Murray et al.⁸⁰ studies are particularly noteworthy because they included the largest cohorts and long length of follow-up (5 years).

In our review of the dependence-related menthol scientific literature, we found 16 publications that compared age of initiation or progression among menthol and nonmenthol smokers. Overall, these studies consistently reported that menthol smokers have the same or later mean age of first use and the same or later mean age of regular smoking. Of the 8 publications that included information on smoking frequency, 5 reported menthol smokers were less likely to be daily smokers and more likely to be some day smokers as compared to nonmenthol smokers, and 3 reported no difference in smoking frequency. We identified 30 studies and dozens of analyses that provide information on CPD among menthol and nonmenthol smokers. More than two dozen analyses found no difference in CPD for menthol versus nonmenthol, including various subgroup analyses and in the overall sample. More than two dozen other analyses found fewer CPD for menthol versus nonmenthol smokers. Only 1 publication reported a higher cigarette consumption among menthol smokers, but it appears there may have been an error in the menthol/nonmenthol coding or analysis. With that one exception, all other studies and analyses report that menthol smokers smoke the same or fewer CPD compared with nonmenthol smokers.

Our review included 19 publications and dozens of analyses of TTFC among menthol and nonmenthol smokers. The published literature related to TTFC includes various TTFC categories. Some publications have focused on the TTFC ≤ 5 minutes comparisons, whereas the TTFC >60 minutes comparison is equally important as a predictor of cessation outcomes.³⁵

Most studies that have examined TTFC within the first 30 minutes of waking and found no difference between menthol and nonmenthol smokers. Of the 2 studies that compared FTND TTFC categories, 1 had a small and unequal sample size of nonmenthol smokers

and the other large study found no difference in any of the four TTFC categories. Studies that included other categorizations of TTFC and studies examining mean TTFC have reported mixed results, including shorter, longer, and no difference in TTFC. The available studies with large, diverse samples and multivariate analyses do not support that menthol smokers overall have shorter TTFC, and some results suggest longer TTFC. Of the 2 studies available that included a measure of night waking to smoke, both studies reported a higher percentage of menthol smokers reporting they sometimes wake at night to smoke compared with nonmenthol smokers. Of these 2 studies, 1 did not adjust for the differences between groups and the other found that menthol was not a predictor of cessation. Among 12 studies that examined smoking duration, 4 reported no difference in smoking duration and the other 8 reported shorter smoking duration among menthol versus nonmenthol smokers. Every published study available with validated and widely accepted dependence measures consistently found that menthol smokers scored the same or lower on established measures of nicotine/cigarette dependence as compared to nonmenthol smokers.

The main limitation of this review and analysis is that most studies were not specifically designed to address the impact of menthol on cigarette dependence. Some studies had small and unequal sample sizes of menthol and nonmenthol smokers, and other studies did not control for differences between the menthol and nonmenthol groups. Although we attempted to be inclusive, there may be additional articles that include dependence measures or indicators as part of the description of sample characteristics that were not identified in our literature search. This review was focused on dependence related analysis and therefore is not inclusive of other menthol-related studies. Although the TES was not designed specifically to assess the effect of menthol status on dependence scores, to our knowledge, this analysis contains the largest sample to date for which overall FTND scores, the HSI, and the results for each of the FTND questions are examined.

SUMMARY AND CONCLUSIONS

The published literature does not support that menthol smokers are more dependent than nonmenthol smokers. Menthol smokers do not have an earlier age of first cigarette smoked or an earlier age of progression to regular smoking compared with nonmenthol smokers. Menthol smokers are not more likely to smoke daily, do not smoke greater CPD, do not consistently have shorter TTFC, and do not have longer duration of smoking. Most directly relevant to answering the questions surrounding menthol and dependence, the published literature consistently demonstrated that menthol smokers do not score higher on validated measures of nicotine/cigarette dependence. Our analysis of the TES data is consistent with the literature in that menthol status also had no statistically significant effect on any single item, the HSI, or overall FTND scores regardless of how the FTND scores were categorized. These results strengthen the existing scientific evidence which demonstrates menthol does not have an effect on nicotine/cigarette dependence.

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