Scientific Review of the Effects of Menthol in Cigarettes on Tobacco Addiction: 1980-2021

Center for Tobacco Products
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SCIENTIFIC REVIEW OF THE EFFECTS OF MENTHOL IN CIGARETTES ON TOBACCO ADDICTION

1980-2021

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I. EXECUTIVE SUMMARY

Menthol is a widely used compound found in drug products, food, cosmetics, and as a flavor additive in cigarettes. Section 907(a) of the Tobacco Control Act bans artificial and natural characterizing flavors in cigarettes and cigarette smoke, but specifically exempts menthol from the ban. The information necessary to inform regulatory actions on menthol in cigarettes can be acquired through thorough examination of the current knowledge about menthol and its effects on public health.

Given that addiction to nicotine drives continued tobacco use, the purpose of this reproducible transparent document (RTD) was to determine the impact of menthol in cigarettes on addiction using a weight of the evidence approach. Specifically, progression to regular cigarette use, dependence, and cessation were explored through a comprehensive, reproducible transparent review of the publicly available scientific literature. The sensory effects of menthol and its contribution to cigarette smoking experiences and effects on smoking topography were also examined through review of original research studies.

Articles published between 1980 and April 30, 2021 were identified through the search engines PubMed, Web of Science, EMBASE, and EBSCOHost (PsychINFO, Academic Search Complete), through hand-searching of select article reference sections, comments from menthol's 2013 Advance Notice of Proposed Rulemaking, and comments from a Citizen Petition received by the Agency. Three independent reviewers conducted an initial screening of the title and abstract of all identified articles to select articles for full text screening. The full text screening was conducted by the three reviewers to determine eligibility for review and inclusion in the document.

For the weight of evidence approach, articles were categorized into tiers based on study design, with human longitudinal analyses having the greatest weight, followed by human cross-sectional analyses, then nonclinical analyses. Individual articles were scored within each tier. Risk of bias areas were incorporated into the scoring system so that they were also evaluated in the weight of evidence for each individual study. After scoring all individual articles, the total number and proportion of strong and moderate analyses was calculated for each study outcome (i.e., positive correlation between menthol and the outcome; negative correlation between menthol and the outcome; no effect of menthol) within each tier, for each topic. A qualitative assessment of the strong and moderate analyses for each topic was used to determine overall conclusions for each addiction outcome.

The weight of evidence supports that the sensory effects of menthol contribute to positive smoking experiences that facilitate repeated use. Evidence also supports that menthol in cigarettes is associated with progression to regular cigarette smoking in youth and young adults and greater dependence in youth. However, evidence is not sufficient to support a conclusion of an association of menthol in cigarettes with dependence among adults due to inconsistent findings. Similarly, evidence is not sufficient to support a conclusion of an association of menthol in cigarettes with altered smoking topography. In the case of cessation, the weight of evidence suggests that menthol in cigarettes is likely associated with reduced cessation success in the general population and is associated with reduced cessation success among Black cigarette smokers.

II.   LIST OF ACRONYMS

- ACP: Acute Cigarette Perceptions
- ANCOVA: Analysis of Covariance
- ANOVA: Analysis of Variance
- AOR: Adjusted Odds Ratio
- APR: Adjusted Prevalence Ratio
- AUTOS: Autonomy Over Smoking Scale
- ALLTURS: American Legacy Longitudinal Tobacco Use Reduction Study
- BOE: Biomarkers of Exposure
- BNA: Brain Nicotine Accumulation
- BQSU: Brief Questionnaire of Smoking Urges
- CARDIA: Coronary Artery Risk Development in Young Adults
- CDS: Cigarette Dependence Scale
- CES: Cigarette Evaluation Scale
- CI: Confidence Interval
- CO: Carbon monoxide
- COMMIT: Community Intervention Trial for Smoking Cessation
- CPD: Cigarettes per Day
- CPP: Conditioned Place Preference
- CReSS®: Clinical Research Support System
- FDA: Food and Drug Administration
- FTND: Fagerström Test for Nicotine Dependence
- FTQ: Fagerström Tolerance Questionnaire
- HONC: Hooked on Nicotine Checklist
- HPHC: Harmful and Potentially Harmful Constituents
- HR: Hazard Ratio
- HSI: Heaviness of Smoking Index
- MNWS: Minnesota Nicotine Withdrawal Scale
- nAChRs: nicotinic acetylcholine receptors
- NCI: National Cancer Institute
- NDSS: Nicotine Dependence Syndrome Scale
- NHANES: National Health and Nutrition Examination Survey
- NHLBI: National Heart, Lung, and Blood Institute
- NHIS- National Health Interview Survey
- NHIS-CCS: National Health Interview Survey Cancer Control Supplement
- NIDA: National Institute of Drug Abuse
- NIH: National Institute of Health
- NIMH: National Institute of Mental Health
- NSDUH: National Survey on Drug Use and Health
- NYAHS: National Young Adult Health Survey
- NYTS: National Youth Tobacco Survey
- OR: Odds Ratio
- PATH: Population Assessment of Tobacco and Health

- PND: Postnatal Day
- RCT: Randomized Controlled Trial
- RRR: Relative Risk Ratio
- RTD: Reproducible Transparent Document
- SCSS: Southern Community Cohort Study
- SPA-D: Smoking Puff Analyzer - Desktop
- TCORS: Tobacco Center of Regulatory Science
- TES: Tobacco Exposure Study
- TPSAC: Tobacco Products Scientific Advisory Committee
- TRPM8: Transient receptor potential melastatin 8
- TSNA: Tobacco specific nitrosamines
- TTFC: Time to First Cigarette
- TUS-CPS: Tobacco Use Supplement to the Current Population Survey
- USDHHS: United States Department of Health and Human Services
- WISDM: Wisconsin Inventory of Smoking Dependence Motives

III.   BACKGROUND AND RATIONALE

Menthol is a widely used compound found in drug products, food, cosmetics, and as a flavor additive in cigarettes. Section 907(a) of the Tobacco Control Act bans artificial and natural characterizing flavors in cigarette tobacco products and smoke. However, menthol as a characterizing flavor was exempted from this ban. Menthol levels in cigarettes labeled as menthol vary depending on the brand (Schneller, Bansal-Travers, Mahoney, McCann, & O'Connor, 2020b). Menthol is also present in cigarettes labeled as non-mentholated (Schneller et al., 2020b).

Menthol imparts a minty taste and cooling sensation when inhaled (Kamatou, Vermaak, Viljoen, & Lawrence, 2013), and has anti-irritant (Ha et al., 2015; Willis, Liu, Ha, Jordt, & Morris, 2011), antitussive (Plevkova et al., 2013; Wise, Breslin, & Dalton, 2012), and analgesic properties (Liu et al., 2013). These properties are mediated through menthol's action at transient receptor potential melastatin 8 (TRPM8) expressed on sensory neurons (Kamatou et al., 2013). Several tobacco industry document reviews suggest that the sensory effects of menthol reduce dryness, irritation, unpleasant taste of tobacco, and other negative sensory attributes of smoking, thus facilitating cigarette smoking (Arendt Nielsen, Nielsen, Wang, Arendt-Nielsen, & Boudreau, 2016; Wayne & Connolly, 2004). However, because menthol can also produce tingling, stinging, and burning in the mouth and throat, menthol levels in cigarettes are critical to achieving the desired subjective response (Arendt Nielsen et al., 2016; Wayne & Connolly, 2004).

In addition to activating receptors on sensory neurons, menthol binds to nicotinic acetylcholine receptors (nAChRs) in the brain (Wickham, 2015). nAChRs are the primary targets for nicotine, the primary addictive substance in tobacco products (U.S. Department of Health and Human Services, 1988). Once nicotine binds to nAChRs, nicotine induces release of the chemical dopamine, which produces rewarding effects that increase motivation to repeat pleasurable experiences, including smoking (De Biasi & Dani, 2011). Nicotine from tobacco products travels to the brain and activates nAChRs. After repeated exposure to nicotine, nAChRs become less responsive to nicotine (nAChR desensitization), prompting increases in the number of brain nAChRs (nAChR upregulation) (Benowitz, 2010). This process of nAChR desensitization and nAChR upregulation has been implicated in the development of nicotine addiction (Benowitz, 2010). After many hours of nicotine abstinence, such as overnight, a smoker's nicotine levels fall, returning nAChRs to a responsive state. As a result of the excess number of responsive nAChRs, abnormal enhancement of brain activity occurs, contributing to the discomfort associated with nicotine withdrawal that drives smoking behavior (Dani & Heinemann, 1996). Although positive reinforcing effects of nicotine (e.g., heightened mood, decreased anxiety and stress, improved concentration) play a role in continued smoking, avoidance of the withdrawal syndrome that occurs after smoking cessation (e.g., irritability, depressed mood, restlessness, anxiety) also greatly contributes to maintenance of smoking behaviors (Benowitz, 2010).

By binding to the nAChRs, menthol enhances nicotine-induced receptor desensitization (Ton et al., 2015). In addition, menthol can upregulate brain nAChRs both independently (Henderson et al., 2016), and in combination with nicotine (Alsharari et al., 2015; Brody et al., 2013; Ton et al., 2015). Studies using animal models to assess the behavioral effects of nicotine indicate that menthol enhances the reinforcing effects of nicotine (Biswas et al., 2016; T. Wang, Wang, & Chen, 2014) and increases the intensity of nicotine withdrawal (Alsharari et al., 2015). Given that the positive and negative reinforcing effects of nicotine are largely mediated through

nAChRs ([Benowitz, 2010](#)), menthol's actions at these receptors and its effects on midbrain dopamine neuron function ([Henderson et al., 2016](#)) likely affect smoking behavior and the addictive potential of menthol tobacco products.

Indeed, previous scientific reviews based on the FDA Preliminary Scientific Evaluation of Menthol ([Food and Drug Administration, 2011](#)) and Reference Addendum ([Food and Drug Administration, 2013](#)) concluded that menthol in cigarettes is likely associated with increased smoking initiation and progression to regular cigarette smoking, increased dependence, and reduced cessation success, particularly among Black menthol smokers. Findings from the Tobacco Products Scientific Advisory Committee (TPSAC) evaluation ([Tobacco Products Scientific Advisory Committee (TPSAC), 2011b](#)) were generally in line with these conclusions, indicating that evidence is sufficient to conclude that the availability of menthol cigarettes increases the likelihood of experimentation and initiation, menthol cigarette smokers are less likely to quit successfully than non-menthol cigarette smokers, and among youth, those who smoke menthol cigarettes tend to be more dependent than those who smoke non-menthol cigarettes; however, among adults, there was little available evidence to support that menthol in cigarettes increases the degree of dependence compared to non-menthol cigarettes. The TPSAC industry members also completed an evaluation, which indicated that the evidence is suggestive of no causal relationship between menthol in cigarettes and smoking initiation behaviors, dependence (adults or adolescents), or cessation success ([Tobacco Products Scientific Advisory Committee (TPSAC), 2011a](#))

However, the various methods, including those for conducting literature searches, inclusion/exclusion criteria, selection of articles for review, and the weight of evidence approach were not transparent within all of the reviews. These methods, when available, were also not comparable across reviews. In response, this review represents a reproducible transparent document (RTD) from 1980 through April 30, 2021 that can be replicated and updated as needed with the acquisition of additional knowledge about the science behind menthol in cigarettes.

This RTD focuses on the impact of menthol in cigarettes on addiction. Specifically, the sensory effects of menthol and contribution to cigarette smoking, the effects of menthol on smoking topography, and the role of menthol in progression to regular cigarette use, dependence, and cessation were explored through a comprehensive, reproducible, and transparent review of the publicly available scientific literature. The conclusions from this RTD may inform potential future regulatory activities related to menthol in cigarettes.

IV. RESEARCH QUESTIONS

This review addresses the following research questions to evaluate the role of menthol in cigarettes on tobacco product addiction:

  I. What is the role of menthol's sensory effects in cigarette smoking? Do the sensory effects of menthol contribute to positive smoking experiences and facilitate smoking?
 II. What is the role of menthol in progression to regular use? Does menthol in cigarettes promote progression to regular smoking?
III. What is the impact of menthol in cigarettes on nicotine dependence? Are regular users of menthol cigarettes more dependent than regular users of non-menthol cigarettes?

IV.   What is the effect of menthol on smoking topography? Does menthol in cigarettes contribute to altered smoking topography compared to non-menthol cigarettes?

V.   What is the impact of menthol in cigarettes on smoking cessation? Do menthol cigarette smokers have reduced cessation rates compared to non-menthol cigarette smokers?

V.   INFORMATION SOURCES 1980-2021

Several search engines were used to retrieve articles, including PubMed, Web of Science, EMBASE, and EBSCOHost (PsycINFO, Academic Search Complete). A series of searches were conducted from 2016 to 2021 to retrieve articles related to menthol and addiction. As discussed in Section IX, a weight of evidence evaluation was conducted at three different time points (2016, 2019, and 2021) on articles identified through these searches.

Searches were conducted on: September 16, 2016 to identify articles publicly available 1980-September 16, 2016; January 2, 2018 to identify articles publicly available September 17, 2016-January 2, 2018; January 2, 2019 to identify articles publicly available January 3, 2018 through January 2, 2019; January 6, 2020 to identify articles publicly available January 3, 2019 through January 3, 2020; and April 30, 2021 to identify articles publicly available January 4, 2020 through April 30, 2021. Additional publications were identified through hand-searching articles, comments from the 2013 Advance Notice of Proposed Rulemaking on menthol in cigarettes, and comments from the 2013 Citizen Petition[1] received by the Agency. Details of search terms, algorithms, and search dates for each database are provided in Appendix A.

VI.   STUDY SELECTION

A screening process was utilized to identify articles for inclusion in the final review. For this process, three independent reviewers conducted an initial screening of the title and abstract to select articles for full text screening. Any articles labeled as "include" from any reviewer underwent a full text screening. The full text screening was conducted by the three reviewers to determine eligibility for review and inclusion in the document. Any disagreements regarding inclusion were discussed and, if needed, final review was determined by a fourth independent reviewer. There were no instances that required resolution by a fourth reviewer.

The following eligibility criteria were used to search and identify articles (via an initial title and abstract screen) for inclusion in the full text screen:

- Years considered: 1980[2] to April 30, 2021
- Language: English

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[1] Citizen Petition: Asking the U.S. Food and Drug Administration to Prohibit Menthol as a Characterizing Flavor in Cigarette. April 12, 2013. https://www.publichealthlawcenter.org/sites/default/files/resources/tclc-fdacitizenpetition-menthol-2013.pdf

[2] Cigarette design and smoke composition have changed since 1950. As a result, we selected 1980 as the cut-off year for inclusion to minimize the potential for differences in cigarette design, other than menthol, that may have influenced study findings (e.g., changes in filter tips) (Hoffmann & Hoffmann, 1997).

- Publication status: Peer-reviewed published or in-press journal articles, full-text available
- Studies that directly measure and compare use of menthol cigarettes (or other combusted tobacco products) to use of non-menthol cigarettes/products
- Analyses of menthol compared to non-menthol smokers or non-menthol cigarettes regarding progression to regular use, topography, sensory effects, dependence, or cessation
- Nonclinical studies evaluating the effects of menthol
- Studies in any demographic population
- All study designs, including meta-analyses
- Study conducted in any U.S. geographic location[3]

Conference abstracts, notes, commentaries, book reviews, editorials, letters, theses, historical pieces, case reports/studies, articles from news media, literature reviews, industry document reviews, and systematic reviews (although these may be mentioned in the background or checked for applicable references) were excluded from review.

After the title and abstract screen, the following study inclusion and exclusion criteria were used during the full text screening to determine studies that should be included for review:

a) Inclusion Criteria:
- Studies that include at least one of the following measures of progression to regular use, dependence, or cessation:
   o Rate or likelihood of progression to regular cigarette use or escalation of smoking behavior among current menthol and non-menthol smokers
   o Primary scales used to evaluate nicotine dependence (e.g., Fagerström Test for Nicotine Dependence [FTND], Heaviness of Smoking Index [HSI])
   o Proxies for nicotine dependence (e.g., cigarettes per day [CPD], time to first cigarette [TTFC], craving)
   o Studies on the effects of menthol on nicotine exposure and/or pharmacokinetics
   o Self-report and/or biochemically-verified cessation rates in current and/or former menthol and non-menthol smokers.
   o Longest duration of abstinence in current and/or former menthol and non-menthol smokers
- Studies on smoking topography, altered palatability to cigarettes, or differences in sensory experiences between menthol and non-menthol cigarettes
- Studies using animal models to assess menthol's behavioral effects related to abuse liability (e.g., self-administration, central nervous system activity, reward, withdrawal) or sensory effects
- Meta-analyses (although these were not scored)

b) Exclusion Criteria:

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[3] Studies were limited to the U.S. to account for potential differences in cigarette design across countries (O'Connor et al., 2008), differences in the prevalence and patterns of menthol use (Giovino et al., 2004), and non-US tobacco regulatory policies (e.g., menthol cigarette restrictions, cigarette packaging bans) (Erinoso et al., 2021) that may influence menthol cigarette use.

- Studies on intent to initiate and continue smoking without a reference to actual product use
- Studies on menthol and effects on non-nicotine biomarkers of exposure (BOE) (e.g., carbon monoxide (CO), tobacco specific nitrosamines [TSNAs])
- Studies on intent to quit, motivation to quit, or the number of quit attempts without reference to actual cessation success

VII.   RESULTS OF STUDY SELECTION 1980-2021
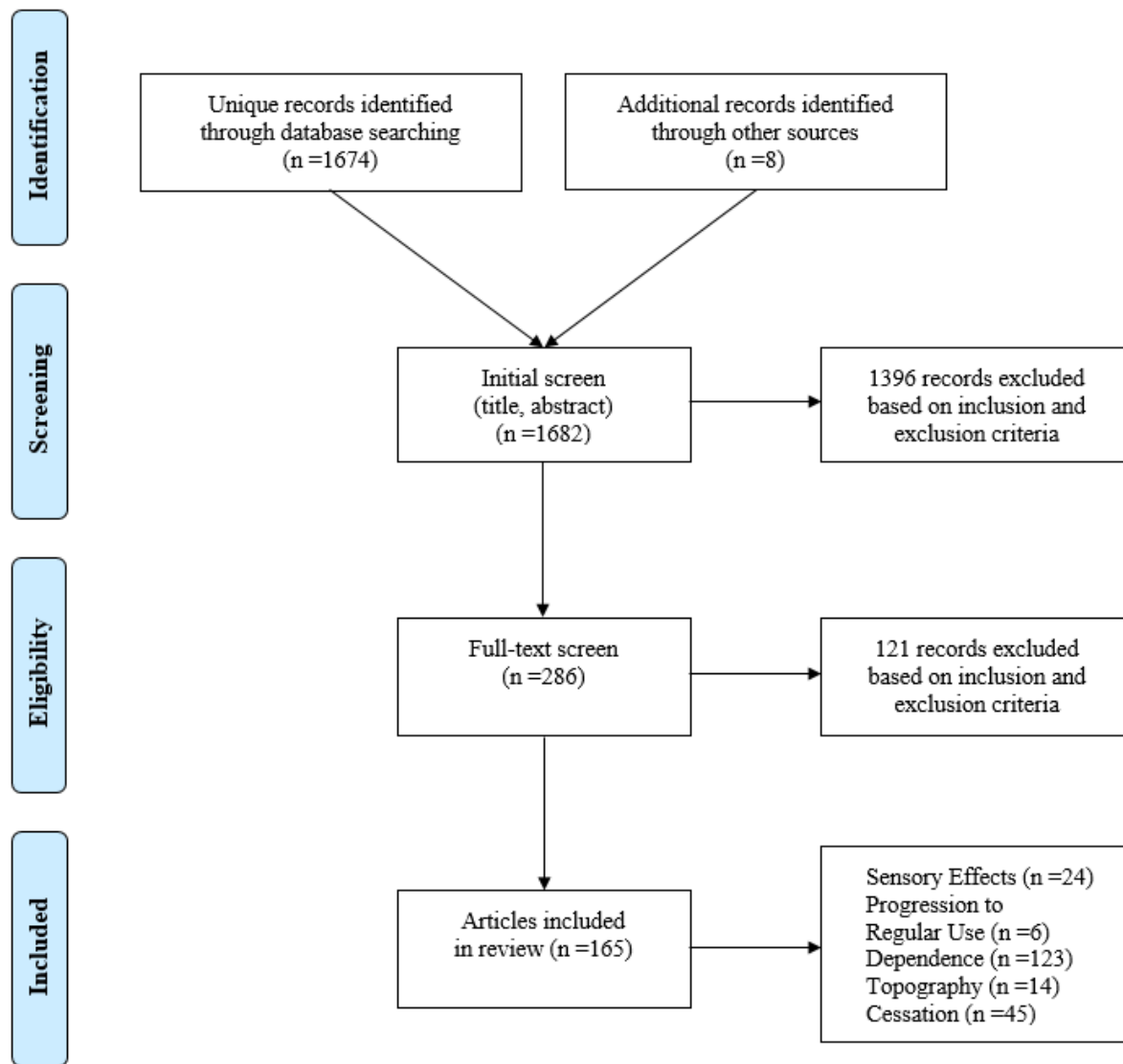
Note: Articles containing multiple outcome measures (e.g., articles that evaluated both dependence and cessation outcomes) are included under each respective topic. As such, there is overlap of addiction assessments across 165 included articles.

VIII.   WEIGHT OF EVIDENCE APPROACH

The Navigation Guide Systematic Review Methodology (NavGuide), an integrated Cochrane-style risk of bias analysis and weight of evidence approach, was adapted and used for this assessment (Higgins, 2008; Woodruff & Sutton, 2014). The NavGuide approach was selected to allow for the rigor of systematic review methods (e.g., specifying explicit study questions, conducting a comprehensive search, rating the quality and strength of the evidence according to consistent criteria) while allowing for combining results of human and nonclinical evidence into a single conclusion about the effects of menthol on the outcomes of interest (Woodruff & Sutton, 2014). Groups of studies were initially rated based on broad characteristic (i.e., study design), with the most consideration given to human longitudinal studies. A tiered approach was utilized to rate study analyses based on study design:

Tier 1: Longitudinal analysis

Tier 2: Cross-sectional analysis

Tier 3: Nonclinical analysis

After grouping analyses by tier based on study design, individual studies were then scored as strong, moderate, or weak based on the "QualSyst" systematic review tool developed by Kmet et al. (2004). The "QualSyst" tool generates a score between 0 and 1 for each article. This system was used to evaluate study quality and bias. The information in the bias table presented in Appendix B was used to assess risk of bias for individual studies when determining overall study quality. The table was adapted from the Cochrane Risk of Bias Tool and other sources,[4] which discuss possible risks of bias in quantitative and qualitative study designs. The risk of bias areas presented in the table were incorporated into the scoring system so that they were evaluated in the quality assessment for each individual study.

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[4] References:
   a) Gordis, L. (2004). *Epidemiology.* Third edition. Philadelphia, PA: Elsevier Saunders.
   b) Schutt, R.K. (2009). *Investigating the Social World: The Process and Practice of Research.* Sixth edition. Thousand Oaks, CA: SAGE Publications, Inc.
   c) Friis, R.H., Sellers, T.A. (2004). *Epidemiology for Public Health Practice.* Fifth edition. Sudbury, MA: Jones and Bartlett Publishers.
   d) Shadish, W.R., Cook, T.D., Campbell, D.T. (2001). *Experimental and Quasi-Experimental Designs for Generalized Causal Inference.* Second edition. Boston, MA: Houghton Mifflin.
   e) Viswanathan, M., Berkman, N.D., Dryden, D.M., Hartling, L. (2013). *Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank. Methods Research Report.* (Prepared by RTI–UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No. 13-EHC106-EF. Rockville, MD: Agency for Healthcare Research and Quality.
   f) Higgins, J.P.T., Green, S. (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
   g) Dixon-Woods, M., Shaw, R., Agarwal, S., and Smith, J. (2004). The problem of appraising qualitative research. *Quality & Safety in Healthcare*, 13: 223–5.
   h) Tong, A., Sainsbury, P., Craig, J. (2007). Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*, 19(6): 349-357.

The checklists for quality in quantitative and qualitative research (Appendices C and D, respectively) were modified to include language related to menthol in cigarettes, additional criteria related to risk of bias (Appendix B), and criteria based on the weight of evidence for individual review sections (e.g., greater weight given to cessation studies that include biochemical measures for validation). Meta-analyses were considered separately and were not scored. Based on Kmet et al. (2004), the following formulas were used to determine scores for quantitative and qualitative studies:

Quantitative studies: [(Total article score)/(Total possible score-(number of "n/a" x 2))]

Qualitative studies: (Total article score) /(Total possible score)

To establish inter-rater consistency (as described by Kmet et al. (2004), up to three articles from each topic were randomly selected for independent scoring by two reviewers and scores were compared. Criteria where assignment disagreement occurred (e.g., discrepancies between reviewers for "yes" vs. "partial" for a given criterion) were discussed for the assigned article, and criteria definitions were adjusted when needed to ensure consistency in scoring for the remaining articles. The scoring cut-points for article exclusion described in Kmet et al. (2004) were used to determine scoring ranges for weighing independent articles:

Strong: 0.75-1.00

Moderate: 0.56-0.74

Weak: 0.00-0.55

All individual articles for each topic were scored and the number of strong, moderate, and weak analyses was determined for each study outcome within each tier (i.e., longitudinal, cross-sectional, nonclinical). Each score was based on the methodological details for each analysis. The rationale for this approach was to address articles that contained multiple topic areas (e.g., dependence vs. cessation). Therefore, an analysis that addressed two topic areas received two independent scores: one for each topic area. The possible study outcomes were: positive correlation between menthol and the outcome; negative correlation between menthol and the outcome; or no effect of menthol on the outcome. Because weak analyses were considered to contain substantial limitations that reduced validity of the conclusions, only the strong and moderate analyses within each tier for each topic were used to weigh the overall evidence. The overall proportion of study outcomes for each topic was then determined by dividing the number of strong and moderate analyses for each outcome (positive, negative, or no effect) by the total number of analyses for the topic. A qualitative assessment of the strong and moderate analyses was then conducted by subject matter experts in fields relevant to the topic areas and articles included in this review (e.g., pharmacology, epidemiology) to weigh the overall evidence, based on the following areas: 1) the proportion of analyses that supported each outcome within each tier; 2) consistent findings across different tiers (i.e., longitudinal, cross-sectional, nonclinical) and across individual studies (e.g., different methods and study populations); 3) the strengths and weaknesses of individual studies; and 4) analyses with overlap between populations, which could reflect duplicate findings. All analyses were considered to be distinct, unless otherwise indicated.

The conclusions were grouped into five possible statements about the overall quality and strength of the evidence. Criteria for each of the five areas are based on NavGuide systematic review methodology (Woodruff & Sutton, 2011):

- *The weight of evidence supports the conclusion that menthol in cigarettes is associated with x*

    o Positive relationship observed between menthol in cigarettes and the outcome(s) of interest where chance, bias, and confounding can be ruled out with reasonable confidence; positive association has been established through multiple well-designed, well-conducted studies.

- *The weight of evidence supports the conclusion that menthol in cigarettes is likely associated with x*

    o Positive relationship observed between menthol in cigarettes and the outcome(s) of interest where chance, bias, and confounding cannot be ruled out with reasonable confidence; data suggest an effect of menthol, but only in a single study, or there are other important limitations in the quality of the body of evidence as specified.

- *The weight of evidence supports the conclusion that menthol in cigarettes is likely not associated with x*

    o No relationship observed between menthol in cigarettes and the outcome(s) of interest where chance, bias, and confounding cannot be ruled out with reasonable confidence; data suggest no effect of menthol, but only in a single study, or there are other important limitations in the quality of the body of evidence as specified.

- *The weight of evidence supports the conclusion that menthol in cigarettes is not associated with x*

    o More than one study showed no effect on the outcome of interest across multiple types of studies used to assess the outcome(s) of interest, where bias and confounding can be ruled out with reasonable confidence. Lack of an association has been established through multiple well-designed, well-conducted studies.

- *The evidence is not sufficient to support a conclusion of an association of menthol in cigarettes with x*

    o A relationship cannot be determined between menthol and the outcome(s) of interest due to the limited number or size of studies, low quality of individual studies, or inconsistency of findings across individual studies.

To test the reproducibility of the weight of evidence approach, FDA evaluated the science, weighed the evidence, and provided updates to this review at three time points (2016, 2019, and 2021) using the methods discussed. In 2016, an independent reviewer tested the scoring approach by evaluating select articles using the scoring criteria and cut-offs. In 2021, a new reviewer, who had not been involved in the development of the weight of evidence approach or updates to the 2016 and 2019 evaluations, independently screened and reviewed articles based on the inclusion/exclusion criteria to further test the reproducibility of the study selection process.

IX.   STUDY SUMMARIES

All studies meeting inclusion criteria (strong, moderate, and weak) are included in a data extraction table (Appendix E). The extraction table provides basic information about the study population, study outcome measures, and the analysis tier and score. Only strong and moderate analyses identified 1980- April 30, 2021 are summarized in the sections below. Each analysis is summarized based on relevant study outcomes and findings related to menthol and addiction. Weak analyses that were not included in the weight of evidence are summarized in Appendix F.

Throughout this document, FDA uses both the terms "Black" and "African American." Though both of these terms may overlap, they are distinct concepts (e.g., a Black person may not identify as African American). As a result, in this document, FDA relies on the specific term used by researchers when citing to specific studies. FDA uses the term "Black" when not citing to a specific study. Regarding study summaries, FDA is aware that the use of the term "Caucasian" originated as a way of classifying White individuals as a race to be favorably compared to other races. Following CDC guidelines (Centers for Disease Control and Prevention, 2021) and APA guidelines (American Psychological Association, 2021), FDA does not endorse the term "Caucasian" and generally uses the term "White" when describing some people of European origin. However, we use the term "Caucasian" in the RTD if it was used by researchers when citing specific studies.

X. STRENGTH OF EVIDENCE: SENSORY EFFECTS

Studies summarized in this section include at least one of the following measures:

- Qualitative or quantitative assessments of the sensory effects of menthol and relation to reasons for use of menthol cigarettes
- Qualitative or quantitative assessments comparing sensory effects of menthol to non-menthol cigarettes
- Nonclinical studies evaluating the sensory effects of menthol and relation to nicotine or tobacco consumption

A simple summary is provided for each study outcome, presented by measure and whether the article found a positive association, negative association, or no association with menthol.

Background

The sensory effects of menthol in cigarettes produce a cooling sensation when inhaled (Harris, 2006). Menthol has also been shown to have anti-irritant (Ha et al., 2015; Willis et al., 2011), antitussive (Plevkova et al., 2013; Wise et al., 2012), and analgesic properties (Liu et al., 2013). Reviews of tobacco industry documents suggest that these perceived sensory effects reduce the unpleasant attributes of smoking and make cigarettes easier to smoke, particularly for new users (Anderson, 2011; Klausner, 2011; Kreslake, Wayne, & Connolly, 2008; Yerger, 2011). However, assessments of tobacco industry documents are limited in several ways: (1) methodologies, data collection, or internal analyses are often unavailable, which makes evaluating the quality of science difficult; (2) the research spans various time periods, different researchers, companies, and departments, resulting in inconsistent and contradictory findings; and (3) the available documents may not reflect the full scope of internal research for a particular topic (Wayne & Connolly, 2004). Therefore, the following section will review the publicly available literature to evaluate the contribution of menthol's sensory effects to positive cigarette smoking experiences.

Summary of Studies on Sensory Effects

Human Research Studies

Cross-sectional analyses (Tier 2)

Eleven cross-sectional analyses suggest that the sensory effects of menthol are associated with positive subjective cigarette smoking experiences.

Cohn et al. (2019) aimed to examine differences between youth (aged 12-17) and young adult (aged 18-24) smokers (n = 2,319) who initiated smoking with a menthol versus a non-menthol cigarette on the intensity of their pleasant and unpleasant subjective responses to their first cigarette. The study was cross-sectional and used Wave 2 (2014-2015) Population Assessment of Tobacco and Health (PATH) study. In regression analyses, initiation with a menthol (vs. non-menthol) cigarette was associated with a more pleasant first smoking experience, in both crude

and adjusted models (AOR [adjusted odds ratio] = 1.36, confidence interval [CI]: 1.08 - 1.71). After controlling for covariates, ever smokers who initiated with a menthol cigarette were nearly 1.5 times more likely to report a highly pleasant first smoking experience compared to smokers who initiated with a non-menthol cigarette. Initiation with a menthol cigarette was unrelated to the intensity of the unpleasant first smoking experience. The study also found that pleasant initial smoking experience was associated with increased odds of past 30-day smoking, non-cigarette tobacco use, and heavy smoking. The findings from this study suggest that smokers who initiate with a menthol cigarette experience a more pleasant first smoking experience, and pleasant experience is associated with regular smoking and use of non-cigarette tobacco products. (Strong)

In another nationally representative cross-sectional study, Cohn et al. (2019) used Wave 1 (2013-2014) PATH data to evaluate differences in perceived ease of smoking cigarettes among youth (aged 12-17) who smoke menthol vs. non-menthol cigarettes (n = 2,797). In crude and adjusted models, perceived ease of smoking menthol cigarettes did not differ between youth who initiated with a menthol or a non-menthol cigarette. However, compared with past 30-day non-menthol smokers, past 30-day menthol smokers had approximately twice the odds of perceiving menthol cigarettes as easier to smoke than non-menthol cigarettes (AOR = 2.12, 95% CI: 1.44 - 3.10, p = 0.0002). Youth who smoked menthol as their usual brand also were more likely to report that menthol cigarettes are easier to smoke than non-menthol cigarettes. It is noted as limitations to the study that this was a secondary analysis of existing data limited to existing survey items. As such, it was not possible to examine whether menthol smokers report the taste and sensation of menthol cigarettes as being more appealing than non-menthol cigarettes (if a youth has tried both), as this was not asked in the survey. Further, the question about ease of menthol smoking could have different connotations for more versus less experienced smokers, but this was not asked of study respondents. Nonetheless, findings from this study support that youth who smoke menthol cigarettes perceive them as easier to smoke, even after adjusting for other factors. (Strong)

Cohn et al. (2020) also examined differences between 600 adult menthol and non-menthol smokers on subjective response to smoking (i.e., satisfaction, reward, "throat hit", aversion) and the association between measurements of reinforcement and subjective response. All data were collected online. The modified Cigarette Evaluation Questionnaire (mCEQ), a 12-item self-report questionnaire that was used to measure subjective responses to cigarette smoking in four domains: reward, satisfaction, aversion, and throat hit. Results showed that menthol cigarette smoking was independently associated with self-reported subjective reward, satisfaction, and throat hit, after adjusting for covariates. Specifically, compared to non-menthol smokers, menthol smokers reported greater subjective reward (Mean [M] adjusted = 24.00 vs. 22.34), satisfaction (M adjusted = 13.85 vs. 13.01), and pleasurable sensations in the throat or chest ("throat hit") (M adjusted = 3.40 vs. 3.04). Findings from the study suggest that menthol smokers find their cigarettes to be more rewarding and satisfying, and to enhance the physical sensations of smoking compared to non-menthol smokers. (Moderate)

D'Silva et al. (2018) used nationally representative cross-sectional data from the July 2013- July 2015 Truth Initiative Young Adult Cohort to examine differences in subjective experiences to the first use of menthol vs. non-menthol cigarettes. Among young adult cigarette smokers (n = 251, aged 18-34) who reported initiating smoking in the last six months, fewer menthol smokers

reported experiencing nausea at first cigarette use compared to non-menthol smokers (p = 0.002). (Strong)

D'Silva et al. (2021) conducted focus group interviews of adult African American smokers (n = 27) in the St. Paul- Minneapolis area to evaluate perspectives of menthol smoking and the local menthol sales restrictions. When discussing reasons for smoking menthol cigarettes, participants said the overall experience of smoking menthol cigarettes was more pleasurable than smoking non-menthol cigarettes. Smoking non-menthol cigarettes was associated with headaches, choking, burning in the throat and other unpleasant sensory experiences. When discussing reactions to local menthol sales restrictions, most participants stated they would not substitute non-menthol for menthol cigarettes because of their strong taste preference for menthol. (Strong)

Richter et al. (2008) conducted small group discussions with adult African American smokers (n = 54) to understand social influences and marketing issues centered around menthol cigarette use. In general, taste was overwhelmingly offered as a reason for smoking menthol rather than non-menthol cigarettes. One participant stated that "the taste [of a non-menthol cigarette] was never really enjoyable," and switching from a non-menthol cigarette to a menthol cigarette was the reason that smoking became enjoyable. Participants also noted that menthol cigarettes were refreshing, soothing, and smooth, whereas non-menthol cigarettes were "strong" or "harsh." Specifically, some participants stated that non-menthol cigarettes made them cough because they are too strong, gave them headaches, and caused a dry mouth. (Moderate)

Strasser et al. (2013) conducted a study among adult menthol smokers (n = 22) to examine smoking behaviors, BOE, and subjective responses when switching from a menthol cigarette to a non-menthol cigarette. Camel Crush cigarettes were used as experimental cigarettes in the study. Across the 35-day study, participants were instructed to smoke their own brand for five days to establish baseline measures, followed by a 15-day period of smoking the Camel Crush menthol condition, and ending with a 15-day period of smoking the Camel Crush non-menthol condition. Subjective responses were assessed using a 100-mm visual analog scale with descriptive anchors. Participants placed a vertical line to indicate their rating. In general, after controlling for sex, race, and nicotine dependence, participants found the Camel Crush cigarettes to be less satisfying than their own cigarettes. Participants rated the non-menthol Camel Crush as tasting worse (p = 0.0004), leaving a worse aftertaste (p = 0.001), having a less pleasant smoke smell (p = 0.002), and being marginally less mild (p = 0.10) compared to the menthol Camel Crush condition. (Strong)

Wackowski et al. (2018) conducted six focus groups of young adult menthol smokers (n = 45, aged 18-24) in New Jersey to assess perceptions of and experiences with menthol cigarettes. While a major theme across all groups was that menthol cigarette smoking initiation was influenced by social factors (e.g., participants' friends primarily smoked menthol cigarettes, menthol cigarettes were perceived as being popular, and that menthol cigarettes were familiar and accepted in their social and environmental communities), participants reported that the taste, coolness, smell, and relative smoothness of menthol cigarettes (i.e., menthol cigarettes are easier to smoke) compared to non-menthol cigarettes were important factors in their initiation of and preference for menthol cigarettes. Some participants stated that, compared to menthol cigarettes, smoking non-menthol cigarettes felt like "inhaling burning fire" or a cigar. Participants also noted that they were not as satisfied after smoking a non-menthol cigarette and some stated that it was like smoking air. (Strong)

Watson et al. (2017) conducted a menthol cigarette cross-over study with adult cigarette smokers (n = 42) to better understand differences in use behavior and exposure when smoking menthol and non-menthol cigarettes. Menthol cigarette smokers reported that non-menthol test cigarettes were not enjoyable, had an unpleasant aftertaste, unpleasant/worse pack and smoke smell, produced greater throat irritation, worse aftertaste, and worse burning smell compared to the menthol test cigarette. It is noted that non-menthol cigarette smokers similarly rated sensory attributes of the menthol test cigarettes unfavorably. As such, a general effect of differences in brand/cigarette preference between menthol and non-menthol smokers may have contributed to these findings. (Moderate)

Wiseman and McMillan (1998) interviewed adult cocaine-dependent outpatients (n = 43) to explore reasons for combining cocaine and cigarette use and for preferring either menthol or non-menthol cigarettes. Patients who preferred menthol felt that they were addicted to menthol/menthol taste, that regular cigarettes were not strong enough, and that menthol cigarettes were stronger in menthol and nicotine. The taste of menthol cigarettes was described as "refreshing", "minty", and "a sharp sting." Compared to non-menthol cigarettes, menthol cigarettes were described as having "better taste", "more taste", "mild taste", and "not tasting nasty like regular cigarettes" and as having an anesthetizing, less irritating effect, cooling effect, or decongestant effect. Specifically, the anesthetizing, less irritating effect was described in several responses, including "soothing effect on the lungs", "doesn't produce headache like regular cigarettes", "less harsh", "not dry", "not as rough on the throat", and "not as strong". Participants also described menthol compared to non-menthol cigarettes as "feels cooler", "cooling effect", "opens my nasal passages", and "helps my sinuses." Patients who preferred non-menthol cigarettes stated that they did not like the menthol flavor or taste, and they thought menthol cigarettes were too strong, too harsh, hurt their throat, gave them a headache, or gave them a heavy feeling. (Moderate)

Young-Wolff et al. (2015) examined sensory correlates associated with menthol preference and conducted qualitative analyses to analyze themes related to reasons for smoking menthol cigarettes (n = 150), non-menthol cigarettes (n = 202), or both (n = 149) in a sample of adult smokers with mental illness. Compared to non-menthol smokers, menthol smokers had distinct sensory preferences. After adjusting for demographics and psychiatric diagnosis in a bivariate model, menthol users reported greater preference for foods with strong mint flavor (p = 0.02) and for cigarettes that were smooth (p = 0.04), soothing (p = 0.02), clean tasting (p = 0.008), cool the mouth and throat (p < 0.0001), have an icy cool taste (p < 0.0001), have a minty aftertaste (p < 0.0001), and smoke with a pleasant smell (p = 0.046). After multivariate multinomial logistic regression analyses, which included all physical and sensory preferences found to be significant in the bivariate analyses, menthol and non-menthol users differed significantly in preference for cigarettes with a minty aftertaste (p < 0.0001) and cigarettes that cool the mouth and throat (p < 0.0001). Sensory characteristics that significantly differed between menthol and non-menthol smokers in reasons for use included texture (e.g., easier on throat) and tobacco strength (e.g., more full tobacco flavor). (Strong)

Six cross-sectional analyses suggest no significant difference in sensory effects of menthol compared to non-menthol cigarettes

Denlinger-Apte et al. (2019) conducted as study among adolescent (aged 15-19) menthol (n = 28) and non-menthol (n = 22) smokers to examine the effects of cigarette nicotine content and

menthol smoking on health risk perceptions, subjective ratings, and CO boost. The Cigarette Evaluation Scale (CES) was used to measure subjective effects of menthol and non-menthol SPECTRUM cigarettes differing in nicotine content. There were no significant main effects of menthol or interactions between menthol and nicotine content on any subscale measured, aside from craving reduction; in this case, female menthol smokers reported less craving reduction from smoking normal nicotine content cigarettes compared to female non-menthol smokers and male menthol and non-menthol smokers. (Moderate)

DiFranza et al. (2004) conducted a retrospective/prospective longitudinal study of seventh grade youth (aged 12-15) who had ever inhaled a cigarette (n = 237) across two urban schools over 30 months. The goal of the study was to examine whether the reaction to the first smoking experience is predictive of future nicotine dependence and whether the impact of the first cigarette can be altered by manipulation of tar, nicotine, and menthol levels. Subjective ratings of irritation, nausea, dizziness, and relaxation were collected. When comparing the reaction to the first inhaled cigarette, bivariate analyses found no significant differences for irritation, nausea, dizziness, or relaxation between adolescents who recalled the first cigarette smoked to be menthol compared to non-menthol. (Moderate)

Gunawan and Juliano (2020) investigated differences between menthol and non-menthol smokers in smoke exposure, smoking topography, and subjective rewarding and sensory effects of smoking. Adult smokers (n = 100) participated in two laboratory sessions over two days, during which participants smoked and rated their usual brand cigarette via a smoking topography device and under natural smoking conditions. The modified CES was used to evaluate the sensory and subjective properties of smoking (i.e., sensory stimulation, smoking satisfaction, psychological stimulation, psychological relaxation, cigarette strength, aversion, and craving reduction). Menthol smokers marginally endorsed lower ratings of sensory stimulation (i.e., enjoyable sensations in "throat and chest" and "lips and tongue) compared to non-menthol smokers (F $_{(1,93)}$ = 4.07, p = 0.046). There were no other differences based on menthol status. Menthol was also not associated with greater rewarding effects except for greater urge reduction. (Strong)

Jarvik et al. (1994) measured chemical and topographic parameters to evaluate the effect of menthol cigarettes in Black and White male cigarette smokers (n = 20) recruited from from the community and the West Los Angeles Veterans Administration Medical Center. The primary goal of the paper was to evaluate differences in smoking topography between menthol and non-menthol smokers. Subjective ratings of harshness, satisfaction, and post-cigarette urge to smoke were collected and analyzed using analysis of variance. Although significant interactions indicated that satisfaction and post-cigarette craving varied based on race and preference for type of cigarette (menthol vs. non-menthol), ratings of harshness did not differ by type of cigarette. Though the study collected information on subjective effects, the primary purpose of the paper was not to evaluate differences in sensory effects of menthol. The data set consisted of only males, including veterans, and may not be representative of the general population of smokers. (Moderate)

Pickworth et al. (2002) conducted a study among adult menthol (n = 18) and non-menthol (n = 18) smokers to determine how nicotine and menthol interact to influence the physiologic and subjective effects of smoking cigarettes with low or high nicotine yields. The Duke Sensory Questionnaire and the CES were used to evaluate the sensory effects and the cigarettes. All

questions were answered on a scale of 1 to 7, ranging from "not at all" to "extremely." Data were analyzed using a repeated measures analysis of variance. There were no significant differences between any ratings on either questionnaire based on cigarette type (menthol vs. non-menthol). This included questions related to cigarette irritation, peripheral sensation, negative effects, psychological reward, and puff satisfaction. For both low and high yield nicotine cigarettes, perceived strength of the cigarettes in the nose, tongue, mouth, windpipe, and lung also did not significantly differ by cigarette type. The overall trend was that nicotine delivery, but not menthol flavoring, determined subjective ratings of strength. (Strong)

Perkins et al. (2018) assessed the effect of menthol on acute subjective perceptions and subsequent choice behavior of SPECTRUM research cigarettes differing in moderate (16-17 mg/g) or very low (0.4 mg/g) nicotine contents. The study recruited nicotine dependent adult smokers (n = 73) to participate in a three-hour session to smoke the cigarettes. Acute subjective perceptions of sensory effects based on five self-report items, termed the Acute Cigarette Perceptions (ACP) scale: how much "nicotine", "flavor", and "liking", and how "satisfying" and "strong" the cigarette was. Menthol cigarettes significantly differed from non-menthol cigarettes on strength (p = 0.003), where menthol cigarettes (48.0 ± 1.9) were rated as stronger than non-menthol cigarettes (38.5 ± 2.3) on the ACP scale. Menthol did not significantly differ from non-menthol cigarettes in any other subjective measure. There were no significant nicotine x menthol interactions, indicating that perceptions of menthol did not differ by nicotine content. The authors concluded that perceptions of cigarettes varying in menthol per se (or in those preferring menthol vs. non-menthol brands) do not differ when cigarettes are carefully matched on nicotine content and smoking topography. (Moderate)

Nonclinical Research Studies (Tier 3)

Seven nonclinical studies suggest that the sensory effects of menthol reduce irritation and enhance the palatability of nicotine and cigarettes

Bagdas et al. (2020) conducted a study in adult male and female Sprague Dawley rats to determine the effect of menthol on oral nicotine consumption. Animals were given a choice of water or drug solution (i.e., 20 mg/mL nicotine, 1 g/L menthol, or nicotine + menthol) for two weeks. Menthol significantly increased nicotine intake and preference in male rats across most days in the study. Alternatively, while there was a small increase in consumption on some days during the study, overall, menthol did not increase nicotine consumption or preference in female rats. The study also tested the effect of menthol intake alone and found that, in both males and females, menthol intake was significantly increased compared to water intake on some days during the study. Findings support a role for the sensory effects of menthol in mediating nicotine consumption and suggest the effects of menthol on nicotine consumption may be sex specific. (Strong)

In another study, Bagdas et al. (2020) used male and female adult and adolescent C57BL/6J mice to examine the impact of menthol on oral nicotine consumption. Menthol was administered orally using the two-bottle choice paradigm, and systemically (via intraperitoneal [i.p.] injection) to elucidate whether the effects of menthol on oral nicotine consumption were driven by orosensory and/or central mechanisms. Oral menthol (30, 60, and 90 µg/mL) dose-dependently increased oral nicotine intake in adult mice; the highest menthol concentration (210 µg/mL) reduced nicotine consumption. Similarly, menthol administered i.p. (0.1 mg/kg) increased oral

nicotine (60 µg/mL) consumption. Age and sex differences were also observed. In female mice, 30 and 60 µg/mL menthol enhanced nicotine intake in adolescents to a greater extent than in adults. Alternatively, among males, menthol increased nicotine intake in adult mice, but not adolescents. High menthol concentrations (90 and 120 µg/mL) induced significantly lower mentholated nicotine intake compared to nicotine alone in adolescent males. Findings support that menthol increases nicotine consumption in a concentration, age, and sex-dependent manner and suggest a role for sensory, peripheral and/or central mechanisms involved in menthol's ability to enhance nicotine consumption. (Strong)

Fan et al. (2016) used the two-bottle choice test to characterize aversion and preference for menthol in mice. Results showed that menthol (50 µg/ml) significantly reduced aversion to solutions of oral nicotine (200 µg/ml; p <0.01). There was a trend for menthol to reduce aversion at 100 µg/ml nicotine (p = 0.08). Of note, concentrations of menthol above 50 µg/ml (i.e., 100 and 200 µg/ml) produced aversion alone (p < 0.01 and p < 0.0001 for the respective menthol doses). Results suggest that menthol reduces the aversion produced by oral nicotine. (Strong)

Ha et al. (2015) conducted a nonclinical study in female mice to evaluate whether menthol modulates cigarette smoke irritancy and nicotine absorption during initial exposures to cigarettes. Acrolein and cyclohexanone were used as cigarette smoke irritants. Menthol blocked the irritant effects of high doses of acrolein (11 ppm, p < 0.0001) and cyclohexanone (1500 ppm, p < 0.05). Menthol also suppressed the sensory irritation effects caused by cigarette smoke (10 mg/m^3 or higher, p < 0.0001). The authors concluded that menthol is a highly efficacious counterirritant that suppresses chemosensory irritant responses from high doses of individual irritants and cigarette smoke. The counterirritant effects are likely due to stimulation of the TRPM8 receptor (Ha et al., 2015). Because menthol was added directly to the generated smoke, it is unclear how the menthol doses used in the study compare to those found in conventional cigarette smoke. (Strong)

Wang et al. (2014) investigated the effect of oral menthol on intravenous (i.v.) nicotine self-administration in adolescent female rats. The study also sought to determine the mechanism by which menthol promotes tobacco product use. Rats that received an oral menthol cue self-administered more nicotine than rats receiving a saline cue in place of menthol (p < 0.01). WS-23, a cooling compound that acts as an agonist at TRPM8 receptors (similar to menthol) also enhanced nicotine self-administration (p < 0.001). Cold water also served as a cue for enhancing nicotine self-administration (p < 0.05), suggesting that an oral cooling sensation in general supports i.v. nicotine intake. The authors concluded that menthol facilitates the reinforcing effects of nicotine in rats, and the effect is likely attributed to the cooling sensation of menthol. (Strong)

Wickham et al. (2018) used oral and i.v. self-administration paradigms to determine how flavorants influence nicotine self-administration. Results showed that nicotine (50 mg/L and 100 mg/L) produced oral aversion in rats compared to water (p <0.05). In a separate cohort of animals, menthol (0.005%) plus nicotine produced greater oral intake compared to nicotine alone (p < 0.001). Results suggest that menthol can mask the aversive taste of nicotine and increase nicotine consumption. (Strong)

Willis et al. (2011) used plethysmography to investigate the effects of menthol on respiratory sensory irritation in female mice elicited by the smoke irritants acrolein, acetic acid, and cyclohexanone. Mice were challenged with irritants, and respiratory parameters were monitored

by a plethysmograph. The sensory irritation response in mice is characterized by a prolonged pause (i.e., braking) due to glottal closing at the onset of each expiration. The duration of braking was assessed as a measure of sensory irritation. Acrolein (2 ppm) induced marked sensory irritation in mice, which was attenuated by 16 ppm menthol ($p = 0.001$). Similar results were observed with acetic acid (149 ppm, $p = 0.02$) and cyclohexanone (1483 ppm, $p < 0.0005$). The authors cited that the estimated menthol concentration in mentholated cigarette smoke is 8 μM, equivalent to ≈ 200 ppm. Thus, these counterirritant effects of menthol were present at concentrations below or equal to those present in mentholated cigarette smoke. The authors also noted that menthol vapor alone (16 ppm) caused a small but significant elevation in braking duration, suggesting a mild irritation response. (Strong)

Conclusions on Menthol and Sensory Effects

Twenty-four analyses of strong or moderate quality examining differences in sensory effects between menthol and non-menthol cigarettes or evaluating the sensory effects of menthol in animal models were included in the weight of evidence assessment. The analyses were from 24 independent publications that evaluated different smoking populations or groups of animals. We note that a pilot study by Schneller et al. (2020), conducted to determine if different menthol delivery routes lead to changes in sensory attributes, was identified and ultimately excluded from review, given the lack of a clear non-menthol condition (i.e., the authors refer to the conditions as "crushed" or "uncrushed"). All analyses were cross-sectional (Tier 2) or nonclinical (Tier 3). Overall, the majority of analyses (n = 18; 75%found that the sensory effects of menthol reduce the irritation and aversion of cigarette smoke and nicotine, contribute to a positive subjective cigarette smoking experience among smokers compared to non-menthol cigarettes, and increase nicotine consumption in animals. This body of evidence includes six strong and five moderate Tier 2 analyses, which include nationally representative studies and focus groups of menthol smokers describing their experiences with menthol and non-menthol cigarettes, and seven strong Tier 3 analyses that examined oral nicotine intake and responses to cigarette smoke. Alternatively, six Tier 2 analyses (25%) found no difference in perceived sensory effects of menthol and non-menthol cigarettes among smokers; this includes two strong and four moderate Tier 2 analyses. This body of evidence consists primarily of laboratory studies designed to evaluate acute sensory and subjective perceptions of menthol vs. non-menthol cigarettes, including three studies that used cigarettes that differed in nicotine content (Perkins et al., 2018; Pickworth et al., 2002) and one study conducted in a small subset of only male smokers (Jarvik et al., 1994); these factors may have influenced interpretation of the findings in the context of menthol's sensory effects and contribution to the overall smoking experience.

The overall breakdown of strong and moderate articles by tier, outcome, and analysis weight is presented in Figure 1.

Figure 1. Summary of analyses on sensory effects (1980-2021)
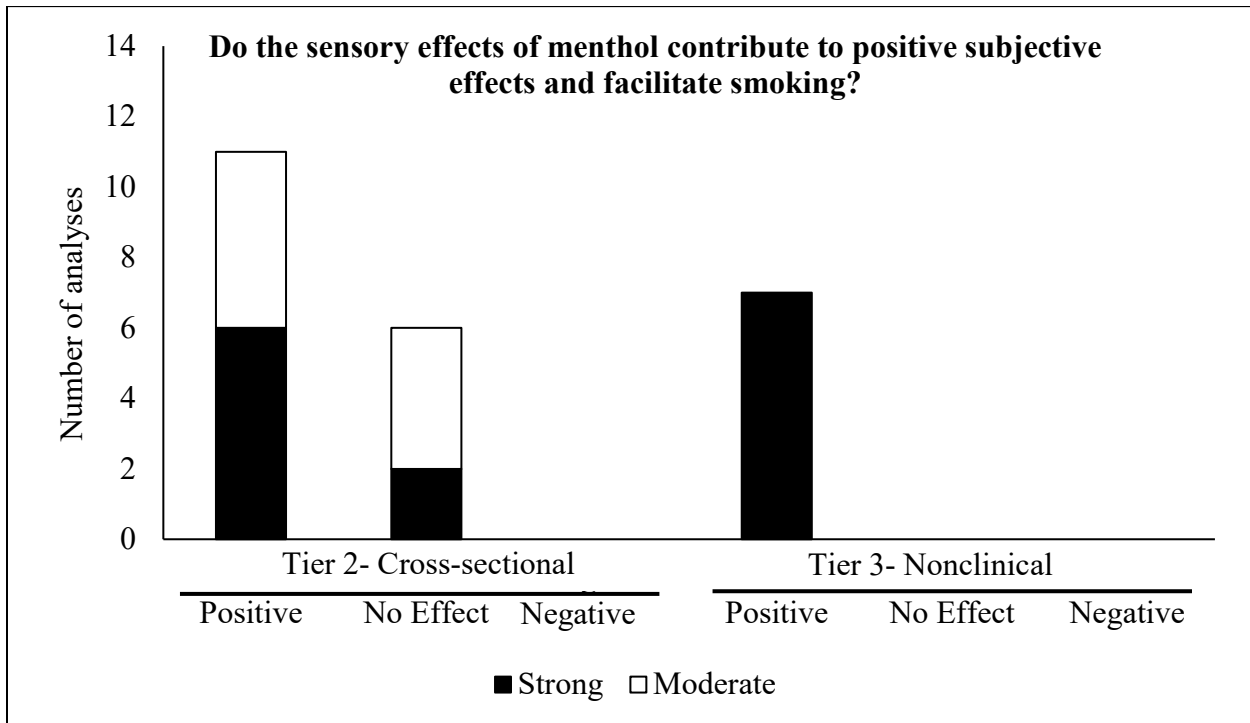
Based on the weight of evidence spanning 1980-2021, **the sensory effects of menthol are associated with positive subjective smoking experiences among menthol cigarette smokers.** The weight of evidence also supports that menthol's sensory effects reduce the harshness and irritation of nicotine and cigarette smoke and facilitate smoking. A positive association is consistent across multiple human and animal studies.

XI. STRENGTH OF EVIDENCE: PROGRESSION TO REGULAR USE

Studies summarized in this section include at least one of the following measures used to evaluate progression to regular cigarette smoking from an addiction perspective:

- Rate and likelihood of smoking escalation among current menthol and non-menthol smokers (e.g., increase in smoking behavior over time)
- Rate and likelihood of progression to regular cigarette use among current menthol and non-menthol smokers (i.e., quantitative comparison of time to regular use comparing menthol and non-menthol users)

A simple summary is presented for each study outcome, presented by measure and whether the article found a positive association, negative association, or no association with menthol. Greater weight was given to longitudinal compared to cross-sectional studies.

Background

This section reviews studies examining the rate and likelihood of progression (e.g., experimentation to established smoking) and escalation (e.g., non-daily to daily smoking) over time in menthol and non-menthol smokers. Longitudinal and nationally representative studies can best capture these transitions and allow for causal conclusions regarding menthol vs. non-menthol effects. Retrospective cross-sectional studies are also included.

The definition of initiation or transition behavior (e.g., first puff, first whole cigarette; regular smoking, daily/non-daily smoking, established smoking) may limit capturing a full trajectory from experimentation to regular or daily smoking. Potential noise in this data, due to recall bias or errors typical of self-report, is expected to be equal across menthol and non-menthol smokers. Data from large, nationally representative, longitudinal studies are not available.

Summary of Studies on Progression to Regular Use

Longitudinal analyses (Tier 1)

Four longitudinal analyses suggest that menthol facilitates smoking progression among youth and young adults

Nonnemaker et al. (2013) analyzed data from a three-wave, longitudinal study of 12 to 17 year old students from 83 middle and high schools (American Legacy Longitudinal Tobacco Use Reduction Study [ALLTURS], 2000-2003) to assess the effect of initiating smoking with menthol cigarettes on the hazard of progressing from non-established to established smoking or to quitting, using a competing-risk survival analysis. Established smoking was defined conservatively as having smoked ≥100 cigarettes and reporting smoking cigarettes on the past 20 of 30 days. The survival analysis included the risk set of 638 adolescents who initiated smoking at wave one or two, were non-established smokers at initiation, and completed all three study waves. In this sample, 32.6% reported initiating smoking with menthol cigarettes, 52.6% quit smoking, 31.9% remained non-established, and 14.9% escalated to established smoking. After controlling for gender, age, and race/ethnicity, the analytical model found a positive and statistically significant association between smoking menthol cigarettes at initiation and

progression to established smoking (OR = 1.80, 95% CI: 1.02-3.16; p < 0.05). The association between initiation with menthol and progression to non-smoking (i.e., from non-established use) was not significant (OR = 1.18, 95% CI: 0.78-1.80). (Strong)

Nonnemaker et al. (2019) analyzed data from a five-wave, nationally representative, longitudinal survey of 11 to 16 year old youth (n = 4,210 completing all waves) to measure the effect of menthol use on smoking progression. Data were collected as part of the Evaluation of Public Education Campaign on Teen Tobacco (ExPECTT) Cohort Study and conducted from 2013 to 2016. The authors used discrete time survival analysis to estimate the effect of prior menthol use on progression from smoking fewer than 100 cigarettes to smoking 100 or more cigarettes and 1) smoking on one or more days in the past 30 days (established, current smoking) and 2) smoking on ≥ 20 of the past 30 days (established, frequent smoking). Adding gender as a covariate strengthened the model significance, suggesting that males are almost twice as likely as females to progress to established, current smoking. Study results found that prior menthol use was significantly associated with progression to established, current smoking (AOR = 1.80, CI: 1.03 – 3.16, p < 0.05). Results were in a similar direction progression to established, frequent smoking, but did not reach significance (AOR = 1.56, CI: 0.80 – 3.03, p < 0.05). Study findings suggest a relationship between menthol cigarettes and progression from experimental to more established smoking among youth. (Strong)

Villanti et al. (2019) analyzed data from the first two waves of the longitudinal, nationally representative PATH study (2013-2015, n's = 11,996 youth and 26,447 adults) to examine the relationship between initiation with flavored tobacco products at Wave 1 and subsequent use at Wave 2, among ever tobacco users. Analyses focused on youth (aged 12-17), young adults (aged 18-24), and adults (aged ≥ 25) to examine current use as well as moderate, frequent, and daily use. Analyses focused on first use of a menthol flavored cigarettes vs. use of non-flavored cigarette (modified Poisson regression models) found that first use of a menthol flavored cigarette was associated with past 12-month and past 30-day cigarette use in all age groups. For youth, menthol/mint cigarette use at Wave 1 was associated with past 12-month use (adjusted prevalence ratio [APR] = 1.18, CI: 1.08 - 1.29) and past 30-day use (APR = 1.19, CI: 1.04 - 1.37, p < 0.05). For young adults, menthol cigarette use at Wave 1 was associated with past 12-month use (APR = 1.10, CI: 1.05 - 1.16, p < 0.05) and past 30-day use (APR = 1.15, CI: 1.07 - 1.23, p < 0.05). For adults, menthol cigarette use at Wave 1 was associated with past 12-month use (APR = 1.13, CI: 1.08 - 1.18, p < 0.05) and past 30-day use (APR = 1.12, CI: 1.07 - 1.17, p < 0.05). Furthermore, multivariate multinomial logistic regression models found that first use of a menthol flavored cigarette at Wave 1 was associated with progression to daily cigarette use at Wave 2 in all age groups (youth: Relative Risk Ratio [RRR] = 1.88, CI: 1.28 - 2.82, p < 0.05; young adults: RRR = 1.66, CI: 1.33 - 2.06, p < 0.05; adults RRR = 1.32, CI: 1.20 - 1.45, p < 0.05). These results suggest initiation of menthol cigarette is associated with higher risk of subsequent, daily smoking among all age groups than initiation with a non-flavored cigarette. (Strong)

Villanti et al. (2021) analyzed data from the first four waves of the longitudinal, nationally representative PATH study (2013-2017; n's = 10,086 youth and 21,281 adults) to examine the relationship between initiation with menthol cigarettes at Wave 2 or 3 and subsequent tobacco use at the next wave. Analyses focused on youth (aged 12-17), young adults (aged 18-24), and adults (aged ≥ 25) to examine past year and past month use as well as frequent, daily, and current regular use. The authors used modified Poisson regression models and bivariate analyses to

measure the association between first menthol use and current tobacco use. Among young adults, first use of a menthol cigarette was associated with past 12-month use of cigarettes at the subsequent wave (APR = 1.43, CI: 1.05 - 1.93, p < 0.05); the magnitude of the relationship was similar for past 30-day use but did not reach significance. There were no significant relationships between first use of a menthol cigarettes (vs. non-menthol) and subsequent use among youth and older adults. Although the direction of the findings is the same (i.e., positive association between initiation with menthol cigarettes and subsequent tobacco use) as the previous study looking at only two PATH waves, the lack of significance may be explained by sample size limitations. Specifically, restricting the analysis to new cigarette use at Wave 2 or 3 (not their first use of a product years ago) resulted in low sample size, particularly for adults aged 25+ where new use of cigarettes is rare. (Strong)

Cross-sectional analyses (Tier 2)

Two cross-sectional analyses suggest that menthol facilitates smoking progression among youth and young adults

Cohn and D'Silva (2019) examined the relationship between initiation with menthol vs. non-menthol cigarettes and subjective response the first smoking experience (pleasant vs. unpleasant sensations) and current use behaviors (past 30-day cigarette and other tobacco product use and past 30-day heavy smoking of > 10 [cigarettes per day] CPD) using data from Wave 2 of the PATH study (2014-2015). Analyses were conducted in youth (aged 12-17) and young adult (age 18-24 years) ever-smokers (n = 2,319). In this cross-sectional study, adjusted multivariable logistic regression models found that initiation with a menthol (vs. non-menthol) cigarette was associated with increased odds of past 30-day smoking (AOR = 1.36, CI: 1.10 - 1.68, p < 0.05) and non-cigarette tobacco use (AOR = 1.52, CI: 1.20 - 1.92, p < 0.05). These findings support that menthol plays a role in progression to subsequent, current smoking among youth and young adults, with sensory effects acting as part of the driving mechanism of progression. (Strong)

Delnevo et al. (2016) analyzed data from the cross-sectional, nationally representative National Young Adult Health Survey (NYAHS, 2011) to assess changes in smoking behavior over one year. In a sample of 909 established ever-smokers (39% menthol smokers) aged 18-34, approximately one quarter changed their smoking behavior. In the previous year, 13.0% reported increases in smoking behavior: 5% increased from some day to daily smoking, 8.0% increased from not at all to current smoking (i.e., relapse or re-initiation). Using multivariate logistic regression, menthol cigarette smoking, in contrast to non-menthol smoking, was associated with increased smoking behavior (AOR = 1.87, 95% CI: 1.06-3.30; p < 0.05) after adjusting for age, gender and race/ethnicity. Progression of smoking in non-established or never-smokers was not evaluated. Moreover, although 14% reported decreased smoking behavior (8.2% quit smoking, 5.8% reported smoking on fewer days), regression analysis was not conducted. (Strong)

Conclusions on Menthol and Progression to Regular Use

Six analyses of strong quality evaluated the contribution of menthol to smoking progression and more frequent smoking compared to non-menthol smokers. The analyses were from six independent publications. All studies conclude that, compared to non-menthol, menthol cigarettes are associated with progression to regular smoking among youth and young adults. Three studies relied on PATH study data (Waves 1-3) and found that initiation with menthol

cigarettes is associated with progression to subsequent, current smoking among youth and young adults compared to initiation with non-menthol cigarettes. One of the studies found an increased risk for subsequent daily smoking among menthol initiators of all age groups compared to initiation with non-menthol cigarettes (Villanti et al., 2019). Although Villanti et al. (2021) did not find these effects among youth, the study is limited by small sample size and low power due to restricting analysis to participants with new cigarette use at Wave 2 or 3 only; the direction of the findings matched the other two studies, identifying a relationship between menthol initiation and progression to regular use. In a separate sample of youth (ExPECTT cohort), Nonnemaker et al. (2019) found a relationship between menthol cigarettes and progression from experimental to established, current smoking. Cohn and D'Silva (2019) suggest that menthol's sensory effects may contribute to the mechanism driving progression. They also found that menthol initiators were more likely to use non-cigarette tobacco products compared to non-menthol initiators, which may reflect greater nicotine dependence. The overall breakdown of strong and moderate articles by tier, outcome, and analysis weight is presented in Figure 2.

Figure 2. Summary of analyses on progression to regular use (1980-2021)
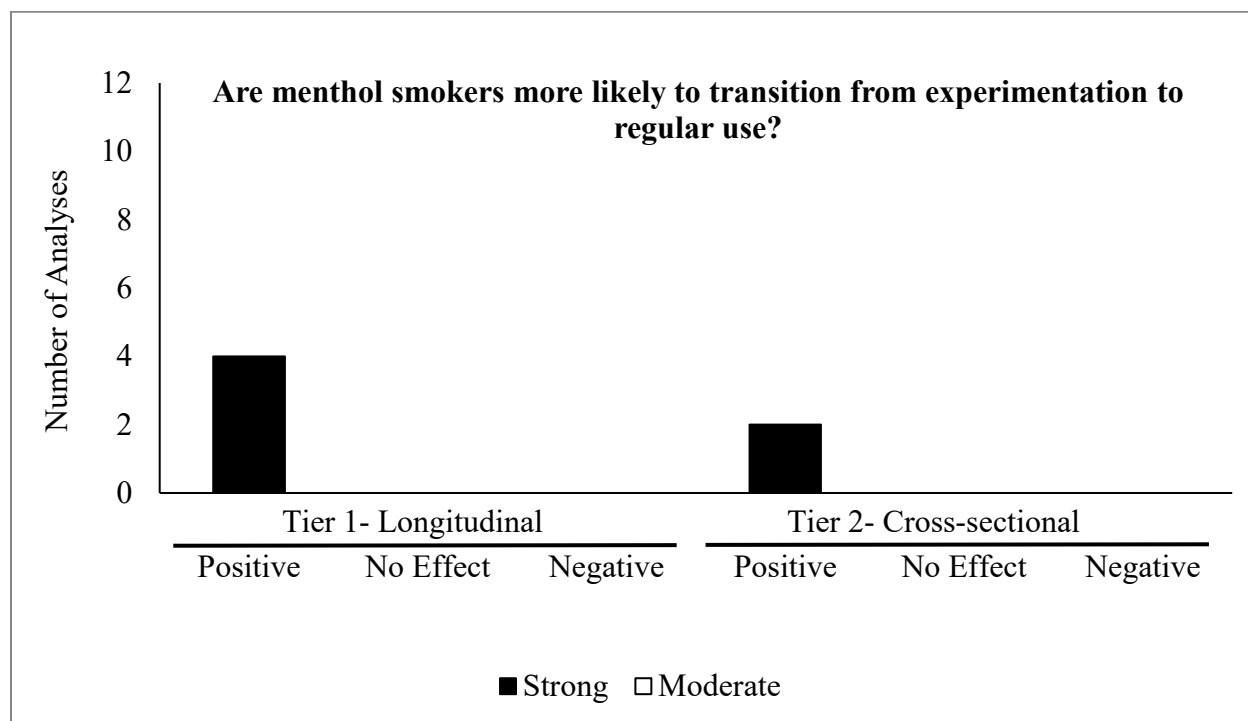
Based on the weight of the evidence spanning 1980-2021, **menthol in cigarettes is associated with progression to regular cigarette smoking among youth and young adults**. This conclusion is supported by multiple, strong, longitudinal, and nationally representative studies of tobacco use among youth and young adults.

XII.   STRENGTH OF EVIDENCE: DEPENDENCE

Studies summarized in this section include at least one of the following measures used evaluate dependence:

- Primary scales used to evaluate nicotine dependence (e.g., FTND, NDSS, HSI)
- Proxies/single-item measures of nicotine dependence (e.g., CPD, TTFC, craving, night waking to smoke, smoking frequency)
- Nicotine BOE or pharmacokinetics
- Nonclinical studies of menthol's behavioral effects related to abuse liability or nicotine pharmacokinetics

A simple summary is provided for each study outcome (presented by measure and whether the article found a positive association, negative association, or no association with menthol.) For dependence, study-specific criteria used to determine weight of evidence included greater weight given to studies of established/validated scales of dependence (e.g., FTND, HSI, Nicotine Dependence Syndrome Scale [NDSS]) vs. proxies of nicotine dependence (e.g., CPD, TTFC).

Background

Nicotine dependence is generally evaluated by self-report questionnaires. The major weaknesses of these questionnaires include potential misunderstanding of the questions, social desirability, and the level of physical and mental capacity required to complete self-report assessments (Jorayeva, 2015). Despite these limitations, their theoretical relationship to the concept of dependence, low cost, and statistical appropriateness make these questionnaires useful tools in the assessment of nicotine dependence (Jorayeva, 2015). Examples of the most commonly-used self-report questionnaires for nicotine dependence include the FTND, Fagerström Tolerance Questionnaire (FTQ), HSI, Cigarette Dependence Scale (CDS), NDSS, Hooked on Nicotine Checklist (HONC), Wisconsin Inventory of Smoking Dependence Motives (WISDM), and the Autonomy Over Smoking Scale (AUTOS). Strengths and weaknesses of these individual scales are discussed in various reviews (Colby, Tiffany, Shiffman, & Niaura, 2000; Jorayeva, 2015; Sato, 2012).

Nicotine dependence has also been evaluated using single item measures, including night waking to smoke (Bover, Foulds, Steinberg, Richardson, & Marcella, 2008), TTFC (Baker et al., 2007), and CPD (Donny, Griffin, Shiffman, & Sayette, 2008). These items, which have been correlated with nicotine dependence scales and behaviors (e.g., relapse, cessation success), can be particularly useful in reducing participant burden associated with long questionnaires. While these measures have been shown to have varying degrees of reliability in measuring nicotine dependence, use of a single item limits the ability to measure the complex and broad construct of nicotine dependence; can create confusion when making inferences about nicotine dependence across studies, as different proxies measure different aspects of dependence; and may reflect extraneous influences (Colby et al., 2000; Jorayeva, 2015).

Animal models of nicotine dependence and abuse liability are also routinely used to elucidate the neurobiological mechanisms that mediate the behavioral effects of nicotine (Cohen & George, 2013). These models include, but are not limited to, conditioned place preference (CPP), dependence induction, self-administration, and choice behaviors. In studies, nicotine is

commonly administered through subcutaneous (s.c.), intraperitoneal (i.p.), oral, or i.v. routes of administration or through exposure to cigarette smoke and nicotine-containing aerosol.

Nicotine is the primary addictive chemical in tobacco, and therefore nicotine BOE can also be used to assess nicotine dependence (Jung et al., 2012; Van Overmeire et al., 2016), with greater nicotine exposure indicating smokers who have greater nicotine dependence. Nicotine exposure parameters, including nicotine C_{max} and AUC[5], total nicotine equivalents (the sum of several nicotine metabolites), and mouth level exposure (MLE), may therefore serve as indirect measures of nicotine dependence. Furthermore, nicotine pharmacokinetics may serve as an indirect measure of nicotine dependence. For example, individuals with greater nicotine metabolite ratios (defined as the ratio of 3-hydroxycotinine/cotinine concentration) may also have greater nicotine dependence (Schnoll et al., 2014) due to the rapidity of nicotine metabolism and the desire maintain adequate nicotine concentrations through self-titration (Ross, Dempsey, St Helen, Delucchi, & Benowitz, 2016). Furthermore, the rate of nicotine absorption impacts the abuse liability of a tobacco product (Henningfield & Keenan, 1993). Therefore, nicotine metabolism, nicotine metabolite ratios, and nicotine absorption may also serve as indirect measures of nicotine dependence.

This section reviews studies examining the impact of menthol in cigarettes using nicotine dependence scales, single-item measures of nicotine dependence, nicotine exposure and nicotine pharmacokinetics as well as animal models of nicotine exposure and dependence.

Nicotine BOE and pharmacokinetics are included here as indirect measures of nicotine dependence, but, as previously stated, these indices are not traditional direct measures of dependence. Furthermore, nicotine concentrations are highly dependent upon when a participant last smoked a cigarette due to nicotine's short half-life ($t_{1/2}$), and therefore interpretations of nicotine concentrations may be limited. Hormone levels (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006) and some medications can interfere with nicotine pharmacology, confounding interpretations.

For instances where one article evaluated several different measures of dependence (e.g., FTND, TTFC, nicotine BOE), each outcome was counted as a separate analysis. Therefore, one article could have several different analyses. Of note, individual weight of evidence scores were calculated separately for behavioral dependence measures (e.g., CPD, FTND) and nicotine BOE/pharmacokinetic analyses. For studies that included both types of analyses, the score presented in the extraction tables in Appendix E represents both behavioral dependence measures and BOE, unless these analyses were in separate tiers or received separate scores in an article. This may have occurred when the main objective of the study was BOE, but other dependence measures (e.g., CPD, TTFC) were presented as background demographic information that may not have controlled for additional factors. The summary of findings below considers each analysis independently.

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[5] Refers to the maximum serum concentration that a drug achieves after dosing (C_{max}) and the total drug exposure over time (area under the curve, AUC)

Summary of Adult Findings

Longitudinal analyses (Tier 1)

One longitudinal analysis found no significant difference in scores on nicotine dependence scales between menthol and non-menthol cigarette smokers

Schneller et al. (2020a) used data from 8,292 current adult cigarette smokers who completed both Wave 1 and Wave 2 PATH surveys (2013-2015) to examine associations between delivery method of menthol and various outcomes, including nicotine dependence via the HSI. Menthol delivery method was categorized into four groups: non-menthol, menthol in tobacco only, menthol using a crushable capsule in the cigarette's filter only, and menthol in both the tobacco and crushable filter capsule. Dependence using the HSI was assessed at Wave 1 and Wave 2. After adjusting for factors, regression models and pairwise comparisons did not show a significant association between non-menthol or any menthol delivery method at Wave 1 and HSI (dependence) at Wave 2. (Strong)

Cross-sectional analyses (Tier 2)

Scales of Nicotine Dependence *Four cross-sectional analyses indicate higher scores on scales of nicotine dependence in menthol compared to non-menthol cigarette smokers*

Curtin et al. (2014b) conducted cross-sectional secondary analyses of data from the 2000-2009 NSDUH survey, which evaluated HSI in menthol and non-menthol smokers. Although unadjusted and adjusted analyses were reported in the original study, here, only analyses adjusted for demographic variables are considered in the weight of evidence and used to formulate conclusions. Secondary analyses of data from NSDUH, after controlling for demographic variables, indicated that past-month menthol smokers had statistically greater odds ($p = 0.003$) of being in a higher HSI category compared to non-menthol smokers. Study strengths included evaluating multiple large, nationally representative surveys, and controlling for baseline demographic differences. Weaknesses included not providing sample sizes and no rationale on how missing data were handled. (Moderate)

Gunawan and Juliano (2020) investigated differences between menthol and non-menthol smokers in smoke exposure, smoking topography, and subjective rewarding and sensory effects of smoking. Dependence outcomes were collected at baseline for African American ($n = 27$ menthol; $n = 17$ non-menthol) and White ($n = 27$ menthol; $n = 29$ non-menthol) smokers. There was a significant main effect of menthol for FTND; menthol smokers had significantly higher FTND scores compared to non-menthol smokers ($p < 0.05$). (Moderate)

Perkins et al. (2017) conducted a study among adult smokers ($n = 40$ menthol, $n = 40$ non-menthol) to examine the threshold dose for behavioral discrimination of cigarette nicotine content using SPECTRUM research cigarettes differing in nicotine content. Baseline demographic data were collected from menthol and non-menthol smokers. FTND scores were significantly higher in menthol compared to non-menthol smokers ($p < 0.005$). (Moderate)

Smith et al. (2014) assessed the relationship between menthol cigarette use and measures of cessation success in a large comparative effectiveness trial of adult menthol ($n = 648$) and non-menthol ($n = 847$) smokers in the Wisconsin Smokers Health Study. Baseline differences in

socio-demographic and smoking-related variables were examined as a function of menthol smoking status using t-tests and chi-square tests. T-tests indicated that menthol smokers had significantly higher mean FTND scores compared to non-menthol smokers ($p = 0.0357$). (Moderate)

Four analyses indicate lower scores on scales of nicotine dependence in menthol compared to non-menthol cigarette smokers

Curtin et al. (2014b) conducted secondary analyses of 2003, 2006/07 TUS-CPS data adult from menthol and non-menthol smokers. Results indicated that regular (OR = 0.89, 95% CI: 0.86-0.92; $p < 0.001$), daily (OR = 0.90, 95% CI: 0.87-0.93; $p < 0.0001$), and past-month (OR = 0.91, 95% CI: 0.88-0.93; $p < 0.001$) menthol smokers had higher odds of being in a lower HSI category compared to non-menthol smokers, indicating lower levels of dependence. Sample sizes were not reported. (Moderate)

Reitzel et al. (2013) conducted a study to examine associations of menthol cigarette use with motivation and confidence to quit smoking among adult smokers in Houston, Texas enrolled in a lung cancer case-control study (n = 313 menthol, n = 754 non-menthol). Preliminary analyses using t-tests to evaluate differences in participant characteristics found that non-menthol smokers had significantly higher HSI scores than menthol smokers ($p = 0.01$). (Moderate)

Schauer et al. (2018) examined demographic and characteristics of marijuana co-use among menthol and non-menthol past month cigarette smokers (ages 12 and older) in the NSDUH between 2013 and 2014. Among participants who report no past month marijuana use, the findings suggest a higher percentage of non-menthol smokers [n = 8509; 61.72 (60.03, 63.38)] have symptoms of nicotine dependence (based on the FTND and NDSS) compared to menthol smokers [n = 5942; 57.44 (55.59, 59.27)]. Results were reported in the text as no difference across nicotine dependence; however, the focus of the study was co-use of marijuana and menthol cigarette use. Thus, statistical analyses may not have specifically examined differences between menthol and non-menthol smokers independently of marijuana use. Data also combined youth, young adults, and adults into one examination of the outcome of interest, which may have confounded results. (Moderate)

Veldheer et al. (2018) examined the acceptability of SPECTRUM research cigarettes in trials of reduced nicotine content cigarette using menthol (n = 200) and non-menthol (n = 141) smokers. Baseline demographic data were reported. Menthol smokers scored significantly lower on the FTND compared to non-menthol smokers ($p = 0.03$). (Moderate)

Twenty-eight analyses found no significant difference in scores on nicotine dependence scales between menthol and non-menthol cigarette smokers

Allen and Unger (2007) conducted a cross-sectional study to examine variables associated with menthol (n = 296) vs. non-menthol (n = 136) use in African American smokers. Bivariate logistic regression analyses, stratified by gender and adjusted for age and employment status, were conducted to determine factors correlated with menthol smoking (vs. non-menthol smoking). FTND scores were not more predictive of menthol smoking in women or men compared to non-menthol smoking. (Moderate)

Benowitz et al. (2010) conducted a study to measure menthol concentrations in relation to BOE to nicotine in adult menthol (n = 60) and non-menthol (n = 67) smokers. Baseline demographic

information collected for FTND scores found no significant difference in average score between menthol and regular cigarette smokers. (Moderate)

Brunette et al. (2018) conducted a study to assess the impact of menthol use among daily young adult (n = 81; aged 18-30) smokers who were in outpatient treatment for severe mental illness. Demographic data were collected from participants, including FTND scores and CPD. Menthol use was not correlated with nicotine dependence based on FTND scores. (Moderate)

Curtin et al. (2014b) conducted an 1999-2010 NHANES study analysis of regular (i.e., smoked ≥10 CPD during the past month), daily (i.e., smoked every day during the past month), and past-month (i.e., smoked ≥1 days during the past month) smokers that found no significant difference in HSI category distributions between menthol and non-menthol smokers. Similar results were found for in 2000- 2009 NSDUH data analyses comparing regular and daily menthol smokers to non-menthol smokers. (Moderate)

Davis et al. (2019) conducted a study among adult smokers with comorbid mental illness, substance use disorder, or socioeconomic disadvantage (n = 61 menthol, n = 108 non-menthol) to investigate response to reduced nicotine content cigarettes. Baseline demographic and smoking characteristics indicated no significant difference in FTND scores between menthol and non-menthol smokers. (Moderate)

Denlinger-Apte (2016) conducted a study among non-treatment seeking menthol (n = 346) and non-menthol (n = 406) adult smokers to examine the effects of very low nicotine cigarettes on smoking behavior and BOE for 20 weeks. Baseline characteristics were collected. There was no significant difference in FTND score between menthol and non-menthol smokers. (Moderate)

DeVito et al. (2016) conducted a study in adult menthol (n = 110) and non-menthol (n = 24) smokers comparing responses to i.v. nicotine administration on a range of outcomes including withdrawal severity, cognitive performance, and physiological and self-report of drug effects following overnight abstinence. Analysis of baseline differences between menthol and non-menthol smokers revealed no significant difference in FTND scores by cigarette type. Sex and race did not contribute to the pattern of significance for menthol or menthol-by-time point (before vs. after i.v. nicotine administration) and were not included the model for analyses of MNWS total score to assess measures of withdrawal. The study found that menthol-preferring smokers exhibited a trend towards lower withdrawal symptoms compared to non-menthol smokers (p = 0.093), but there were no significant menthol-by-time point interactions for this measure. (Strong)

Fagan et al. (2015) conducted a study among White, Filipino, and Native Hawaiian young adults (age 18-35) to compare findings of nicotine dependence among daily menthol (n = 127) and non-menthol (n = 59) smokers using the FTND, NDSS, and the brief WISDM. Multiple regression was used (ANCOVA) to estimate differences between menthol and non-menthol smokers, controlling for gender, race/ethnicity, body mass index (BMI), marital status, education, employment status, number of quit attempts, and current use of alcohol and marijuana. Adjusted analyses found no significant difference in total scores for FTND, NDSS, or the brief WISDM scale between menthol and non-menthol smokers. (Strong)

Faseru et al. (2011) examined demographic, psychological, and smoking factors associated with menthol smoking in African American light smokers (n = 452 menthol; n = 88) who were enrolled in a randomized controlled trial for smoking cessation. Bivariate analyses were

conducted to explore the relationship between variables. The study found no significant difference in mean FTND or MNWS score (p = 0.093) between menthol and non-menthol smokers. (Moderate)

Frost-Pineda et al. (2014) used the Tobacco Exposure Study (TES) data of adult smokers (n = 1,044 menthol; n = 2,297 non-menthol) to examine the relationship between menthol smoking status and nicotine dependence using FTND and HSI scores. The authors used logistic regression models, and analyses were adjusted for age, gender, race, education level, annual income, and machine-measured tar yield category. Individual FTND categories and race by menthol status interactions were also analyzed. Menthol cigarette smoking did not increase the odds of having higher FTND scores. There was no significant increase in odds of menthol use for any individual FTND question, including TTFC and CPD. Race by menthol status interaction did not indicate that menthol smoking status affects FTND scores differently in African American and White smokers. Similarly, no significant effect of menthol on HSI scores was observed. (Strong)

Hooper et al. (2011) conducted a secondary analysis of data from current smokers (n = 876 menthol, n = 2,520 non-menthol) in the Florida Behavioral Risk Factor Surveillance System and a follow-up survey (conducted two weeks to three months after the initial survey). The study aimed to examine associations between preference for menthol cigarettes and subjective physical and mental health. Nicotine dependence was assessed using six items from the NDSS: "You have trouble going more than a few hours without smoking"; "Even in a bad rainstorm, if you ran out of cigarettes, you would probably go to the store to get some more"; "When you go without smoking for a few hours, you experience craving"; "If you were in a public place where smoking isn't allowed, you'd probably go outside to smoke a cigarette, even in cold or rainy weather"; "How long before you go to bed do you have your last cigarette?"; and "How soon after you wake up do you have your first cigarette?" Univariate analyses found that menthol smokers reported greater dependence compared to non-menthol smokers (p = 0.005). After controlling for potentially confounding variables, multivariate logistic regression analyses found that odds of menthol smoking were not related to nicotine dependence. Analyses were based on unweighted data. (Moderate)

Hsu et al. (2017a) conducted a laboratory study using 105 daily smokers to evaluate the impact of menthol in cigarettes on metabolic pathways and smoking behavior. Participant characteristics were collected and differences in FTND score were assessed between menthol and non-menthol smokers. There was no significant difference in FTND score between menthol and non-menthol smokers in this study. (Moderate)

Jao et al. (2017) evaluated whether cigarette type (menthol or non-menthol) modified the association between nicotine metabolite ratio (NMR) and smoking abstinence among 474 cigarette smokers. Fast and slow nicotine metabolizers were recruited. Baseline characteristics indicate no significant difference in HSI score between menthol and non-menthol smokers. (Moderate)

Jarvik et al. (1994) evaluated differences in topography between Black and White menthol (n = 10) and non-menthol (n = 10) smokers recruited from the community and the West Los Angeles Veterans Administration Medical Center. Dependence measures (FTND scores, Stanford dependence scores) were assessed at baseline for all participants. Findings indicated no significant main effects of cigarette type on either dependence measure. (Moderate)

Kosiba et al. (2019) examined the relationship between menthol cigarette use and pain reporting among a sample of African American menthol (n = 90) and non-menthol (n = 25) smokers. Cigarette dependence was measured using the HSI. The study found that both menthol and non-menthol smokers in the study exhibited a moderate level of cigarette dependence; there were no significant differences between groups. (Moderate)

Miller et al. (1994) conducted a laboratory study to measure smoking topography and carbon monoxide exposure among African American male smokers (n = 6 menthol; n = 6 non-menthol) in a drug and alcohol treatment program. Demographic information was collected prior to examining differences in smoking topography for cigarettes injected with 0, 4 mg, or 8 mg menthol. Based on descriptive statistics, the study found no significant difference in FTND scores between menthol and non-menthol smokers. (Moderate)

Murray et al. (2007) examined baseline characteristics of smokers with early evidence of obstructive lung impairment (n = 1,216 menthol; n = 1,671 non-menthol) from the Lung Health Study enrolled in a clinical trial of smoking cessation and ipratropium in the prevention of chronic obstructive pulmonary disease. FTND score was based on three questions from the original 1978 FTQ: smoking when ill, smoking during the night, and finding it difficult to refrain from smoking. There was no significant difference in partial FTND score between non-menthol and menthol smokers. The study adjusted for gender and randomization group (smoking cessation intervention vs. no intervention). Results may be limited by the fact that the study only asked three questions from an outdated version of the FTND to assess dependence. (Moderate)

Muscat et al. (2009) conducted a community-based study among Black and White menthol (n = 255-270) and non-menthol (n = 226-230) smokers to measure the effects of menthol on tobacco smoke exposure, nicotine dependence, and NNAL glucuronidation. For dependence, the study evaluated the association between high FTND scores and menthol status. After adjusting for race, age, sex, and education, there was no significant association between high FTND scores and use of menthol cigarettes. (Strong)

Okuyemi et al. (2003) collected baseline demographic data on smoking characteristics in a sample of African American individuals enrolled in a randomized smoking cessation trial for bupropion (n = 471 menthol; n = 129 non-menthol). Chi square and two-sample t-tests were used to assess baseline variables. There was no significant difference in the mean FTND score between menthol and non-menthol smokers. (Moderate)

In another study, Okuyemi et al. (2007) evaluated the relationship between menthol cigarettes and smoking cessation among African American light smokers (i.e., ≤ 10 CPD; n = 615 menthol, n = 138 non-menthol), analysis of baseline smoking characteristics data found no significant difference in mean NDSS score or MNWS score between menthol and non-menthol smokers. (Moderate)

Reitzel et al. (2013) analyzed short-term cessation rates among menthol (n = 83) and non-menthol (n = 100) smokers and reported participant characteristics by menthol status, including HSI score. Although White menthol smokers had higher HSI scores than White non-menthol smokers, this difference was not statistically significant. In the overall sample, there was no significant difference in HSI score between menthol and non-menthol smokers. (Moderate)

Rojewski et al. (2014) conducted a study among weight-concerned menthol (n = 61) and non-menthol (n = 105) smokers seeking treatment for smoking cessation. Participant characteristics

were collected in a study designed to examine smoking cessation and post-cessation weight gain in weight-concerned smokers. Assessments of FTND in menthol and non-menthol smokers indicated no significant difference between mean scores. (Moderate)

Tanner et al. (2020) conducted an analysis of secondary data from 14,123 current and former menthol (n = 3210) and non-menthol (n = 10,888) smokers in the National Lung Screening Trial to assess the association between cigarette type and nicotine dependence. Adjusted analyses found no significant difference in FTND scores between menthol and non-menthol smokers. (Strong)

In the same study, Tanner et al. (2020) also used HSI to evaluate dependence. Adjusted analyses also found no significant difference in HSI scores between menthol and non-menthol smokers. (Strong)

Veldheer et al. (2018) conducted a study on SPECTRUM research cigarette acceptability among menthol (n = 200) and non-menthol (n = 141) smokers. Baseline characteristics for the HONC and Penn State Cigarette Dependence Index (PSDCI) were collected. The study found no significant difference in dependence between menthol and non-menthol smokers based on either scale. (Moderate)

Watson et al. (2017) conducted a study among 42 participants to examine use behavior and exposure when smoking menthol and non-menthol cigarettes. HSI was calculated at baseline using the sum of CPD and TTFC measures collected. The authors reported percentages of menthol and non-menthol smokers across low, moderate, and high levels of dependence. The distribution of menthol and non-menthol smokers across the three dependence levels was comparable, though twice the percentage of menthol smokers (12%) reported low levels of percentage compared to non-menthol smokers (6%). (Moderate)

Winhusen et al. (2013) conducted a study in cocaine-dependent (n = 201 menthol, n = 100 non-menthol) and methamphetamine-dependent (n = 33 menthol, n = 176 non-menthol)smokers to evaluate the effect of menthol cigarettes on dependence of these stimulants. Baseline demographic and cigarette smoking characteristics were collected, but analyses did not control for confounding variables. FTND score did not significantly differ between cocaine- or methamphetamine-dependent menthol and non-menthol smokers. (Moderate)

Zuo et al. (2015) conducted a study among male and female menthol (n = 10) and non-menthol (n = 9) smokers to evaluate whether menthol increased the rate of brain nicotine accumulation during smoking. Baseline smoking characteristics analyzed via t-test found no significant difference in FTND score between menthol and non-menthol smokers. (Moderate)

Time to First Cigarette (TTFC)

Fourteen analyses and one meta-analysis found that menthol cigarette smoking was associated with a shorter TTFC compared to non-menthol cigarette smoking

Ahijevych and Parlsey (1999) recruited Black and White female smokers (n = 49 menthol; n = 46 non-menthol) to identify differences in smoke constituent exposure by ethnicity and menthol preference. Menthol smokers had a significantly shorter TTFC compared to non-menthol smokers (19.0 vs. 37.4 min, p = 0.02). The authors note previous studies, which reported that

Black women were more likely than White women to smoke within 10 minutes of waking and indicate that menthol cigarettes were used by a higher percentage of Black women than White women in their study; however, it is unclear whether the study independently controlled for effects of race in the TTFC measure. (Moderate)

Ahijevych and Ford (2010) used secondary data from the TUS-CPS (2006-2007) to examine associations between menthol brand preference and smoking behaviors of young adult (aged 18-24) daily (n = 2241) and non-daily (n = 688; defined as smoking 1-29 of the last 30 days) smokers. Multivariate analyses revealed that among non-daily smokers, menthol smokers were significantly more likely to smoke within 30 minutes of waking compared to non-menthol smokers (p < 0.05). Although non-daily smokers who lived in states with clean air laws were also more likely to smoke within 30 minutes of waking than those who lived in states with less strict laws, there were no significant cross-level interactions found for state tobacco control policies and associations between menthol brand preferences and TTFC. (Strong)

Curtin et al. (2014b) evaluated TTFC using 2000-2009 NSDUH data. After controlling for demographic variables, secondary analyses of NSDUH data indicate that adult regular (i.e., smoked ≥ 10 CPD during the past month; p < 0.001), daily (i.e., smoked every day during the past month; p = 0.002), and past-month (i.e., smoked ≥1 days during the past month; p = 0.04) menthol smokers had a shorter TTFC compared to non-menthol smokers. (Moderate)

D'Silva et al. (2012) assessed baseline smoking characteristics in a study of cessation outcomes between menthol (n = 1,172) and non-menthol (n = 5,085) smokers. Frequency distributions indicated that menthol smokers were more likely than non-menthol smokers to report smoking within five minutes of waking (p < 0.05). The study did not control for demographic variables for the TTFC assessment. (Moderate)

Fagan et al. (2010) conducted secondary analyses of 2003, 2006/07 TUS-CPS data to examine the associations among usual cigarette brand, TTFC after waking, and quitting behaviors. TTFC was used assess nicotine dependence among menthol (n = 11,671) and non-menthol (n = 33,644) smokers. The researchers conducted multivariate logistic regression to examine associations and controlled for covariates found to be significant in bivariate models. Menthol smokers who consumed 6-10 CPD were more likely to smoke within the first five minutes of waking compared to non-menthol smokers (OR = 1.22, 95% CI = 1.05-1.43). (Strong)

Gandhi et al. (2009) provided an analysis of the characteristics of menthol smokers seeking treatment. Baseline variables between menthol (n = 778) and non-menthol (n = 910) smokers were compared using chi-square tests for categorical variables and two-sample t-tests for continuous variables. Results found that more menthol smokers smoked their first cigarette within five minutes of waking compared to non-menthol smokers (p = 0.021). (Moderate)

Gunawan and Juliano (2020) investigated differences between menthol and non-menthol smokers in smoke exposure, smoking topography, and subjective rewarding and sensory effects of smoking. Dependence outcomes were collected at baseline for African American (n = 27 menthol; n = 17 non-menthol) and White (n = 27 menthol; n = 29 non-menthol) smokers. Results showed that a greater percentage of menthol smokers smoked less than 5 min after waking compared to non-menthol smokers (p <0.05). (Moderate)

Hickman et al. (2014) used 2008 and 2009 NSDUH data to examine the association of mental distress and menthol use in a nationally representative sample of smokers (n = 9,198 menthol; n

= 14,959 non-menthol). While Pearson's chi square tests found no significant difference in prevalence of menthol smokers who smoked within 30 minutes of waking vs. after 30 minutes, multivariate logistic regression analysis examined the independent association of TTFC with menthol smoking status. The model included age, gender, race/ethnicity, education, income level, marital status, health insurance status, and CPD as covariates. Menthol smoking was significantly associated with smoking within 30 minutes of waking ($p < 0.001$). (Strong)

Muscat et al. (2009) evaluated the association between TTFC and menthol among current smokers (n = 255-270 menthol, n = 226-230 non-menthol) in a community-based cross-sectional study on cigarette smoke exposure. The study adjusted for age, race, sex, and education. TTFC intervals were collapsed into two categories: ≤30 minutes or >30 minutes. The authors report that among menthol smokers, there was an increased risk of smoking a cigarette sooner (≤30 minutes) after waking (OR = 2.1, 95% CI: 0.96-3.8). (Strong)

In another community-based study, Muscat et al. (2012) evaluated the relationship between menthol cigarette smoking and TTFC in Black and White smokers using the intervals ≤15 minutes, 16-30 minutes, 31-60 minutes, and >60 minutes (n = 221 menthol; n = 274 non-menthol). The authors found that among Black smokers, menthol smokers were more likely to smoke within 15 minutes of waking compared to non-menthol smokers ($p = 0.04$). The study did not indicate whether these results were adjusted for demographic variables. There also appears to be mislabeling of the table presenting the menthol and TTFC results, causing confusion in interpreting these findings. (Moderate)

Odani et al. (2020) used 2014-2015 TUS-CPS data to assess measures associated with flavored tobacco product use and dependence among US adults (n = 163,920). Smoking within 30 min of waking was used to measure dependence. Data indicate that the proportion of respondents who reported smoking within 30 min of waking was lower among menthol smokers than among non-menthol smokers ($p < 0.05$). Adjusted analyses also found that menthol use was significantly associated with increased odds of smoking within 30 minutes after waking among current cigarette smokers (AOR = 1.11; 95% CI = 1.03 to 1.28). (Strong)

Okuyemi et al. (2003) collected baseline demographic data on smoking characteristics in a sample of African Americans (n = 471 menthol; n = 129 non-menthol) in a randomized smoking cessation trial for bupropion. Chi-square and two-sample t-tests were used to assess baseline variables. Menthol smokers were more likely to smoke within 30 minutes of waking compared to non-menthol smokers ($p = 0.003$). The assessment did not adjust for demographic variables. (Moderate)

Rosenbloom et al. (2012) used analysis of variance with menthol and race as independent variables to measure TTFC (5 minutes or less vs. more than 5 minutes) in female smokers seeking tobacco dependence treatment (n = 335 menthol; n = 593 non-menthol). Results showed that menthol smokers were more likely to smoke within 5 minutes of waking compared to non-menthol smokers ($p < 0.001$). Regression analyses were not conducted for these data. (Moderate)

Watson et al. (2017) collected baseline information about TTFC from 42 smokers in a study examining use behavior and exposure when smoking menthol and non-menthol cigarettes. The authors report that half of the menthol smokers reported smoking their first cigarette within 5 minutes of waking rather than at later times. Alternatively, a larger percentage of non-menthol

smokers reported smoking their first cigarettes within 30 minutes (44%) than within 5 minutes (38%). The authors did not report levels of significance for these findings. (Moderate)

Meta-analysis

Sanders et al. (2017) conducted a meta-analysis of published studies to determine whether menthol smokers are more likely to smoke the first cigarette per day sooner than non-menthol smokers. The PubMed database and the Cochrane database were searched using the terms "time to first cigarette [and] menthol", "dependence [and] menthol", and "time to first cigarette." Sudies cited in the FDA preliminary evaluation of menthol were also included. Eighteen (out of 57 identified) studies of TTFC met criteria for inclusion in the meta-analysis. Of these 18 studies, 15 studies contained the 30 non-overlapping estimates of TTFC that were used in the meta-analysis. When evaluating TTFC based on the shortest time period for each study (n = 20), results indicate an overall significant difference between menthol and non-menthol smokers, with menthol smokers being more likely to smoke their first cigarette in the morning than non-menthol smokers [Fixed effects OR (95% CI): 1.10 (1.07-1.13); Random effects OR (95% CI): 1.14 (1.06- 1.23)]. When comparing studies that examine TTFC within 5 min of waking (n = 13), estimates report that menthol smokers are more likely to smoke their cigarette within 5 min of waking compared to non-menthol smokers [Fixed effects OR (95% CI): 1.10 (1.07-1.13); Random effects OR (95% CI): 1.12 (1.04- 1.21)]. However, examination of the less than 30 min timeframe did not find that menthol smokers are more likely to smokes within 30 min of waking compared to non-menthol smokers [Fixed effects OR (95% CI): 1.10 (0.99-1.04); Random effects OR (95% CI): 1.06 (0.96- 1.16)]. The meta-analysis also found the effect of TTFC in menthol smokers was greater in studies with a small number of participants (< 1000, n = 8)) [Fixed effects OR (95% CI): 1.57 (1.32-1.86); Random effects OR (95% CI): 1.51 (1.13- 2.00)] compared to large studies (>1000, n = 12) [Fixed effects OR (95% CI): 1.08 (1.05-1.11); Random effects OR (95% CI): 1.08 (1.00- 1.16)]. Across studies, the authors note a considerable amount of heterogeneity, based on the index of heterogeneity-attributable variance percent for the ouctomes. The authors conclude that the meta-analysis supports a real association between menthol cigarette smoking and shorter TTFC. (Not scored)

Two analyses found that menthol cigarette smoking was associated with a longer TTFC compared to non-menthol cigarette smoking

Curtin et al. (2014b) conducted secondary analyses of 2003, 2006/07 TUS-CPS data. Findings indicate a statistically longer TTFC among past-month menthol smokers (p = 0.001) compared to non-menthol smokers. (Moderate)

Hyland et al. (2002) conducted analyses of participants (n = 3,188 menthol, n = 10,080 non-menthol) in the Community Intervention Trial for Smoking Cessation (COMMIT) cohort measured associations with menthol use and smoking cessation, amount smoked, and TTFC. After controlling for demographic covariates, menthol smoking was associated with smoking >60 minutes after waking compared to <10 minutes after waking (OR = 1.16, 95% CI: 1.00-1.35). (Strong)

Fourteen analyses found no significant difference in TTFC between menthol and non-menthol cigarette smokers

Ahijevych et al. (2002) examined factors influencing cotinine half-life in African American and Caucasian women during abstinence (n = 20 menthol; n = 12 non-menthol). Menthol preference

group comparisons using participant baseline characteristics identified a trend toward a shorter TTFC in menthol smokers compared to non-menthol smokers; however, the difference did not reach statistical significance. (Moderate)

Ahijevych and Ford (2010) used 2006/07 TUS-CPS data to complete a secondary analysis of menthol brand preference and smoking behaviors among young adult (aged 18-24) daily (n = 2,241) and non-daily (n = 688) smokers. Among daily smokers, there was no significant association between menthol brand preference and smoking within 30 minutes of waking. Analyses revealed that this effect was not moderated by state tobacco control policies (i.e., 2006 youth access tobacco laws, 2006 clean indoor air laws, 2006 cigarette excise tax) or the 2006-2007 state prevalence of current smoking. (Strong)

Ahijevych et al. (2018) conducted a 36 hour inpatient study among African American and White menthol and non-menthol smokers (n = 136). The study explored the utility of urine menthol levels as a predictor of nicotine dependence and exposure, which supports evaluations of menthol's dose-dependent effect in humans. TTFC, CPD, biomarkers of nicotine and carcinogenic exposure, and puff topography were assessed. There were no significant differences between menthol and non-menthol smokers in TTFC based on menthol cigarette preference; however, results showed that urine menthol is significantly associated with a shorter TTFC. Thus, while there were no significant differences by menthol preference, these results suggest that urine menthol is a predictor of nicotine dependence. The authors note that the dichotomous variable of menthol or non-menthol smoking does not capture the range of potential menthol exposures as found in a 24 hour data collection. (Strong)

Benowitz et al. (2010) measured menthol concentrations in relation to nicotine BOE in menthol (n = 60) and non-menthol (i.e., "regular cigarette", n = 67) smokers. There was no significant difference in TTFC between menthol and regular cigarette smokers. (Moderate)

Curtin et al. (2014b) conducted secondary analyses of data from 1999-2010 NHANES indicate no significant differences across the distributions of TTFC (≥5, 6–30, 31–60 and >60 minutes) among menthol regular, daily, or past-month smokers compared to non-menthol smokers. (Moderate)

In the same study, Curtin et al. (2014b) also analyzed 2003, 2006/07 TUS-CPS data, which indicated no significant difference in TTFC between regular and daily menthol and non-menthol smokers. (Moderate)

Fagan et al. (2015) compared findings of nicotine dependence among White, Filipino and Native Hawaiian young adult (aged 18-35) daily menthol (n = 127) and non-menthol (n = 59) smokers. A dichotomized variable of "first cigarette within 5 min of waking" (yes/no) was used to examine characteristics of menthol and non-menthol smokers. There was no significant difference in percentage of menthol vs. non-menthol smokers who smoked their first cigarette within 5 minutes of waking. (Moderate)

Faseru et al. (2011) assessed factors associated with menthol smoking among treatment-seeking African American light smokers (i.e., ≤ 10 CPD; n = 452 menthol, n = 88 non-menthol). Bivariate analyses revealed no significant difference in TTFC (≤ 30 minutes) for menthol smokers compared to non-menthol smokers. (Moderate)

Gubner et al., (2018) examined menthol use among individuals in treatment for substance use disorders. Participants were current smokers (n = 863, aged 31-55 years) and data were collected from three annual surveys conducted in 24 substance use disorder centers. Bivariate comparisons between menthol and non-menthol smokers indicated no difference in TTFC between menthol and non-menthol smokers. (Strong)

Jones et al. (2013) used 1999-2010 NHANES data to examine levels of tobacco-related biomarkers comparing White, African-American, and Mexican-American smokers of menthol (n = 1,393) and non-menthol (n = 3,210) cigarettes. Bivariate analyses were used to assess participant characteristics by cigarette type. There were no significant differences in TTFC for any categories examined (i.e., ≤ 5, 6-30, 31-60, >60 minutes). (Strong)

Lawrence et al. (2010) examined national patterns and correlates of menthol cigarette smoking using data from current or someday adult smokers in the 2003 and 2006/07 TUS-CPS (n = 16,294 menthol; n = 46,899 non-menthol). Multivariate logistic regression models adjusting for demographic variables examined TTFC as a predictor of menthol use and found no significant association with smoking cigarettes within the first 30 minutes of waking and menthol use among all current menthol smokers. (Strong)

Rojewski et al. (2014) collected participant characteristics in a study designed to examine smoking cessation and post-cessation weight gain in weight-concerned smokers (n = 61 menthol, n = 105 non-menthol). TTFC was evaluated as ≤30 minutes or >30 minutes. Chi-square tests found no significant differences between menthol and non-menthol smokers for either TTFC category. (Moderate)

Soulakova and Danczak (2017) used the nationally representative 2010 and 2011 TUS-CPS to evaluate whether menthol smoking and race/ethnicity are associated with nicotine dependence in daily smokers. The study consisted of larger subsample of 18,849 non-Hispanic smokers White smokers, non-Hispanic Black smokers, and Hispanic smokers, and a smaller subsample 1112 non-Hispanic American Indian/Alaska Native smokers, non-Hispanic Asian smokers, non-Hispanic Hawaiian/Pacific Islander smokers, and non-Hispanic Multiracial smokers. Respondents were asked "How soon after you wake up do you typically smoke your first cigarette?" If the respondent could not specify the exact time, then the respondent was asked the follow-up question "Would you say you smoke your first cigarette of the day within the first 30 min?" (SW30). Responses to these two questions were pooled to define (approximately) the Sw30 measure, which was used to evaluate dependence. The study found no significant effect of menthol on the Sw30 measure in any ethnic group. (Strong)

Tanner et al. (2020) conducted an analysis of secondary data from 14,123 current and former menthol (n = 3,210) and non-menthol (n = 10,888) smokers in the National Lung Screening Trial to assess the association between cigarette type and nicotine dependence. Adjusted analyses found no significant difference in TTFC between menthol and non-menthol smokers. (Strong)

Cigarettes per Day (CPD)

Twenty-five analyses found that menthol smokers smoke fewer CPD than non-menthol smokers.

Blot et al. (2011) assessed the lung cancer risk among menthol smokers using data from the Southern Community Cohort Study (SCSS) (n = 7,886 menthol; n = 4,487 non-menthol). Among Black ever-smokers, menthol smokers smoked fewer CPD than non-menthol smokers (95% CI:

1.3-2.0). Similar findings were observed among White ever-smokers, where menthol smokers reported smoking fewer CPD than non-menthol smokers (95% CI: 1.3-2.3). (Moderate)

Brinkman et al. (2012) examined how exposure to fine and ultrafine particles differed when participants smoked menthol and non-menthol test cigarettes. The study consisted of 1 menthol and 8 non-menthol smokers. Results indicated that participants smoked fewer menthol CPD than non-menthol CPD (p = 0.017). However, the majority of smokers in the study were regular smokers of non-menthol cigarettes and only used menthol cigarettes for the purposes of this study. As such, the effect of smoking fewer menthol CPD may have been due in part to cigarette type preference. (Moderate)

Curtin et al. (2014b) conducted secondary analyses of 1999-2010 NHANES data. After adjusting for demographic variables, results showed that regular smokers (i.e., smoked ≥10 CPD during the past month) and daily smokers (i.e., smoked every day during the past month) who used menthol cigarettes smoked fewer CPD than non-menthol smokers (p = 0.01, p = 0.04, respectively). (Moderate)

Curtin et al. (2014b) also conducted secondary analyses of 2005 and 2010 NHIS in the same study. Findings were similar in that regular (p = 0.01) and daily (p = 0.001) menthol smokers, as well as past-month (i.e., smoked ≥1 day during the past month, p = 0.01) menthol smokers smoked fewer CPD than non-menthol smokers. (Moderate)

Additionally, Curtin et al. (2014b) secondary analysis of 2003 and 2006/07 TUS-CPS data was conducted in the same study. Again, results showed that regular and daily menthol smokers, as well as past-month (i.e., smoked ≥1 day during the past month) menthol smokers smoked fewer CPD than non-menthol smokers (p < 0.0001). (Moderate)

D'Silva et al. (2012) conducted a study to examine cessation outcomes among treatment seeking menthol (n = 1,172) and non-menthol (n = 5,058) smokers. Baseline smoking characteristics of callers to the quitline showed found that menthol smokers were more likely to smoke <10 CPD than non-menthol smokers (p < 0.05). The study did not control for demographic variables in assessing CPD. (Moderate)

Denlinger-Apte (2019) conducted a study among non-treatment seeking menthol (n = 346) and non-menthol (n = 406) adult smokers to examine the effects of very low nicotine cigarettes on smoking behavior and BOE for 20 weeks. Baseline characteristics were collected. Results showed that menthol smokers smoked significantly fewer CPD compared to non-menthol smokers (p < 0. 001). (Moderate)

Fagan et al. (2010) examined CPD among menthol and non-menthol smokers in a secondary analysis of 2003 and 2006/07 TUS-CPS data. Chi-square tests to determine the relationship between smoking variables and menthol preference found that menthol smokers smoked significantly fewer CPD than non-menthol smokers (p < 0.001). (Strong)

Gan et al. (2016) conducted an analysis of the NHANES 1999-2004 nationally representative survey data to determine associations between menthol cigarette smoking and the existence of headache (n = 739 menthol smokers; n = 1,719 non-menthol smokers).Baseline characteristics reported that menthol smokers smoked fewer CPD compared to non-menthol smokers (p < 0.001) and had fewer pack-years (p = 0.007). (Moderate)

Gandhi et al. (2009) analyzed baseline characteristics of menthol smokers seeking treatment (n = 778 menthol; n = 910 non-menthol). Results showed that menthol smokers smoked fewer CPD than non-menthol smokers (p < 0.001). These analyses did not adjust for confounding variables. When categorized by race/ethnicity, African American (p < 0.001) and Hispanic (p = 0.017) menthol smokers smoked fewer CPD than non-menthol smokers, but there was no difference in CPD between White menthol and non-menthol smokers. (Moderate)

Hickman et al. (2014) used 2008 and 2009 NSDUH data to examine the association of mental distress and menthol use in a nationally representative sample of smokers (n = 9,198 menthol; n = 14,959 non-menthol). Multivariate logistic regression analysis, which included age, gender, race/ethnicity, education, income level, marital status, and health insurance status as covariates, examined the independent association of CPD with menthol smoking status. Menthol smoking was associated with smoking significantly fewer CPD (p = 0.03). (Strong)

Hyland et al. (2002) conducted analyses of participants (n = 3,188 menthol, n = 10,080 non-menthol) in the Community Intervention Trial for Smoking Cessation (COMMIT) cohort measured associations with menthol use and smoking cessation, amount smoked, and TTFC. Data were from menthol smokers identified by telephone survey in 1988. After controlling for demographic covariates at baseline, menthol smoking was associated with higher odds of smoking <5 CPD compared to 15-24 CPD (OR: 0.79, CI: 0.64- 0.98). (Strong)

Jain et al. (2014) conducted a study using 1999-2010 NHANES data to evaluate trends for in serum cotinine levels among current daily smokers (n = 1,181 menthol; n = 2,604 non-menthol). Unadjusted means with 95% confidence intervals reported average number of cigarettes smoked during the last five days (CPD) among menthol and non-menthol daily cigarette smokers. CPD was significantly lower in menthol compared to non-menthol smokers (p < 0.01). (Moderate)

Jarvik et al. (1994) collected baseline demographic information was collected in a study that evaluated differences in smoking topography between menthol (n = 10) and non-menthol (n = 10) smokers. Results revealed no significant main effects of cigarette type or race in CPD; however, a significant race x cigarette preference interaction indicated that White menthol and Black non-menthol smokers smoked fewer CPD than White non-menthol and Black menthol smokers (p < 0.05). (Moderate)

Jones et al. (2013) examined levels of tobacco-related biomarkers comparing White, African-American, and Mexican-American smokers of menthol (n = 1,393) and non-menthol (n = 3,210) cigarettes who participated in NHANES (1999-2010). Menthol smokers were significantly more likely to smoke fewer CPD than non-menthol smokers (p < 0.001). (Strong)

Lawrence et al. (2010) assessed CPD as a predictor of menthol use among current male and female smokers (n = 16, 294 menthol; n = 46,899 non-menthol) in a cross-sectional study using 2003 and 2006/07 TUS-CPS data to examine correlates of menthol use. Using ≤5 CPD as the reference, menthol smoking was associated with significantly lower odds of smoking ≥20 CPD (OR = 0.84, 99% CI: 0.74-0.96). (Strong)

Mendiondo et al. (2010) used 2005 NHIS data to examine health profile differences for current (n = 6,055 [40.8%] menthol) and former (n = 5,949 [51.9%] non-menthol] smokers . Bivariate analyses of health characteristics revealed that current and former menthol smokers consumed fewer CPD than non-menthol smokers. Bivariate analyses in current and former smokers by ethnicity revealed that Non-Hispanic White menthol smokers consumed fewer CPD than non-

menthol smokers, with no difference in CPD between Black and Hispanic menthol and non-menthol smokers. After controlling for age, race, and sex in multivariate logistic regression models, mean CPD was significantly lower for menthol smokers compared to non-menthol smokers (OR = 0.99, 95% CI: 0.98-1.00). (Moderate)

Muscat et al. (2002) conducted a cross-sectional analysis of case-control data on smoking and lung cancer among 16,540 non-menthol and 3,005 menthol smokers. Chi-square analysis revealed that menthol cigarette smokers were significantly more likely to smoke fewer CPD than non-menthol smokers. These results did not control for demographic variables; however, prevalence odds ratios for smoking ≥ 21 CPD vs. ≤ 0 CPD and association with menthol smoking were also determined. After adjusting for age, education, sex, case-control status, and years smoking, results indicated that current and former menthol smokers were less likely to smoke ≥ 21 CPD compared to non-menthol smokers (p < 0.001). The authors reported that most study subjects who smoked menthol cigarettes during their lifetime also reported having smoked non-menthol cigarettes. Classification as a menthol smoker was based on the last brand of cigarette smoked. (Moderate)

Pletcher et al. (2006) used data from the CARDIA study to assess the relationship between menthol cigarette smoking and cessation among current young adult smokers (aged 18-30; n = 563 menthol, n = 972 non-menthol). Analysis of baseline demographic data found that menthol smokers consumed fewer CPD than non-menthol smokers (p < 0.001). (Moderate)

Rostron (2013) analyzed CPD as part of an analysis of NNAL exposures using smokers (n = 1,098 menthol; n = 465 non-menthol) from 2007-2010 NHANES data. Results showed that overall and among White smokers, non-menthol smokers smoked more CPD than menthol smokers. Although not reported in the publication, p-values were converted from the summary statistics in the published report: overall (p < 0.001); White smokers (p < 0.001). (Strong)

Schauer et al. (2018) examined the overlap between menthol cigarette smoking and marijuana using data from the NSDUH collected between 2013 and 2014 (n = 5,942 menthol, n = 8,509 non-menthol). Compared with non-menthol groups, a higher percentage of menthol smokers, regardless of marijuana smoking status, reported smoking ≤ 5 CPD. (Moderate)

Smith et al. (2014) assessed the relationship of menthol cigarette use with measures of cessation success in a large comparative effectiveness trial (n = 648 menthol, n = 847 non-menthol). Baseline differences in CPD were examined. Statistical analyses using t-tests showed that menthol smokers consumed significantly fewer CPD than non-menthol smokers (p = 0.012). (Moderate)

Soulakova and Danczak (2017) examined the effect of menthol on heavy smoking (i.e., smoking 1–15 CPD vs. smoking 16+ CPD) in a nationally-representative 2010-2011 TUS-CPS study evaluating the effect of menthol smoking and race/ethnicity on nicotine dependence (n = 19,961 daily smokers). Compared to non-menthol smoking, within each racial/ethnic group the proportion of menthol smokers was consistently lower among heavy smokers (i.e., those who smoked 16+ CPD) than among less heavy smokers (i.e., those who smoked 1–15 CPD). Findings overall suggest that menthol smoking is negatively associated with heavy smoking. (Strong)

Stahre et al. (2010) evaluated racial/ethnic differences in menthol cigarette smoking and population quit ratio. The authors collected baseline demographic and smoking differences between adult current (n = 1,700 menthol; n = 4,355 non-menthol) and former (n = 1,515

menthol; n = 4,344 non-menthol) smokers. Current and former menthol smokers reported smoking fewer CPD than non-menthol smokers (p's < 0.001). (Moderate)

Veldheer et al. (2018) collected baseline demographic information from menthol (n = 200) and non-menthol (n = 141) smokers in a study examining SPECTRUM nicotine research cigarette acceptability. Compared to non-menthol smokers, menthol smokers reported smoking significantly fewer CPD (p < 0.001). (Moderate)

Thirty-three analyses found no significant difference in CPD between menthol and non-menthol smokers.

Ahijevych et al. (2002) conducted a study to examine factors influencing cotinine half-life in African American and Caucasian women during abstinence (n = 20 menthol; n = 12 non-menthol). Menthol preference group comparisons were conducted using participant baseline characteristics. Statistical analyses found that the number of CPD did not significantly differ between menthol and non-menthol smokers, overall or when stratified by race/ethnicity. (Moderate)

Ahijevych and Ford (2010) used 2006/07 TUS-CPS data to complete a secondary analysis of menthol preference and smoking behaviors in daily (n = 2241) and non-daily (n = 688) young adult (age 18-24) smokers. Multivariate analyses indicated no significant difference in the average number of CPD between menthol and non-menthol smokers. State tobacco control policies (i.e., 2006 youth access tobacco laws, 2006 clean indoor air laws, 2006 cigarette excise tax) and the 2006-2007 state prevalence of current smoking did not moderate associations between menthol brand preference and CPD. (Strong)

Ahijevych et al. (2018) conducted a 36 hour inpatient study among African American and White menthol and non-menthol smokers (n = 136). TTFC, CPD, biomarkers of nicotine and carcinogenic exposure, and puff topography were assessed. There were no significant differences between menthol and non-menthol smokers in CPD based on menthol cigarette preference. (Strong)

Benowitz et al. (2011) analyzed the relationship between CPD and biomarkers of nicotine and carcinogen exposure in Black and White smokers. The main objective of the study was not to examine the effect of menthol on CPD, but this measure was included as background demographic information. No significant difference was found for CPD between menthol and non-menthol smokers. (Moderate)

Brunette et al., (2018) conducted a study to assess the impact of menthol use among daily young adult (n = 81; aged 18-30) smokers who were in outpatient treatment for severe mental illness. Demographic data were collected from participants, including FTND scores and CPD. Menthol use was not correlated with CPD. (Moderate)

Benowitz et al. (2010) measured menthol concentrations in relation to nicotine BOE in menthol (n = 60) and non-menthol (i.e., "regular cigarette"; n = 67) smokers. Baseline CPD data collected over three days found no significant difference between menthol and regular cigarette smokers. (Moderate)

Cubbin et al. (2010) used data from the 2005 NHIS-CCS (n = 31,428) to assess CPD independently in Black, Hispanic, and White menthol and non-menthol smokers. After adjusting

for age, income and education, there were no significant differences for any group in CPD by cigarette type (menthol vs. non-menthol). (Moderate)

Curtin et al. (2014b) conducted secondary analyses of 1999-2010 NHANES data and found no significant difference in CPD between menthol and non-menthol adult past-month smokers (i.e., smoked ≥1 days during the past month). In the same study, adjusted analyses of 2000-2009 NSDUH data, which assessed CPD based on categories (≤10, 11-20, and >20 CPD) showed no statistically significant differences in the odds of smoking ≤10 CPD between adult regular, daily, or past-month menthol and non-menthol smokers. (Moderate)

Davis et al. (2019) conducted a study among adult smokers with comorbid mental illness, substance use disorder, or socioeconomic disadvantage (n = 61 menthol, n = 108 non-menthol) to investigate response to reduced nicotine content cigarettes. Baseline demographic and smoking characteristics indicated no significant difference in CPD between menthol and non-menthol smokers. (Moderate)

DeVito et al. (2016) conducted a study in menthol (n = 100) and non-menthol (n = 24) smokers comparing the effect of menthol preferring status on responses to i.v. nicotine administration. There was no significant difference in baseline CPD between menthol and non-menthol smokers. (Strong)

Duffy et al. (2019) conducted a laboratory study to compare chemosensory function in smokers and non-smokers, and among menthol (n = 51) and non-menthol (n = 84) smokers as a function of menthol preference. There was no significant difference in CPD at baseline. (Moderate)

Fagan et al. (2015) compared findings of nicotine dependence among daily menthol (n = 127) and non-menthol (n = 59) smokers in a cross-sectional study of White, Filipino, and Native Hawaiian young adults (aged 18-30) in Hawaii. Smoking behaviors, including CPD and mean days smoked in past 30 days, were analyzed using chi-square goodness of fit tests and t-tests to examine differences in menthol and non-menthol smokers. There were no significant differences in CPD or days smoked in the past month between menthol and non-menthol smokers. This assessment did not control for demographic variables. (Moderate)

Fagan et al. (2016) conducted another study among youth adult daily menthol (n = 127) and non-menthol (n = 59) smokers in Hawaii to compare biomarkers of tobacco smoke exposure. Sociodemographic characteristics of the sample indicated no significant differences in CPD between menthol and non-menthol young adult smokers. P-values were not adjusted for multiple comparisons. (Moderate)

Faseru et al. (2011) conducted a study among African American treatment-seeking smokers to examine demographic, psychological, and smoking factors associated with menthol smoking (n = 452 menthol, n = 88 non-menthol). Bivariate analyses revealed no significant difference in CPD between menthol smokers and non-menthol smokers. (Moderate)

Gubner et al., (2018) examined menthol use among individuals in treatment for substance use disorders. Participants were current smokers (n = 863) and data were collected from three annual surveys conducted in 24 substance use disorder centers. Bivariate comparisons between menthol and non-menthol smokers indicated lower CPD for menthol versus non-menthol smokers (p = 0.008); however, after adjusting for demographic variables in the logistic regression model, there was no difference between menthol and non-menthol smokers for the CPD measure. (Strong)

Gunawan and Juliano (2020) investigated differences between menthol and non-menthol smokers in smoke exposure, smoking topography, and subjective rewarding and sensory effects of smoking. Dependence outcomes were collected at baseline for African American (n = 27; n = 17 non-menthol) and White (n = 27 menthol; n = 29 non-menthol) smokers. There were no significant differences in CPD between menthol and non-menthol smokers. (Moderate)

Heck et al. (2009) evaluated levels of biomarkers of smoke exposure in menthol (n = 54) and non-menthol (n = 58) smokers. Participant characteristics for CPD were reported. Chi-square tests found no significant difference between menthol and non-menthol smokers in the CPD measure. (Moderate)

Ho et al. (2009) examined the association of menthol smoking with CPD in a sample of African American light smokers enrolled in a smoking cessation program (n = 131 menthol; n = 569 non-menthol). The study was designed to examine whether biomarkers derived from *ad libitum* smoking were associated with self-reported cigarette consumption. Pearson's correlation tests found that menthol smokers showed a trend towards reporting fewer CPD than non-menthol smokers (p = 0.05). However, in a multiple regression model including predictors of CPD (significant in univariate analyses), menthol cigarette use was no longer associated with fewer CPD, though the authors report that a trend was still present (p = 0.08). (Moderate)

Jao et al. (2017) study among 474 cigarette smokers that assessed the effect of menthol on nicotine metabolism and smoking cessation, and CPD were collected at baseline. Results show no significant difference in CPD between menthol or non-menthol cigarettes classified as fast or slow nicotine metabolizers. (Moderate)

Kosiba et al. (2019) examined the relationship between menthol cigarette use and pain reporting among a sample of African American menthol (n = 90) and non-menthol (n = 25) smokers. Information on CPD was collected for demographic characteristics. There were no significant differences in CPD between menthol and non-menthol smokers. (Moderate)

Mendiondo et al. (2010) used 2005 NHIS data to examine health profile differences for current (n = 6,055 [40.8%] menthol) and former (n = 5,949 [51.9%] non-menthol] smokers. After controlling for race, sex, and age, results showed that menthol smoking status was not significantly associated with CPD among former smokers. (Moderate)

Miller et al. (1994) evaluated a sample of African American males in a drug and alcohol treatment center (n = 6 menthol; n = 6 non-menthol) to examine differences in smoking topography for cigarettes injected with 0, 4 mg, or 8 mg menthol. Based on descriptive statistics, the study found no significant difference in CPD between menthol and non-menthol smokers. (Moderate)

Murray et al. (2007) examined CPD in the participant baseline characteristics in a study of menthol (n = 1,216) and non-menthol (n = 1,671) smokers from the Lung Health Study. After adjusting for gender and randomization group (smoking cessation intervention vs. no intervention), there was no significant difference in CPD between menthol and non-menthol smokers. (Moderate)

Mustonen et al. (2005) explored the relationship between tobacco exposure variables with respect to race, gender, and menthol content in a sample of cigarette smokers participating in a smoking cessation trial (n = 88 menthol; n = 219 non-menthol). Unadjusted univariate main

effects of cigarette type found no significant difference in CPD between menthol and non-menthol smokers. After adjusting for age, education, and FTQ scores as covariates, there was no significant main effects of cigarette type. However, a significant gender x race x cigarette type indicated that among White menthol smokers, men reported more CPD than women. (Strong)

Okuyemi et al. (2003) collected baseline demographic data on smoking characteristics in a sample of African Americans in a randomized smoking cessation trial for bupropion (n = 471 menthol, n = 129 non-menthol). Chi-square and two-sample t-tests found no significant difference in the mean CPD between menthol and non-menthol smokers. (Moderate)

Okuyemi et al. (2007) also evaluated the relationship between menthol cigarettes and smoking cessation among African American light smokers (i.e., smoke ≤10 CPD; n = 615 menthol, n = 138 non-menthol). Analysis of baseline smoking characteristics (mean CPD in the past seven days) found no significant difference between menthol and non-menthol smokers in mean CPD. (Moderate)

Perkins et al. (2017) examined the threshold for nicotine discrimination between menthol (n = 44) and non-menthol (n = 29) smokers and obtained baseline demographic information. There was no significant difference in CPD between menthol and non-menthol smokers. (Moderate)

Rojewski et al. (2014) collected participant characteristics in a study designed to examine smoking cessation and post-cessation weight gain in weight-concerned smokers (n = 61 menthol, n = 105 non-menthol). Statistical analysis by t-test revealed no significant differences in CPD between menthol and non-menthol smokers. (Moderate)

Rosenbloom et al. (2012) measured CPD in women smokers seeking tobacco dependence treatment (n = 335 menthol, n = 593 non-menthol). ANOVA with menthol and race as independent variables showed no significant difference in CPD between menthol and non-menthol smokers. (Moderate)

Sarkar et al. (2012) used data from smokers in the TES (n = 1,044 menthol; n = 2,297 non-menthol) to evaluate the impact of menthol on nicotine metabolism. Data on participant characteristics showed that CPD did not differ between menthol and non-menthol smokers, overall or when stratified by race. (Moderate)

Watson et al. (2017) collected information on CPD from participants (n = 42) in a study examining use behavior and exposure when smoking menthol and non-menthol cigarettes. No significant differences in CPD were reported at baseline. During the four week study, participants were randomly assigned to exclusively smoke either the menthol or non-menthol test cigarettes for two weeks, followed by the alternate cigarettes for two weeks. Cigarette butts were collected from participants to determine mouth level nicotine exposure. There was no significant difference in CPD by test cigarette or menthol preference. (Moderate)

Winhusen et al. (2013) collected baseline demographic and cigarette smoking characteristics in a study evaluating the role of menthol cigarette smoking among cocaine-dependent (n = 201 menthol, n = 100 non-menthol) and methamphetamine-dependent (n = 33 menthol, n = 176 non-menthol) smokers. CPD did not significantly differ between cocaine or methamphetamine-dependent menthol and non-menthol smokers. Analyses did not control for confounding variables. (Moderate)

Zuo et al. (2015) collected baseline smoking characteristics from male and female menthol (n = 10) and non-menthol (n = 9) smokers in a study designed to evaluate the effects of menthol on brain nicotine accumulation. Results analyzed via t-test showed a trend-level effect for menthol smokers reporting to smoke fewer CPD than non-menthol smokers (p = 0.051). (Moderate)

Other Aspects of Dependence

Night waking to smoke

Three analyses indicated that menthol smokers are more likely to report night waking to smoke than non-menthol smokers.

Bover et al. (2008) evaluated night waking to smoke as a measure of dependence and its relationship to cessation treatment outcomes in a sample of treatment-seeking smokers (n = 1,048 menthol; n = 1,226 non-menthol). The question "Do you sometimes awaken at night to have a cigarette or use tobacco?" was asked of all participants. Univariate associations based on baseline participant information indicated a significant association with menthol smoking and night waking to smoke. Multivariate logistic regression models, which controlled for 14 variables found to be significantly associated with night waking to smoke in the univariate analysis, including CPD, TTFC, age of first cigarette, race/ethnicity, age, and education were also conducted. Similar to univariate analyses, after controlling for relevant variables, menthol smokers were more likely to report night waking to smoke than non-menthol smokers (AOR = 1.497, 95% CI:1.195-1.874; p = 0.004). (Moderate)

Gandhi et al. (2009) assessed night waking to smoke among a sample of treatment-seeking smokers (n = 778 menthol; n = 910 non-menthol). Analysis of baseline characteristics indicated that menthol smokers were more likely to report night waking to smoke compared to non-menthol smokers (p < 0.001). (Moderate)

Soulakova and Danczak (2017) examined night waking to smoke among several ethnicities in the 2010 and 2011 TUS-CPS to evaluate the effect of menthol and race/ethnicity on nicotine dependence. Compared to non-menthol smoking, menthol smoking had an overall significant effect on odds of night waking to smoke. The effect differed across ethnic groups. Compared to non-Hispanic White menthol smokers, Non-Hispanic Black menthol smokers had higher odds of night waking to smoke (OR = 1.9, 99.99% CI = 1.1-3.1 p = 0.012) and Hispanic menthol smokers had lower odds (OR = 0.0, 99.99% CI = 0.0-0.6; p = 0.011). (Strong)

Individual item assessments

Four analyses found that menthol smokers are more dependent based on single-item assessments from scales of dependence

Fagan et al. (2015) conducted a study among White, Filipino, and Native Hawaiian young adults (aged 18-35) to compare findings of nicotine dependence among daily menthol (n = 127) and non-menthol (n = 59) smokers using the FTND, NDSS, and the brief WISDM. Multiple regression was used (ANCOVA) to estimate differences between menthol and non-menthol smokers, controlling for gender, race/ethnicity, body mass index (BMI), marital status, education, employment status, number of quit attempts, and current use of alcohol and marijuana. Examination of individual questions indicated significantly higher mean scores for menthol smokers on two FTND items: difficulty refraining from smoking in places where it is

forbidden and hating to give up the first cigarette in the morning more than any other ($p = 0.05$ for this measure). (Strong)

In the same study, Fagan et al. (2015) also compared findings of nicotine dependence among daily menthol and non-menthol smokers using the brief WISDM. The social/environmental goals subscale score of the WISDM scale was significantly higher for menthol smokers compared to non-menthol smokers. (Strong)

Watson et al. (2017) collected baseline information about TTFC in a study of 42 smokers examining use behavior and exposure when smoking menthol and non-menthol cigarettes. The authors found that a higher percentage of non-menthol smokers (75%) reported that it would be harder to give up the first cigarette of the day compared to menthol smokers (58%). The authors did not report levels of significance for these findings. (Moderate)

Craving

One analysis suggested that menthol cigarette smokers report less alleviation of craving following nicotine administration after overnight abstinence compared to non-menthol cigarette smokers.

DeVito et al. (2016) compared responses to i.v. nicotine administration on a range of outcomes including withdrawal severity, cognitive performance, and physiological and self-report drug effects following overnight abstinence in menthol ($n = 110$) and non-menthol ($n = 24$) smokers. The Brief Questionnaire of Smoking Urges (BQSU) was used to assess craving. After controlling for sex and race, menthol smokers, relative to non-menthol smokers, reported less alleviation of short-term abstinence-induced craving following i.v. nicotine administration, for both urges to alleviate negative withdrawal effects ($p = 0.022$) and urges to pursue rewarding effects ($p = 0.036$). The authors indicate that these findings reflect the possibility that menthol smokers are less sensitive to the primary reinforcing effects of nicotine, and alleviation of craving may be driven by menthol-related cues. (Strong)

One analysis found no significant difference in cigarette cravings between menthol and non-menthol smokers.

Faseru et al. (2011) examined demographic, psychological, and smoking factors associated with menthol smoking in a sample of treatment seeking African American light smokers ($n = 452$ menthol, $n = 88$ non-menthol). Urges and cravings to smoke were assessed using the BQSU. The study found no significant difference in mean BQSU score between menthol and non-menthol smokers. (Moderate)

Smoking Frequency

Four analyses suggest increased smoking frequency (daily/every day vs. nondaily/some day use) in menthol compared to non-menthol cigarette smokers.

Curtin et al. (2014a) analyzed data from nationally representative survey data from the TUS-CPS (2003, 2006/7). The study evaluated progression, defined as the odds of transitioning from non-daily to daily smoking, using logistic regression models that accounted for sociodemographic variables and dependence measures, which differed across surveys. However, given the cross-sectional nature of the study, it is unclear how the assessment of odds of being a daily vs. nondaily smoker could be classified as progression without a baseline reference point of initial

use. As such, this measure was evaluated as "smoking frequency" under a dependence measure in the context of this review. When accounting for demographic and dependence variables (i.e., TTFC, age of first regular smoking, CPD, and attempted quitting), adult non-menthol smokers had lower odds of being daily vs. nondaily smokers compared to menthol smokers (OR = 0.94, CI: 0.91-0.97, p = 0.0004). Study strengths included evaluating multiple large, nationally representative surveys and controlling for baseline demographic differences. Weaknesses included not providing sample sizes for each analysis. (Moderate)

Kosiba et al. (2019) examined the relationship between menthol cigarette use and pain reporting among a sample of African American menthol (n = 90) and non-menthol (n = 25) smokers. Information on cigarette use frequency was collected for demographic characteristics. Smokers were separated into categories of light (<10 CPD), moderate-heavy (10-15 CPD), and heavy (>15 CPD). Significant differences were reported between menthol and non-menthol smokers, where a greater proportion of menthol smokers were in heavier smoking frequency categories than non-menthol smokers (p <0.05); however, it is noted that some categories contained fewer than 5 subjects for this assessment, and chi-square tests for group differences were interpreted as unreliable. (Moderate)

Odani et al. (2020) used 2014-2015 TUS-CPS data to assess measures associated with flavored tobacco product use and dependence among US adults (n = 163,920). Daily tobacco use was used as a proxy for dependence. Following adjustments for confounding factors, menthol cigarette use was significantly associated with increased odds of daily use among smokers (AOR = 1.13; 95% CI = 1.03 to 1.35). (Strong)

Schauer et al. (2018) examined co-use of marijuana and menthol cigarettes and reported cigarette smoking frequency among smokers (age 12 and up) from the 2013-2014 NSDUH (n = 5,942 menthol, n = 8,509 non-menthol). Among smokers who did not report past month marijuana use, a greater percentage of menthol smokers reported daily cigarette smoking [37.79 (95% CI: 35.68, 39.95)] compared to non-menthol smokers [32.72 (95% CI: 31.27, 34.20)]. (Moderate)

One analysis suggests lower odds of increased smoking frequency (daily/every day vs. nondaily/some day use) in menthol compared to non-menthol cigarette smokers.

Curtin et al. (2014a) conducted analysis of the 2000-2009 NSDUH adult sample. After controlling for demographic and dependence variables (i.e., age at first cigarette and CPD) found that menthol smokers have lower odds of being daily vs. nondaily smokers compared to non-menthol smokers (OR = 1.08, 95% CI: 1.03-1.14, p = 0.002). Study strengths and limitations are described above. (Moderate)

Five analyses suggest no significant difference in smoking frequency (daily/every day vs. nondaily/some day use) between menthol and non-menthol cigarette smokers.

Curtin et al. (2014a) found no difference in the odds of being a daily vs. a nondaily smoker between adult menthol and non-menthol smokers in the 1999-2010 NHANES sample. This analysis controlled for demographic and dependence variables (i.e., TTFC, age of first whole cigarette smoked, and CPD). (Moderate)

In the same study, Curtin et al. (2014a) analyzed data from the 2005 and 2010 NHIS. Although a trend toward menthol smokers having higher odds of being daily smokers was observed in the NHIS adult sample after controlling for demographic and dependence variables (i.e., age of first

regular smoking, CPD, attempted quitting, and intent to quit; OR = 0.81, CI: 0.65-1.10, p = 0.07), these results did not reach statistical significance. Study strengths and limitations are described above. (Moderate)

Fernander et al. (2010) analyzed data from the 2003 and 2006/7 TUS-CPS in established, current smokers (n = 61,447; approximately 25% menthol). A logistic regression model, with age of smoking initiation and purchasing unit as factors and demographic variables as covariates, found that daily smoking was not a predictor for menthol smoking status. (Moderate)

Gubner et al. (2018) examined menthol use among individuals in treatment for substance use disorders. Participants were current smokers (n = 863)and data were collected from three annual surveys conducted in 24 substance use disorder centers. Bivariate comparisons between menthol and non-menthol smokers indicated lower CPD for menthol versus non-menthol smokers (p = 0.008); however, after adjusting for demographic variables in the logistic regression model, there was no difference between menthol and non-menthol smokers for the CPD measure. (Strong)

Lawrence et al. (2010) analyzed data from the 2003 and 2006/7 TUS-CPS in current daily or someday adult smokers (n = 16,294 menthol; n = 46,899 non-menthol). Using a sample of smokers from this survey, this analysis examined whether menthol smoking was associated with smoking frequency (i.e., smoke some days vs. every day). Using a multivariate logistic regression model, the study found no significant association of menthol use with smoking frequency; menthol smokers were not more likely to smoke every day than some days. This finding did not change with gender stratification. (Strong)

Behavioral Choice Procedure

One analysis found no effect of menthol on cigarette choice.

Perkins et al. (2018) assessed the effect of menthol on acute subjective perceptions and subsequent choice behavior of SPECTRUM research cigarettes differing in nicotine content (moderate: 16‑17 mg/g; very low:0.4 mg/g). The goal was to examine the interaction between menthol and nicotine content. The study recruited dependent smokers (n = 73),to participate in a three-hour session to smoke the cigarettes and complete a choice procedure. Cigarette choice involved participants being instructed to smoke four puffs, following automated puffing instructions, from some combination of the two cigarettes differing in nicotine content, presented concurrently. The number of puffs from the moderate nicotine cigarette determined nicotine's relative reinforcing effects. Participants chose significantly more puffs from the moderate vs. low nicotine cigarette, but there were no significant differences in puff choices due to menthol, and no nicotine x menthol interactions. The authors conclude that choice of cigarettes does not differ between menthol and non-menthol smokers when cigarettes are carefully matched on nicotine content and smoking topography. (Moderate)

Nonclinical Behavioral Research Studies (Tier 3)

Seven analyses found that menthol enhances the behavioral effects of nicotine in adult animal models of abuse liability

Alsharari et al. (2015) used a mouse model of nicotine withdrawal to examine whether menthol treatment would enhance nicotine withdrawal in mice. Male adult mice were chronically treated with nicotine (12 mg/kg/day) or saline for seven days and with vehicle or menthol (100 mg/kg)

once a day. Somatic withdrawal responses and affective measures (anxiety-related behavior, hyperalgesia) were evaluated in mice on day eight, 16-18 hours after mini-pump removal. Menthol pre-treatment significantly enhanced anxiety-related behavior ($p < 0.001$), somatic withdrawal signs ($p < 0.001$), and the hyperalgesia response ($p < 0.001$) in nicotine-withdrawn mice compared to saline and vehicle. Results suggest that menthol increases nicotine withdrawal intensity. (Strong)

Biswas et al. (2016) used a rat model (i.e., male adult rats) of i.v. self-administration to examine the effects of menthol on the nicotine dose-response curve. Five minutes pre-treatment with menthol (5 mg/kg, i.p.) significantly enhanced nicotine self-administration ($p < 0.05$). Specifically, doses of nicotine that did not support self-administration after vehicle pre-treatment produced significantly more active lever responses after menthol treatment ($p < 0.05$). In contrast, responses for nicotine doses of 0.03 mg/kg/infusion were significantly reduced following menthol treatment compared to vehicle treatment, indicating that menthol pre-treatment resulted in a leftward shift of nicotine's inverted U-shaped dose-response curve. A menthol dose-response indicated that menthol at 2.5 and 5 mg/kg, but not 0.1 and 1 mg/kg, enhanced nicotine self-administration at low nicotine doses (0.015 mg/kg/infusion) (2.5 mg/kg: $p < 0.01$, 5 mg/kg: $p < 0.001$). Lever presses for nicotine (0.015 mg/kg/infusion) under a progressive ratio schedule of reinforcement were also increased after menthol (5 mg/kg) pre-treatment compared to the vehicle condition ($p < 0.01$). It is noted that pre-treatment with menthol at the doses that reduced nicotine self-administration also decreased food self-administration in rats, though this effect did not reach statistical significance ($p = 0.057$). The authors concluded that menthol enhances the reinforcing effects of nicotine, and that this effect is specific to nicotine. As such, menthol may contribute to tobacco smoking by directly facilitating nicotine consumption. (Strong)

Fait et al. (2017) examined whether menthol differently contributed to greater nicotine intake and altered hyperlocomotion in male and female adult (PND 77-91) and adolescent (PND 21-28) mice. Drinking solutions of nicotine (200 µg/mL) in 2% saccharin or nicotine + menthol (10 µg/mL) + 2% saccharin were provided to mice as their sole source of liquid. Menthol significantly increased nicotine intake in adult male mice ($p < 0.001$) and decreased locomotor activity ($p = 0.0019$) compared to nicotine alone. Adolescent males showed a trend toward similar behavioral responses as adult males, but effects did not reach statistical significance. Adult male mice exposed to menthol + nicotine showed a decrease in locomotor activity when compared to nicotine alone, despite greater intake of nicotine and similar cotinine levels. This was not observed in adolescent mice or adult female mice. These results suggest that effects of menthol on nicotine intake are influenced by age and sex-dependent mechanisms. For example, the authors highlight the possibility that the sensory effects of menthol, in particular the cooling effects, are more important for increasing susceptibility to tobacco addiction in adolescents and women than the pharmacological effects, which appear to have greater impact in males. (Strong)

Harrison et al. (2017) assessed the effect of menthol on maintenance and relapse of nicotine seeking behavior in rats. Male Sprague Dawley rats received an injection of menthol (0.1 mg/kg, i.p.) given 5 min prior to each self-administration session. Menthol alone ($p < 0.05$), the cue (auditory/visual stimulus) alone ($p < 0.01$), and menthol + cue ($p > 0.001$) produced significantly greater responding than vehicle alone. Though animals in the menthol + cue group responded more than the menthol and cue groups alone, this effect did not reach statistical significance. In the reinstatement session, however, menthol alone ($p < 0.05$), the cue alone ($p < 0.05$), and

menthol + cue (p > 0.0001) conditions reinstated extinguished responding on the active lever, with the menthol + cue group producing significantly more responding than the menthol alone (p < 0.01) and cue alone (p < 0.05) groups. Menthol did not produce reinstatement or interact with the nicotine cue in rats that had not received menthol pre-treatment, and had no effect on food-seeking behavior. These results indicate that menthol acts as a cue in maintenance and relapse of nicotine seeking behavior, and may do so at menthol doses comparable to those in cigarettes not labeled as menthol. (Strong)

Henderson et al. (2017) examined the effect of menthol on nicotine reward, midbrain dopamine activity, and nAChR upregulation in adult mice. Using the conditioned place preference (CPP) paradigm to measure nicotine reward, menthol (1.0 mg/kg/h via osmotic minipumps) produced a significant increase in nicotine CPP at 0.25 mg/kg and 0.5 mg/kg (i.p.) compared to the respective nicotine doses alone (p < 0.05). Midbrain cultured neurons treated with nicotine (200 nM) or nicotine plus menthol (500 nM) for 10 days were also evaluated for effects on dopamine activity. Menthol significantly increased baseline neuron firing frequency (p < 0.05) and nAChR-stimulated neuron excitability (p < 0.05) compared to nicotine alone. Menthol also selectively enhanced α4α6* nAChR upregulation (*denotes the potential presence of other subunits) on ventral tegmental area dopamine (p > 0.001) and substantia nigra GABA neurons (p = 0.006) compared to nicotine alone. The authors conclude that menthol enhances nicotine reward behavior, which may be due to menthol's ability to enhance nicotine induced dopamine firing and α4α6* nAChR upregulation in nicotine reward pathways. (Strong)

Palmatier et al. (2020) conducted a study using male CD rats to determine if oral tobacco flavors enhance i.v. nicotine self-administration. Menthol (160 or 320 µM) was presented in sucrose or tap water and examined as one of two flavor conditioned reinforcers in the study (the other being licorice root extract). The menthol conditioned reinforcer increased responding to low nicotine doses (1.5, 3.25, and 7.5 µg/kg) relative to the neutral and water groups (Main effects of group $[F_{(2,22)} = 11.26, p\ 0 < .001]$; dose $[F_{(6,132)} = 7.8, p < 0.001]$; group × dose interaction $[F_{(12,132)} = 3.83, p < 0.001]$). The effect of menthol on increased responding was evident at both menthol concentrations tested (Main effects of group $[F_{(1,23)} = 12.5, p < 0.01]$; sipper $[F_{(1,23)} = 20.3, p < 0.001]$; group × sipper × session interaction $[F_{(2,46)} = 3.34, p = .04]$). Findings support that menthol can promote i.v. nicotine self-administration. (Strong)

Zhang et al. (2018) conducted a study using male Sprague-Dawley rats to examine whether and how menthol affects nicotine-induced dopamine release in the rat nucleus accumbens (NAc) core. Rats self-administered nicotine (15 µg/kg/infusion) across 20 daily 1 hr sessions. Dopamine levels were assessed the following morning before (baseline) and following drug treatment (i.e., s.c. injection of nicotine [0.2 mg/kg], menthol [1, 2.5, and 5 mg/kg], or nicotine + menthol). The two-way repeated-measures ANOVA revealed a significant main effect of nicotine ($F_{1,16} = 6.74$, p < 0.05) and a significant nicotine × menthol interaction ($F_{3,48} = 3.68$, p < 0.05), with no main effect of menthol ($F_{3,48} = 3.68$, p = 0.096). Pre-treatment with menthol significantly elevated dopamine levels in the Nac in rats that subsequently received nicotine. Bonferroni's post hoc test confirmed a significant (p < 0.05) difference between 2.5 and 5 mg/kg menthol vs. vehicle and 1 mg/kg menthol. Examination of the trajectory of dopamine release revealed that dopamine levels following nicotine and menthol+ nicotine were significantly higher at each time point compared with baseline and menthol administration alone. In particular, there was a significant difference between menthol + nicotine and nicotine alone groups in the first three dialysate samples

following drug administration. Results from this study demonstrate that menthol has an enhancing effect on nicotine-induced dopamine release in the NAc. (Strong)

One analysis found that menthol decreases the behavioral effects of nicotine in adult animal models of abuse liability.

Henderson et al. (2016) used an unbiased mouse model of CPP to characterize menthol's effect on nicotine reward-related behavior. Male and female adult mice were chronically infused with menthol (2 mg/kg/h) or vehicle for 20 days to continuously deliver the compounds 10 days before and during CPP training. Over a nine-day protocol, mice received i.p. injections of nicotine (0.5 mg/kg) or saline on alternating sides of a CPP chamber. Nicotine-treated mice infused with vehicle displayed a significant CPP, indicated by a preference for the drug-paired CPP compartment. Alternatively, nicotine-treated mice infused with menthol did not display nicotine-induced reward-related behavior. These results indicate that menthol abolishes nicotine reward-related behavior in mice. The authors suggested that these effects indicate that menthol may act differently alone than when combined with nicotine. (Strong)

One analysis found that menthol has no significant effect on nicotine-induced behaviors in adult animal models of abuse liability.

Wickham et al. (2018) conducted a study to determine the effects of orally administered flavorants on nicotine self-administration in rats. Flavorants (sucrose, saccharin, menthol) were administered orally (i.o.) with i.v. nicotine. Fast scan cyclic voltammetry was used to examine dopamine release from the Nac core. The study found that sucrose and saccharin alone, but not menthol alone, increased dopamine release. The study did not evaluate dopamine release of the flavorants in the presence of nicotine. While sucrose and saccharin also significantly increased nicotine self-administration, menthol had no effect on this behavior. The authors note that menthol did increase oral nicotine intake, suggesting that menthol reduces the aversive effects of nicotine. These findings are discussed under sensory effects, as these findings support menthol's effects on reducing nicotine's aversion and promoting tobacco use. (Strong)

Summary of Findings on Nicotine Exposure and Pharmacokinetics

Nicotine Exposure[6] Longitudinal analyses (Tier 1)

Three longitudinal analyses found that menthol is associated with higher nicotine exposure

Benowitz et al. (2004) evaluated the impact of menthol cigarette smoking on nicotine metabolism in a cross-over study where participants (n = 14) smoked both menthol and non-menthol cigarettes. Each cigarette was smoked for one week, and plasma nicotine levels and nicotine metabolism were assessed with deuterium-labeled nicotine and cotinine. Although nicotine exposure was similar overall between menthol and non-menthol conditions, African American smokers (n = 7) had higher nicotine exposures when smoking menthol cigarettes compared to non-menthol cigarettes; alternatively, White (n = 7) smokers had lower nicotine exposures when smoking menthol cigarettes compared to non-menthol cigarettes. Nicotine intake did not differ between menthol and non-menthol smokers. The effects of race may be

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[6] Includes nicotine and cotinine C_{max}, AUC; total nicotine equivalents; mouth level nicotine exposure (MLE)

impacted by usual brand products (menthol for African American smokers and non-menthol for White smokers). (Strong)

Brinkman et al. (2012) evaluated the effects of *ad libitum* smoking on urinary cotinine and nicotine MLE in a cross-over study where participants (n = 9) smoked commercially-available menthol and non-menthol cigarettes. Non-menthol cigarettes were the usual brand for eight participants. MLE was assessed based on spent cigarette butts from *ad libitum* smoking for one week and urinary cotinine was measured following one week of *ad libitum* use. Menthol and non-menthol cigarettes had similar nicotine yields. Menthol cigarette smoking was associated with significantly greater MLE/cigarette (p < 0.0001), but not MLE/day. Furthermore, urinary cotinine did not differ significantly between cigarette groups. (Moderate)

Watson et al. (2017) compared nicotine MLE between menthol and non-menthol cigarettes in a cross-over study where 42 adult smokers smoked menthol or non-menthol cigarettes *ad libitum* for two weeks. Study cigarettes were selected from the commercial market, based on parametric and non-parametric correlation coefficients of publicly available data on mainstream smoke constituent levels. Cigarette butts were collected and analyzed for solanesol, which was used to estimate the smokers' nicotine MLE based on machine smoking data for the study cigarettes. The nicotine MLE was significantly higher with menthol (1.03 mg/cig) compared to non-menthol (0.87 mg/cig) cigarette smoking (p = 0.02). (Strong)

One longitudinal analysis found that menthol is associated with lower nicotine exposure.

As previously described, Watson et al. (2017) measured urinary cotinine levels in a cross-over study where 42 adult smokers smoked menthol or non-menthol cigarettes *ad libitum* for two weeks. Both menthol and non-menthol smokers had significantly greater cotinine levels after smoking the non-menthol study cigarettes (p = 0.04). Although these data appear to contradict the higher nicotine MLE with menthol smoking reported above, the authors suggest that menthol's reported influences on inhibiting nicotine metabolism may help to explain these urinary cotinine results, and therefore these data should be interpreted with caution. (Moderate)

One longitudinal analysis found no significant effect of menthol on nicotine exposure.

Strasser et al. (2013) conducted a randomized cross-over study to evaluate the impact of menthol cigarette smoking on biomarkers. Participant inclusion criteria required that they reported smoking menthol cigarettes more than 80% of the time. After smoking own brand cigarettes for five days, participants were randomized to smoke either menthol Camel Crush for 15 days followed by 15 days of smoking non-menthol Camel Crush (n = 22), or to smoke own brand cigarettes for the entire duration (n = 10). Participants provided a urine sample for nicotine and cotinine analyses on days 5 (baseline), 20, and 35. There were no significant differences in nicotine or cotinine concentrations based on smoking menthol or non-menthol Camel Crush cigarettes. (Strong)

Cross-sectional analyses (Tier 2)

Nine cross-sectional analyses found that menthol is associated with higher nicotine exposure.

Ahijevych and Parsley (1999) conducted an experimental study to evaluate plasma nicotine and cotinine after smoking one cigarette. Study participants (n = 95) were women (50% menthol and 50% non-menthol smokers). At baseline, urinary cotinine and cotinine/cigarette levels were

significantly higher in menthol smokers (p = 0.04) compared to non-menthol smokers. (Moderate)

Ahijevych et al. (2002) measured urinary cotinine and half-life during smoking abstinence in women. In this inpatient study, participants smoked own brand cigarettes on the first study day and abstained from smoking for the next six days; urine was collected every eight hours for cotinine analysis. Menthol smokers (n = 20) had higher baseline cotinine concentrations (p = 0.019) and cotinine/cigarette ratios (p < 0.05) than non-menthol smokers (n = 12). (Moderate)

Clark et al. (1996) examined the effect of menthol on serum cotinine levels in a population of Black and White smokers. Serum samples were collected following a one-hour confirmed smoking abstention. Serum cotinine levels were significantly higher in menthol (n = 76) compared to non-menthol (n = 85) smokers (p = 0.0005). These relationships remained significant (p = 0.03) after adjusting for race, CPD, and mean amount of each cigarette smoked. (Strong)

Fagan and colleagues (2016) measured nicotine and cotinine in young adult (aged 18-35 years) daily menthol (n = 127) and non-menthol (n = 59) smokers in Hawaii. At study baseline, participants provided a salivary sample for analysis. In unadjusted sub-analyses for racial groups, White menthol smokers had higher nicotine and cotinine/CPD ratios than White non-menthol smokers. In adjusted models, the cotinine/CPD ratio remained significantly higher in White menthol smokers (p = 0.03) compared to White non-menthol smokers. No relationships between cigarette type and study outcomes were found in Native Hawaiian and Filipino smokers. (Strong)

Hsu and colleagues (2017a) conduced a laboratory study that primarily focused on the metabolic profile of cigarette smokers (n = 105). The authors reported that baseline urinary menthol-glucuronide (a detectable menthol metabolite) levels were associated with increased baseline cotinine levels among all smokers (p = 0.04) and among menthol smokers (p = 0.008). Menthol-glucuronide levels were also associated with increased nicotine boost after participants smoked two own-brand cigarettes (p = 0.04); this analysis controlled for baseline plasma cotinine levels. Study results also showed that menthol-glucuronide levels were significantly higher in menthol, compared to non-menthol, smokers. These results suggest that increased menthol exposure is associated with increased nicotine intake. (Strong)

Jones et al. (2013) used data from the 1999-2010 NHANES to evaluate differences in serum cotinine concentrations between menthol (n = 1,393) and non-menthol (n = 3,210) smokers. In models that adjusted for age, sex, education, BMI, and CPD, menthol smokers had greater serum cotinine levels than non-menthol smokers (OR = 1.24, 95% CI: 1.14-1.34), but the effect was lost when adjusting for race (serum cotinine ratio = 1.03). When stratified for race, serum cotinine levels were non-significantly higher in African American and Mexican American menthol smokers. (Strong)

Ross et al. (2016) collected 24-hour urine samples for total nicotine equivalents (TNE) analysis during *ad libitum* smoking in menthol (n = 50) and non-menthol (n = 10) African American smokers as a part of an inpatient study that examined the influence of puff characteristics, dependence, and rate of nicotine metabolism. In linear regression models, menthol smoking status was shown to predict higher TNE (p = 0.048). (Moderate)

Wang et al. (2010), using data from the TES, measured nicotine equivalents and serum cotinine in menthol and non-menthol smokers. In unadjusted analyses, nicotine equivalents (p = 0.0183)

and nicotine equivalents/cigarette (p = 0.0388) were significantly greater in menthol (n = 1,044) compared to non-menthol (n = 2,297) smokers. These findings were not significant in ANCOVA models. These models, however, did find an interaction between menthol and serum cotinine (p = 0.002), although the least-squares mean cotinine values did not differ between menthol and non-menthol smokers. (Strong)

Williams et al. (2007) measured serum nicotine after participants smoked one cigarette. Patients with schizophrenia and healthy control participants were enrolled in a consortium of studies to determine the effectiveness of the nicotine patch or studies of serum nicotine levels. Immediately after participants smoked one cigarette, serum nicotine and cotinine levels were higher in menthol (n = 79) compared to non-menthol (n = 63) smokers (p < 0.01, p < 0.04, respectively) in unadjusted analyses. In stepwise linear regression analysis, which controlled for nicotine metabolite ratio (NMR) and age, menthol smoking was an independent determinant of serum nicotine (p < 0.01). (Strong)

Three cross-sectional analyses found that menthol is associated with lower nicotine exposure.

Benowitz et al. (2010) measured urinary menthol concentration in relation to nicotine BOE. Menthol (n = 60) and non-menthol (n = 67) smokers provided urine samples. In unadjusted analyses, urinary nicotine equivalents (nicotine and its major metabolites) were significantly higher in non-menthol smokers (p = 0.04) compared to menthol smokers. In multiple regression analyses, urinary menthol concentrations were associated with nicotine exposure (p < 0.001). (Strong)

Benowitz and colleagues (2011) examined the relationship between CPD and biomarkers of nicotine and carcinogen exposure in Black and White smokers. Blood and urine samples were collected for nicotine, TNE, and cotinine concentrations. Plasma nicotine concentrations were significantly higher in non-menthol (n = 60) compared to menthol (n = 67) smokers (p < 0.05). (Strong)

Denlinger-Apte (2019) conducted a study among non-treatment seeking menthol (n = 346) and non-menthol (n = 406) adult smokers to examine the effects of very low nicotine cigarettes on smoking behavior and BOE for 20 weeks. Baseline characteristics were collected in a cross-sectional analysis. Results showed that menthol smokers had significantly lower TNE compared to non-menthol smokers (p < 0. 001). (Strong)

Twenty-three cross-sectional analyses found no significant effect of menthol on nicotine exposure.

Ahijevych & Wewers (1994) assessed salivary cotinine concentrations in a population of African American female smokers,. There were no significant differences in cotinine concentrations between menthol (n = 130) and non-menthol (n = 12) smokers. (Moderate)

Ahijevych et al. (1996) measured plasma nicotine and cotinine levels in women (recruitment stratified by race) before and immediately following smoking one own brand cigarette. Baseline cotinine levels and baseline cotinine/cigarette were not significantly different between menthol (n = 18) and non-menthol (n = 19) smokers. Similarly, there were no significant differences in nicotine boost by cigarette type. (Moderate)

Ahijevych et al. (2018) evaluated whether menthol cigarettes impact several addiction outcomes, including pre- and post-smoking plasma nicotine and cotinine levels. During an in-patient study,

participants (menthol n = 71; non-menthol n = 65) smoked usual brand cigarettes for 36 hours. Cigarette type had no impact on plasma cotinine levels in regression models. When the population was stratified by race, menthol smoking was associated with lower baseline plasma nicotine and cotinine levels among African Americans and higher baseline plasma nicotine and cotinine levels among White individuals. Menthol smoking was also associated with higher post-smoking nicotine levels in White individuals and lower post-smoking nicotine levels in African Americans (interaction p = 0.024). (Strong)

Allen and Unger (2007) conducted an analysis of the sociocultural correlates of menthol cigarette smoking. They reported that salivary cotinine concentrations did not differ between menthol (n = 296) and non-menthol (n = 136) African American smokers (p = 0.065). (Moderate)

Caraballo et al. (2011) compared the serum cotinine concentrations of menthol (n = 677) and non-menthol (n = 1241) smokers in the 2001-2006 NHANES. Their analysis found that menthol was not a significant predictor of serum cotinine concentrations when stratified for White and Black smokers. (Strong)

DeVito et al. (2016) measured several nicotine biomarkers at baseline for an experimental study in non-treatment-seeking smokers. Baseline plasma cotinine and plasma nicotine concentrations did not differ between menthol (n = 110) and non-menthol (n = 24) smokers. (Strong)

Faseru et al. (2011) assessed serum cotinine concentrations in African American light smokers who were enrolled in a randomized controlled trial (RCT) for smoking cessation. Cotinine concentrations did not differ between menthol (n = 452) and non-menthol (n = 88) smokers . (Moderate)

Heck (2009) provided 112 smokers with menthol (0.34 mg menthol) and non-menthol study cigarettes (based on usual brand preferences), and analyzed six urinary nicotine metabolites after the participants smoked the cigarettes *ad libitum* for one week. There were no associations between cigarette status (menthol n = 54, non-menthol n = 58) and levels of urinary nicotine metabolites or TNE in 24-hour urine samples. Results were similar when creatinine-adjusted data were stratified by race. (Strong)

Ho et al. (2009) used baseline data from a smoking cessation RCT in African American light smokers to evaluate plasma nicotine and its metabolites. There were no differences in plasma cotinine concentrations between menthol (n = 569) and non-menthol (n = 131) smokers. (Moderate)

Hsu et al. published cross-sectional results from a clinical study where smokers smoked two of their preferred cigarettes in a laboratory setting; BOE and topography were measured. At baseline, there were no significant differences in plasma cotinine levels between menthol (n = 71) and non-menthol (n = 34) smokers. Furthermore, there were no differences in the nicotine boost between menthol and non-menthol smokers upon smoking their preferred cigarette. (Moderate)

Jain et al. (2014) compared serum cotinine values in menthol (n = 1,181) and non-menthol (n = 2,604) smokers using NHANES 1999-2010 data. There were no significant differences in unadjusted cotinine concentrations, nor were there significant effects of menthol in regression models that did and did not control for race/ethnicity. (Strong)

Murray and colleagues (2007) compared baseline serum cotinine concentrations between menthol (n = 1,216) and non-menthol (n = 4,667) smokers enrolled in a smoking cessation trial. All participants had early evidence of obstructive lung impairment. Baseline cotinine concentrations were not significantly different between menthol and non-menthol smokers. (Moderate)

Muscat et al. (2009) compared cotinine concentrations between menthol and non-menthol smokers in a community sample of Black and White smokers. Plasma and urinary cotinine concentrations did not differ between menthol (n = 255-270) and non-menthol (n = 226-230) smokers overall or when stratified by race. (Strong)

Muscat and colleagues (2012) used data from a community-based cross-sectional study in Black and White smokers to evaluate the effects of menthol smoking on plasma cotinine levels. In two linear regression models that adjusted for race, CPD, and age, there were no significant effects of menthol (menthol n = 221; non-menthol n = 274) on plasma cotinine concentration. (Strong)

Mustonen and colleagues (2005) examined the effect of menthol smoking on baseline salivary cotinine levels in a population of smokers recruited for a smoking cessation trial. In unadjusted analyses, cotinine levels tended to be higher in menthol (n = 88) compared to non-menthol (n = 219) smokers, although the difference was not significant; menthol smokers did have a higher cotinine/CPD ratio compared to non-menthol smokers (p = 0.004). These findings were not replicated in adjusted interaction models. (Strong)

Nelson et al. (2011) surveyed nicotine MLE to menthol and non-menthol cigarette smoke during *ad libitum* smoking of participants' own brand. In regression analyses, smoking menthol cigarettes (n = 280) tended to be associated with lower nicotine MLE/cigarette compared to non-menthol cigarettes (n = 1,050), although these results were not significant. (Moderate)

Okuyemi et al. (2003) measured baseline salivary cotinine in African American smokers enrolled in a smoking cessation trial. The researchers concluded that cotinine concentrations did not differ between menthol (n = 471) and non-menthol (n = 129) smokers. (Moderate)

Okuyemi et al. (2007) evaluated baseline cotinine concentrations in African American light smokers who were enrolled in a smoking cessation trial. Serum cotinine concentrations did not differ between menthol (n = 615) and non-menthol (n = 138) smokers. (Moderate)

Rostron (2013) analyzed serum cotinine concentrations in daily smokers in 2007-2010 NHANES. There were no differences overall or by race (i.e., White, Black, Hispanic) between menthol (n = 464) and non-menthol (n = 939) smokers. (Strong)

Signorello et al. (2009) used the SCSS to evaluate the effect of menthol smoking on baseline serum cotinine. Using multivariate adjustment (adjusting for race, sex, age, CPD in past 24 hours, and environmental tobacco smoke exposure), blood cotinine concentrations did not differ between menthol (n = 139) and non-menthol (n = 116) smokers . Findings were not significant when stratified by race and gender. (Moderate)

St. Helen et al. (2021) analyzed data from a reduced nicotine content cigarette study among Black (n = 182) and White (n = 184) menthol and non-menthol smokers to evaluate racial differences in biomarkers of toxic volatile organic compounds in tobacco smoke. Differences in urinary TNE across menthol use were assessed. The study found no significant differences in TNE between menthol and non-menthol smokers of either race. (Strong)

Veldheer et al. (2018) reported, in a study evaluating the acceptability of research cigarettes, that baseline (while smoking usual brand cigarettes) plasma cotinine values were not different between menthol (n = 138) and non-menthol (n = 108) smokers. (Moderate)

Watson et al. (2017) compared nicotine MLE and urinary cotinine levels between cigarette types in a cross-over study where 42 adult smokers smoked menthol or non-menthol cigarettes *ad libitum* for two weeks. Although the data were not provided, the study reported that baseline urinary cotinine levels were not significantly different between menthol (n = 26) and non-menthol (n = 16) smokers in their cross-sectional study described above. (Moderate)

Nicotine Pharmacokinetics[7]

Longitudinal analyses (Tier 1)

One longitudinal analysis found that menthol is associated with attenuated nicotine pharmacokinetics.

Benowitz and colleagues (2004) evaluated the impact of menthol cigarette smoking on nicotine metabolism in a cross-over study where participants (n = 14) smoked both menthol and non-menthol cigarettes. Each cigarette was smoked for one week, and nicotine metabolism was assessed with deuterium-labeled nicotine and cotinine. Menthol cigarette smoking slowed total and non-renal nicotine clearance (p = 0.02) and lowered the rate of nicotine metabolism to its glucuronide compared to non-menthol cigarette smoking. The authors concluded that menthol inhibits both the oxidative and glucuronide conjugation pathways of nicotine metabolism. (Strong)

Cross-sectional analyses (Tier 2)

One cross-sectional analysis found that menthol is associated with augmented nicotine pharmacokinetics.

DeVito et al. (2016) measured NMR at baseline for an experimental study in non-treatment-seeking smokers. NMR was significantly greater (p < 0.001) in menthol (n = 110) compared to non-menthol (n = 24) smokers. (Strong)

Two cross-sectional analyses found that menthol attenuates nicotine pharmacokinetics.

Fagan and colleagues (2016) measured the NMR in young adult (aged 18-35) daily menthol (n = 127) and non-menthol (n = 59) among smokers in Hawaii. In unadjusted models, NMR was significantly lower among menthol smokers compared to non-menthol smokers (p = 0.001). This relationship remained significant when adjusted for gender, race, body mass index, and CPD (p = 0.04). (Strong)

Ross and colleagues (2016) evaluated the impact of race on NMR. After selecting participants from a parent clinical trial study for low and high NMR, menthol cigarette preference was queried. They reported that among African American smokers, but not White smokers, a greater percentage of menthol smokers were slow metabolizers (86%) compared to fast metabolizers (75%; p = 0.03). (Moderate)

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[7] Includes nicotine metabolite ratio (NMR); nicotine metabolism; nicotine absorption

Nine cross-sectional analyses found no significant effect of menthol on nicotine pharmacokinetics.

Benowitz and colleagues (2011) examined nicotine BOE in Black and White smokers. Plasma 3HC/cotinine (NMR) levels did not differ according to use of menthol (n = 67) or non-menthol (n = 60) cigarettes. (Strong)

Chenoweth et al. (2014) compared baseline plasma NMR between menthol (n = 550) and non-menthol (n = 605) smokers in an intention-to-treat (ITT) subgroup of smokers seeking cessation treatment. Menthol smokers had significantly lower (16%) NMR than non-menthol smokers (p < 0.001). However, there was no main effect of menthol on NMR. A regression analysis found that menthol smoking did not contribute to NMR variation. (Moderate)

Hsu et al. (2017a) published results from a clinical study where smokers smoked two of their preferred cigarettes in a laboratory setting; BOE and topography were measured. At baseline, there were no significant differences in NMR between menthol (n = 71) and non-menthol (n = 34) smokers. (Strong)

Jao and colleagues (2017) performed a secondary analysis (n = 474) of an RCT of smoking cessation with the transdermal nicotine patch to evaluate whether menthol smoking moderates the established relationship between NMR and smoking cessation. As measured in either continuous and categorical (slow vs. fast) measures, NMR did not differ between menthol (n = 302) and non-menthol (n = 172) smokers. (Strong)

Sarkar et al. (2012) evaluated the urinary NMR and nicotine glucuronide metabolite ratios between adult menthol (n = 1,044) and non-menthol (n = 2,297) smokers as part of the Total Exposure Study (TES). Due to small numbers in other racial/ethnic groups, analysis was limited to White and African American smokers. There were no significant differences in the NMR or nicotine glucuronide metabolite ratios between menthol and non-menthol smokers and between White and African American individuals. The authors concluded that menthol does not inhibit the metabolism of nicotine-to-nicotine glucuronide. (Strong)

Vogel et al. (2021) examined correlates of NMR in a sample of Alaskan Native smokers (n = 244) living in the Norton Sound Region of Alaska. Sample descriptive characteristics were collected and 65.8% (n = 160) of participants were non-menthol smokers. NMR was not significantly associated with menthol use in the study. (Moderate)

Wang and colleagues (2010) also measured urinary NMR in menthol and non-menthol smokers using data from the TES. NMR did not differ between menthol (n = 1,044) and non-menthol (n = 2,297) smokers in the overall population, or within African American or White individuals. (Strong)

Williams and colleagues (2007) measured NMR after smoking one cigarette. Schizophrenia patients and healthy control participants were enrolled in several studies to determine the effectiveness of the nicotine patch or studies of serum nicotine levels. After adjustments for group, CPD, and race, there were no differences in NMR between menthol (n = 79) and non-menthol (n = 63) smokers. (Strong)

Zuo et al. (2015) measured brain nicotine accumulation (BNA) following a single puff of a menthol or non-menthol cigarette (identical Federal Trade Commission [FTC] nicotine yields, 0.8 mg). Following a smoking period to adapt to the study cigarettes, PET images were

conducted simultaneously to participants' inhalation of 30 mL smoke. Paired t-tests showed no significant differences for BNA pharmacokinetic parameters between menthol (n = 10) and non-menthol (n = 9) cigarettes. In analyses that considered sex as a between-subjects factor, the initial slope of BNA was significantly faster for menthol smoking in men (n = 9; p = 0.008). There were no significant differences when race was considered as the between-subjects factor. Due to the small number of men included in the study (with a statistically significant finding), only the overall population was considered for study conclusions and interpretations. (Strong)

Nonclinical Biomarker Research Studies (Tier 3)

Nicotine Exposure

Two analyses found that menthol is associated with higher nicotine exposure.

Alsharari et al. (2015) investigated menthol's impact on nicotine pharmacology in adult male mice. Menthol (100mg/kg, i.p.) or vehicle was given prior to nicotine (2.5 mg/kg, s.c.), and plasma samples were obtained for 180 minutes following nicotine administration. Menthol had no effects on nicotine C_{max} or $t_{1/2}$, but it was associated with increased AUC_{0-3hrs} (p < 0.05) and reduced nicotine clearance (p < 0.05). (Strong)

Ha et al. (2015) assessed the effects on L-menthol in cigarette smoke on respiratory irritation in adult female mice. The associated plasma cotinine levels were also measured following six to nine minutes of cigarette smoke exposure. L-menthol was added to the smoke at a concentration (60 ppm) several fold lower than the average menthol concentrations in cigarette smoke. Plasma cotinine levels were significantly greater following cigarette smoke exposure with L-menthol than without (p < 0.05). (Strong)

One analysis found that menthol is associated with lower nicotine exposure.

Abobo and colleagues (2012) assayed nicotine and cotinine in a nonclinical study to assess the effects of menthol on nicotine pharmacokinetics. Adult male rats were exposed to single (10 puffs in 10 minutes) and multiple (10 puffs every 12 hours, 17 times) exposures to cigarette smoke. Study cigarettes were similar in their nicotine yield (2.2 mg nicotine/cigarette) and nicotine content (menthol, 13.28mg/cigarette; non-menthol, 14.58 mg/cigarette). After single smoke exposure, menthol decreased the nicotine C_{max} (p < 0.005) and AUC_{0-4hrs} (p < 0.05). Results for plasma cotinine were similar. Multiple menthol smoke exposures significantly decreased nicotine C_{max} (p < 0.05), $AUC_{dosing\ interval}$ (p < 0.0002), average steady-state plasma concentration (p < 0.001), and decreased the terminal half-life of nicotine (p < 0.03). Multiple menthol smoke exposures also decreased cotinine average steady-state plasma concentration (p < 0.03). (Strong)

Two analyses found no significant effect of menthol on nicotine exposure.

Fait et al. (2017) conducted a study to evaluate menthol's impact on nicotine intake and locomotion. Researchers administered nicotine with and without menthol to mice via drinking water and measured nicotine and cotinine levels after locomotion tests were conducted. Menthol did not have an effect on cotinine levels, but adult females had higher nicotine to cotinine ratios when menthol was added to the nicotine solutions. (Strong)

Oviedo et al. (2016) conducted a 90-day inhalation study to measure urinary nicotine metabolites in rats after exposure to filtered air, the Tobacco Heating System (a candidate modified risk tobacco product), two menthol reference cigarettes (high and low menthol content), or the 3R4F non-menthol reference cigarette. Nicotine content was matched between the reference cigarettes. They reported that urinary nicotine metabolites were similar between the two menthol reference cigarette groups; additionally, there were no significant differences between menthol and non-menthol reference cigarettes. Furthermore, the relative distribution of the measured nicotine metabolites was not different, suggesting that menthol did not affect nicotine metabolism. (Moderate)

Nicotine Pharmacokinetics

One analysis found that menthol is associated with augmented nicotine pharmacokinetics.

Squier et al. (2010) measured the effects of menthol on nicotine permeability in *ex vivo* porcine buccal mucosa. Menthol (0.08%) was applied to the tissues at a concentration similar to the lower range found in menthol cigarettes for 0.5, 1, 2, or 12 hours. The presence of menthol (compared to no menthol conditions) significantly increased ($p < 0.001$) nicotine flux at all exposure durations, and therefore enhanced nicotine uptake. (Moderate)

One analysis found that menthol is associated with attenuated nicotine pharmacokinetics.

MacDougall et al. (2003) studied the effects of menthol on microsomal oxidation of nicotine to cotinine in human liver microsomes. Results showed that menthol (100μm) was a competitive inhibitor of microsome-mediated nicotine metabolism to cotinine (significance not reported). (Moderate)

Summary of Adolescent Findings

Longitudinal analyses (Tier 1)

Scales of Nicotine Dependence

One analysis indicated higher scores on scales of nicotine dependence in adolescent menthol compared to non-menthol cigarette smokers.

Nonnemaker et al. (2013) conducted a longitudinal study in middle and high school students (n = 638) to determine whether young people who first tried menthol cigarettes were at greater risk of becoming established smokers and dependent on nicotine than those who started smoking non-menthol cigarettes. Although the study is longitudinal, data on dependence was only collected at wave 3, and was therefore scored as cross-sectional. Nicotine dependence was evaluated using a scale of five items based on survey questions available in all three waves of the American Legacy Longitudinal Tobacco Use Reduction Study (ALLTURS) survey: (i) "How soon after you wake up do you usually smoke your first cigarette on weekdays?"; (ii) "How soon after you wake up do you usually smoke your first cigarette during the weekend?"; (iii) "If you are sick with bad cold or sore throat, do you smoke cigarettes?"; and "How true is this statement for you?"; (iv) "When I go without a smoke for a few hours, I experience cravings"; and (v) "I sometimes have strong cravings for cigarettes where it feels like I'm in the grip of a force that I can't control". Based on least-squares regression analysis, results indicated that initiation with menthol cigarettes was positively associated with nicotine dependence (β = 1.25, 95% CI: 0.1–

2.4). Those who initiated with menthol and switched to non-menthol cigarettes were also significantly more likely to have higher dependence scores than adolescents who initiated with and currently smoked non-menthol cigarettes (β = 2.0, 95% CI: 0.51–3.49). However, youth who started and remained with menthol cigarettes had an equivalent level of dependence to those who started and remained with non-menthol cigarettes. (Strong)

One analysis found no significant difference in scores between adolescent menthol and non-menthol cigarette smokers on scales of nicotine dependence.

Villanti et al. (2021) conducted a longitudinal analysis of Wave 1-4 PATH data in youth (aged 12-17), young adults (aged 18-24), and adults (aged 25+) to examine past 12-month and past 30-day cigarette and cigar use, and nicotine dependence. Nicotine dependence was assessed among youth at Wave 3 or 4 following new use at either Wave 2 or 3. Nicotine dependence was based on a respondent's average score on a 16-item nicotine dependence scale created by PATH investigators. Findings indicate there were no significant bivariate relationships between first menthol cigarette compared with first non-menthol cigarette and subsequent nicotine dependence in youth. The analysis is limited by small sample size and low power due to restricting analysis to youth participants with new cigarette use at Wave 2 or 3 only. (Moderate)

Cross-sectional analyses (Tier 2)

Scales of Nicotine Dependence

Three analyses indicated higher scores on scales of nicotine dependence in adolescent menthol compared to non-menthol cigarette smokers.

Cwalina et al. (2020) examined whether adolescent (age 12-17 years) menthol smokers reported higher nicotine dependence than their non-menthol-smoking counterparts. The data collection source was Wave 2 of the Youth PATH survey public use files (n = 434). Nicotine dependence was measured using eight items from the Wisconsin Inventory of Smoking Dependence Motives (WISDM) that each reflected a separate dependence construct. Results indicated that 49.5% of past 30-day cigarette smokers reported smoking menthol cigarettes, and that menthol smokers had significantly higher nicotine dependence than non-menthol smokers on three WISDM constructs: craving, affiliative attachment, and tolerance. No differences between menthol and non-menthol smokers were observed for loss of control, negative reinforcement, cognitive enhancement, automaticity, or social environment. Overall, study findings indicate that adolescent menthol cigarette smokers experience stronger nicotine craving, tolerance, and affiliative attachment—three distinct aspects of nicotine dependence—compared to adolescents who smoke non-menthol cigarettes. (Strong)

Denlinger-Apte et al. (2019) conducted as study among adolescent (age 15-19 years) menthol (n = 28) and non-menthol (n = 22) smokers to examine the effects of cigarette nicotine content and menthol smoking on health risk perceptions, subjective ratings, and CO boost. Mean mFTQ were collected at baseline. Results indicate that menthol smokers had significantly higher mFTQ scores compared to non-menthol smokers (p <0.01). (Moderate)

Hersey et al. (2006) used the Nicotine Dependence Scale for Adolescents to compare menthol and non-menthol smokers using current middle and high school adolescent smoker data from the 2000 and 2002 NYTS surveys (n = 1,552, non-menthol n = 1,650). Logistic regression models

with nicotine dependence as the dependent variable controlled for demographic variables (i.e., age, gender, race/ethnicity) and smoking behavior (i.e., length, frequency, level of smoking). Results indicated that youth who smoked menthol cigarettes were more likely to be above the median on the Nicotine Dependence Scale for Adolescents than youth non-menthol smokers (OR = 1.45, p = 0.006). (Strong)

Five analyses found no significant difference in scores between adolescent menthol and non-menthol cigarette smokers on scales of nicotine dependence.

Collins and Moolchan (2006) evaluated dependence measures in a sample of European American and African American adolescent smokers (mean age = 15.6 ±1.6 years) applying to a cessation treatment study. Independent t-tests showed no significant difference in FTND score between menthol (n = 531) and non-menthol (n = 41) smokers. The study is limited in that the authors did not control for race or account for the substantially smaller number of menthol than non-menthol smokers in the study. (Moderate)

Curtin et al. (2014b) conducted secondary analyses of data from the 1999-2010 NHANES. Data were only available for youth past-month (i.e., smoked ≥1 day during the past month) smokers due to small sample sizes (sample sizes not presented in the study). After adjusting for gender, race/ethnicity, and current age, analyses indicated no significant difference in his category distributions between youth menthol and non-menthol past-month smokers. Weaknesses included not providing sample sizes for each analysis as well as using creating categorical variables for current age (youth: aged 12-15, 16-19; adult: aged 20-25, 26-29, ≥30) and including adults aged 18-19 in the youth category for NHANES analyses. The weaknesses raise significant concerns regarding calculation and interpretation of the results. (Moderate)

Similarly, in the same Curtin et al. (2014b) article, data from the 2003, 2006/7 TUS-C– -- which, in addition to youth past-month smokers, includes youth regular (i.e., smoked ≥10 CPD during the past month) and daily (i.e., smoked every day during the past month) smoke indicated no significant differences HSI category distributions between menthol and non-menthol smokers. Study strengths included evaluating multiple large, nationally representative surveys, controlling for baseline demographic differences. Weaknesses are as presented for the NHANES analysis above. (Moderate)

DiFranza et al. (2004) conducted a longitudinal study to determine if youths' (n = 237; aged 12-15 years) reaction to the first smoking experience is predictive of future nicotine dependence and whether the impact of the first cigarette can be altered by manipulating levels of tar, nicotine, and menthol. Seventh graders who had ever inhaled a cigarette were recruited and followed for 30 months. The number of reported HONC symptoms was used as a measure of nicotine dependence and was evaluated by menthol status. HONC scores did not differ according to menthol status of the favorite brand (Marlboro vs. Newport). This particular variable was not adjusted for confounding factors. While the overall study on first smoking experience and relationship to nicotine dependence was longitudinal, questions related to first experience with inhaling and first brand smoked (mentholated vs. non-mentholated) were not introduced until round six out of eight total interview rounds. It is also unclear whether the question related to brand was only asked during this sixth round or at subsequent rounds. (Moderate)

Time to First Cigarette (TTFC)

One analysis found that adolescent menthol cigarette smoking was associated with a shorter TTFC compared to non-menthol cigarette smoking.

Collins and Moolchan ([2006](#)) conducted a study among adolescent smokers (n = 531 menthol, n = 41 non-menthol; mean age = 15.6 ±1.6 years) who applied to a cessation treatment study. Results showed that menthol smokers had a shorter TTFC compared to non-menthol smokers (p = 0.04). (Moderate)

Two analyses found that adolescent menthol cigarette smoking was associated with a longer TTFC compared to non-menthol cigarette smoking.

Curtin et al. ([2014b](#)) conducted secondary analyses of data from the 1999-2010 NHANES. Due to small sample sizes in each category, study data were only available for youth past-month (i.e., smoked ≥1 days during the past month) smokers in the NHANES analyses. After controlling for gender, race/ethnicity, and current age, data from the NHANES study indicated that youth past-month menthol smokers had a higher odds of reporting a longer TTFC after waking than non-menthol smokers (p = 0.003). (Moderate)

In the same Curtin et al. ([2014b](#)) study, data were analyzed for youth regular (i.e., smoked ≥10 CPD during the past month), daily (i.e., smoked every day during the past month), and past-month (i.e., smoked ≥1 days during the past month) smokers in the 2003, 2006/07 TUS-CPS. Analyses indicated that daily and regular youth menthol smokers were more likely to be in a longer TTFC category (i.e., smoke the first cigarette within 31-60 minutes) compared to non-menthol smokers (p = 0.04). (Moderate)

One analysis found no significant difference in TTFC between adolescent menthol and non-menthol cigarette smokers.

Curtin et al. ([2014b](#)) found among youth in the 2003, 2006/07 TUS-CPS study that there was no significant difference in TTFC category between youth past-month menthol and non-menthol smokers. We note that this is the same TUS-CPS youth sample described immediately above, which found both longer and no difference in TTFC depending on how the youth subgroup is defined (Moderate).

Cigarettes per Day (CPD)

Two analyses found that adolescent menthol smokers smoke more CPD than non-menthol smokers.

Cohn et al. ([2019](#)) examined demographic factors and menthol cigarette smoking patterns as correlates of youth harm perceptions of cigarette smoking, and ease of smoking menthol versus non-menthol cigarettes. The data collection source was Wave 1 of the youth sample (aged 12-17) of the PATH survey (n = 13,651). Although not a primary outcome, bivariate analyses conducted prior to adjusted multiple logistic regression modeling indicated that past 30-day menthol smokers were more likely to have smoked 6-10 cigarettes per day (CPD) (11.6% vs. 6.1%), and less likely to have smoked 1-5 CPD (81.5% vs. 89.0%, p = 0.04) compared to past 30-day non-menthol smokers. (Moderate)

Muilenburg and Legge ([2008](#)) conducted an analysis on youth (n = 2,068; aged 12-19) data gathered from a 2006 survey based on the NYTS survey and the Centers for Disease Control's Question Inventory on Tobacco. The study evaluated race and menthol effects on cigarette consumption using a population of menthol and "other brand" smokers. The population was 73% African American and 27% White. Ordered logit analysis found significant main effects of menthol smoking, indicating higher odds of smoking more total cigarettes ever, smoking more days and more cigarettes in a month, having smoked more recently, and having ever smoked daily (all p's < 0.01). A significant interaction was also identified, indicating that these effects of menthol were more likely to occur in African American compared to White menthol smokers. The authors did not state whether these results regarding menthol and smoking behavior were adjusted for the control variables assessed (i.e., age, gender, suspended from school, parents or friends smoke, home restrictions, beliefs that smoking is dangerous). The study also does not specify what constitutes "other brand". Given that the study was conducted prior to the FDA 2009 ban on characterizing flavors in cigarettes, and with the high proportion of other brand smokers in this study (81.4%) relative to menthol smokers (18.6%), it is possible that some youth in this category smoked flavored, non-menthol cigarettes. Data are also limited by the small sample size of daily smokers (n = 21, 1.0% of sample). (Moderate)

Four analyses found no significant difference in CPD between adolescent menthol and non-menthol smokers.

Collins and Moolchan ([2006](#)) evaluated dependence measures in a sample of European American and African American menthol (n = 531) and non-menthol (n = 41) adolescent smokers (mean age = 15.6 ±1.6 years). Analyses did not find a significant difference in CPD between adolescent menthol and non-menthol smokers. (Moderate)

Curtin et al. ([2014b](#)) conducted secondary analyses on data from the nationally representative 1999-2010 NHANES. Regression analyses that controlled for demographic variables indicated no significant difference in CPD among youth regular (i.e., smoked ≥10 CPD during the past month) or daily (i.e., smoked every day during the past month) menthol smokers compared to non-menthol smokers. (Moderate)

In the same article, Curtin et al. ([2014b](#)) also conducted secondary analysis on data from the 2003, 2006/07 TUS-CPS. Results that controlled for gender and race/ethnicity among regular, daily, and past-month menthol and non-menthol smokers also found no significant difference in CPD. (Moderate)

Denlinger-Apte et al. ([2019](#)) conducted as study among adolescent (age 15-19 years) menthol (n = 28) and non-menthol (n = 22) smokers to examine the effects of cigarette nicotine content and menthol smoking on health risk perceptions, subjective ratings, and CO boost. Mean CPD were collected at baseline. Although results marginally suggest that menthol smokers smoke more CPD than menthol smokers, this effect did not reach statistical significance (p = 0.06). (Moderate)

Other Aspects of Dependence

Four analyses found that adolescent menthol cigarette smokers exhibit greater signs of dependence than non-menthol cigarette smokers.

Craving

Hersey et al. (2010) used 2006 NYTS survey data to evaluate the association of menthol cigarette smoking with nicotine dependence in middle and high school youth (n = 1,552 menthol; n = 1,650 non-menthol). To measure nicotine dependence, the study used a dichotomous measure of responding to the question, "How long can you go without smoking before you need a cigarette?" Two other items that measure aspects of dependence were also assessed: feeling restless or irritable without smoking and feeling cravings without smoking. The study controlled for demographic variables (i.e., school level, gender, race/ethnicity) and smoking characteristics (i.e., length of smoking, frequency of smoking, level of smoking [CPD]). The odds of needing a cigarette within 1 hour after smoking were significantly higher among current menthol smokers (having smoked within the past 30 days; OR = 1.86, p = 0.003) and established menthol smokers (current smokers who smoked 100 or more cigarettes in their lifetime; OR = 2.06, p = 0.001), compared to non-menthol smokers. Established, but not current, menthol smokers were also more likely than non-menthol smokers to report feeling restless and irritable without smoking (OR = 1.39, p = 0.049) and experiencing cravings after going without smoking for a few hours (OR = 1.35, p = 0.035). (Strong)

Wackowski and Delnevo (2007) used 2004 NYTS data to evaluate the association of menthol use with nicotine dependence among current established (i.e., current smokers who smoked 100 or more cigarettes in their lifetime) high school smokers (n = 1,345). The following dependence-related questions from the 2004 NYTS were used to measure dependence in youth: how long they could go without smoking before needing a cigarette, the extent to which they experience craving after not smoking for a few hours, the extent to which they feel restless or irritable after not smoking for a while, and their perception about their ability to quit smoking now if they wanted to. Logistic regression analyses controlled for demographics and smoking patterns. Established high school menthol smokers were more likely than non-menthol smokers to report needing a cigarette within 1 hour of smoking (OR = 2.6, 95% CI:1.6, 4.3) and experiencing cravings after not smoking for a few hours (OR = 1.6, 95% CI: 1.1, 2.2). There was no significant difference by menthol status in the extent to which youth feel irritable or restless after not smoking or their perceptions about ability to quit smoking. (Moderate)

Smoking frequency

Azagba et al. (2020) examined relationships between menthol cigarette use and smoking frequency, intention to continue smoking, and intention to quit smoking among 1,707 youth (grades 6-12) who completed the 2017 and 2018 National Youth Tobacco Surveys (NYTS) and reported smoking a cigarette within the past 30 days. Menthol cigarette users had significantly higher odds of reporting smoking ≥ 10 of the past 30 days than non-menthol smokers (AOR = 1.48, 95% CI:–1.14 - 1.94). This relationship was found among both middle school students (AOR = 2.36, 95% CI:–1.01 - 5.49) and high school students (AOR = 1.41, 95% CI: –1.09 - 1.82). Findings suggest that menthol cigarette use is associated with smoking more frequently among youth. (Strong)

Similarly, Sawdey et al. (2020) used data from the 2011-2018 NYTS to examine trends and factors associated with youth (n = 427- 683; aged 12-17) menthol and non-menthol cigarette smoking. In the analyses of pooled 2016–2018 data, compared to non-menthol smokers, menthol smokers were significantly more likely to report smoking ≥ 20 days in the past 30, smoking ≥ two CPD, and ≥ 100 lifetime cigarettes. Youth smokers who reported higher smoking

frequencies had greater odds of being menthol smokers compared to youth who reported lower levels of smoking. (Strong)

Two analyses found no difference in signs of dependence between adolescent menthol and non-menthol cigarette smokers

Smoking frequency

Curtin et al. (2014a) analyzed youth data from the 2000-2009 NHANES sample (ages 12-19 years) and found that, after controlling for demographic and dependence variables (i.e., TTFC, age of first whole cigarette smoked, and CPD), menthol smokers had a trend for lower odds of being daily (vs. nondaily smokers) compared to non-menthol smokers (OR = 1.63, 95% CI: 0.95-2.78, p = 0.07); however, these findings did not reach significance. (Moderate)

In the same study, Curtin et al. (2014a) analyzed youth data from the 2003 and 2006/07 TUS-CPS and also found no significant difference between youth menthol and non-menthol smokers in the odds of being a daily vs. nondaily smoker. This analysis also controlled for demographic and dependence variables (i.e., TTFC, age of first regular smoking, CPD, and attempted quitting). While this overall study is strengthened by inclusion of multiple nationally representative surveys, sample sizes are not provided for each analysis and adults aged 18-19 were included in the youth category for NHANES and TUS-CPS analyses. As such, data should be interpreted with caution. (Moderate)

Nonclinical Research Studies (Tier 3)

Two analyses found that menthol enhances the behavioral effects of nicotine in animal models of abuse liability.

Thompson et al. (2018) evaluated the psychoactive effects of menthol in adolescent and adult rats by assessing locomotor sensitization and brain functional connectivity following treatment with nicotine (0.4 mg/kg, s.c.) with or without menthol (0.05 mg/kg or 5.38 mg/kg, s.c.) for nine days. Compared to the nicotine only group, the highest concentration of menthol significantly enhanced locomotor activity in adolescent rats that had been subjected to restraint acclimation (i.e., acclimation to the procedures for awake neuroimaging [p = 0.013]); however, in adolescents and adults that were not subjected to restraint acclimation, menthol did not have a significant effect on locomotor activity compared to nicotine only at any menthol dose tested. The addition of menthol to nicotine also induced functional connectivity alterations in various brain regions implicated in the addiction process (e.g., ventral tegmental area, striatum) in adolescent rats. The authors conclude that menthol administered with nicotine shows evidence of psychoactive properties by enhancing nicotine-induced behavior and increased nicotine-induced brain activity. These findings suggest that stress may be a factor in menthol's actions, though additional studies are necessary to formulate conclusions on the interaction between menthol and stress. Functional connectivity was not measured in adult rodents or adolescent rodents that had not been subjected to the restrain acclimation; thus, it is unknown if menthol had an effect on this measure, despite the absence of a behavioral effect. Adult animals also were not tested after restraint acclimation; thus, it is unknown if the effect of menthol on locomotor activity would have been similar to adolescents, had the adults been subjected to the same procedure. (Strong)

Wang et al. (2014) investigated the effect of oral menthol on i.v. nicotine self-administration in adolescent female rats. Rats that received an oral menthol cue self-administered more nicotine than rats receiving an oral saline cue ($p < 0.01$). Rats that received a menthol cue plus nicotine also exhibited menthol-induced reinstatement of drug-seeking behavior, an effect that was absent in rats that received a menthol cue with a saline ($p < 0.001$). WS-23, a cooling compound that acts as an agonist at TRPM8 receptors (similar to menthol) and cold water also enhanced nicotine self-administration (p's < 0.001). The authors concluded that menthol facilitates the reinforcing effects of nicotine in female adolescent rats, and the effect is most likely attributed to the cooling sensation of menthol. (Strong)

One analysis found that menthol decreases the effects of nicotine in adolescent animal models of abuse liability.

Nesil et al. (2018) examined the effects of menthol on nicotine self-administration and relapse vulnerability in male adolescent Sprague Dawley rats. For administration, menthol was added directly to the i.v. nicotine solutions which allowed for fast and concurrent nicotine/menthol exposure with precisely controlled doses to simulate the low, moderate, and high menthol dose exposure conditions that are observed in humans. The final dose for nicotine used in the study was 0.01 mg/kg/infusion and 0.16, 0.32, and 0.64 mg/kg/infusion for the low, moderate, and high concentrations of menthol, respectively. The authors state that the selected doses approximate levels of menthol exposure in humans. Concurrent delivery of menthol with nicotine did not cause an increase in nicotine self-administration in adolescent rats. The moderate dose of menthol (0.32 mg/kg/infusion) also decreased nicotine self-administration, indicating that it decreased nicotine's reinforcing effects. Menthol also dose-dependently decreased reinstatement responding, with the high dose (0.64 mg/kg/infusion) inducing a significant decrease. Taken together, these results demonstrate that pharmacological interactions of menthol with nicotine reduce, rather than increase, nicotine's reinforcing effects and some measures of relapse vulnerability. (Strong)

One analysis found that menthol has no significant effect on nicotine-induced behaviors in adolescent animal models of abuse liability.

Fait et al. (2017) examined whether menthol differently contributed to greater nicotine intake and altered hyperlocomotion in male and female adult (PND 77-91) and adolescent (PND 21-28) mice. Drinking solutions of nicotine (200 µg/mL) in 2% saccharin or nicotine + menthol (10 µg/mL) + 2% saccharin were provided to mice as their sole source of liquid. Menthol significantly increased nicotine intake in adult male mice ($p < 0.001$) and decreased locomotor activity ($p = 0.0019$) compared to nicotine alone. Adolescent males showed a trend toward similar behavioral responses as adult males, but effects did not reach statistical significance. Adult male mice exposed to menthol + nicotine showed a decrease in locomotor activity when compared to nicotine alone, despite greater intake of nicotine and similar cotinine levels. This was not observed in adolescent mice or adult female mice. These results suggest that effects of menthol on nicotine intake are influenced by age and sex-dependent mechanisms. For example, the authors highlight the possibility that the sensory effects of menthol, in particular the cooling effects, are more important for increasing susceptibility to tobacco addiction in adolescents and women than the pharmacological effects, which appear to have greater impact in males. (Strong)

Conclusions on Menthol and Dependence

A total of 122 articles and one meta-analysis in adults, adolescents, and nonclinical models were reviewed to evaluate the effect of menthol in cigarettes on nicotine dependence. After scoring, 119 articles were considered in the weight of the evidence (excluding 3 weak articles). Dependence outcomes were evaluated as individual outcomes because one article could contain multiple different analyses of dependence (e.g., scales of dependence, CPD, and TTFC). As such, 244 analyses were included (n = 215 in adults, n = 29 in adolescents). These analyses of nicotine dependence included scales of nicotine dependence (e.g., FTND, NDSS, MNWS, HSI), TTFC, CPD, smoking frequency (e.g., daily vs. nondaily smoking), craving, night waking to smoke, nicotine BOE and pharmacokinetics, and nonclinical studies.

Studies in adults were evaluated separately from studies in adolescents to formulate conclusions about menthol and dependence.

Adult findings

One hundred four (104) articles were reviewed to evaluate dependence in adult menthol smokers. One article evaluated both adult and adolescent populations and is included in both analyses. One hundred and one (101) articles (excluding 3 weak articles) were included in the weight of evidence based on strong or moderate weight.

Two hundred fourteen (214) total analyses of nicotine dependence were conducted across 101 articles in adult populations. We note there are several studies that contained multiple dependence outcomes for review. The same population datasets were used to conduct analyses in some cases: three articles used 2003, 2006/2007 TUS-CPS; two articles used 2005 NHIS; three studies present data from the 1999-2010 NHANES; two studies presented data from the TES; two studies present data from the SCSS. Of studies that utilized the same survey data, common measures were used in some instances to evaluate dependence among different, albeit possibly overlapping subsets of the data sample (e.g., assessments of CPD and TTFC among adult daily smokers in the 2003, 2006/07 TUS-CPS). However, given differences in adjusting for covariates and statistical analyses, particular attention was paid to consistency and robustness of the findings across these different analyses.

In total, there were seven Tier 1 analyses, 191 Tier 2 analyses, and 16 Tier 3 analyses. Of these analyses, 24.3% (n = 52) found evidence of significant associations with menthol and increased dependence; 19.2% (n = 41) found that menthol in cigarettes was associated with lower levels of dependence in adult smokers; 56.5% (n = 121) of analyses found no significant difference in level of dependence between adult menthol and non-menthol smokers.

Based on the weight of evidence spanning 1980-2021, **the evidence is not sufficient to support conclusions of an association of menthol in cigarettes with dependence among adults**. A relationship between menthol and dependence among adults cannot be determined due to the inconsistency of findings across the body of evidence. The weight of evidence breakdown by tier, outcome, and analysis weight is presented in Figure 3. The breakdown for each outcome, total number, and percentage of total analyses (in parentheses) is presented by Tier in Table 1.

Figure 3. Summary of analyses on dependence in adults (1980-2021)

Among adults, are menthol smokers more dependent than non-menthol smokers?
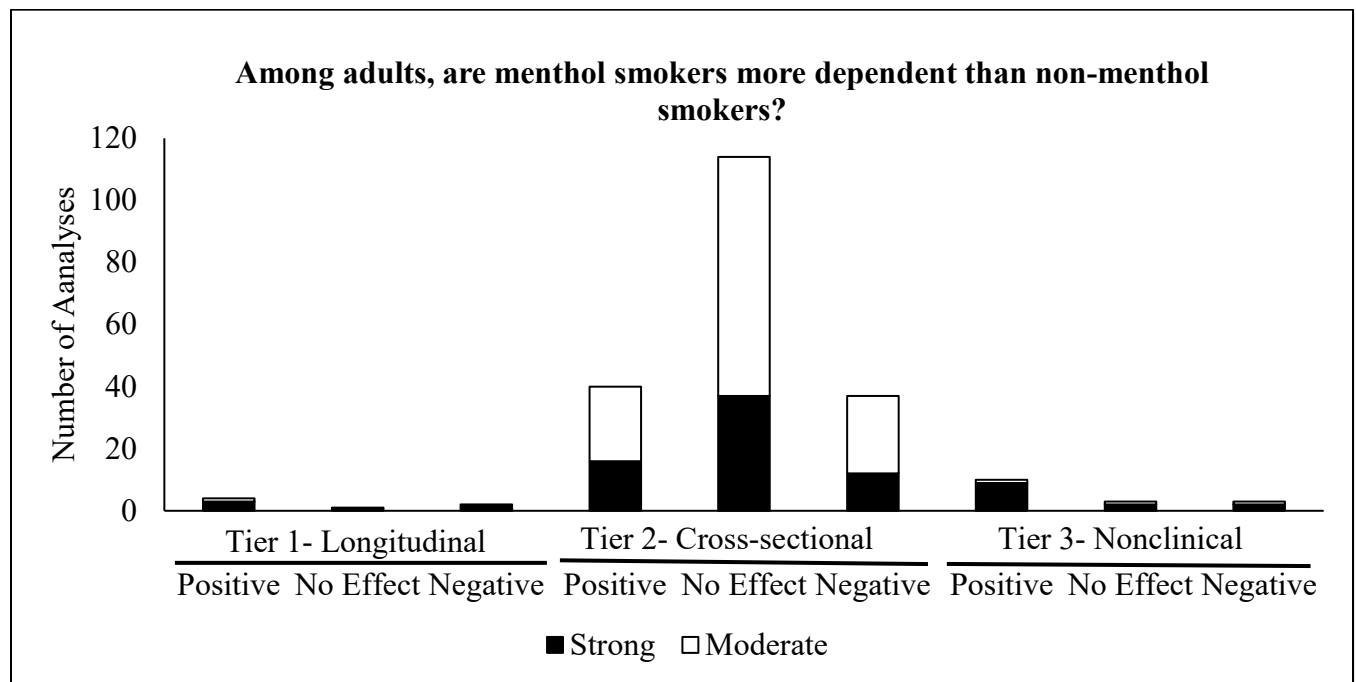
Table 1. Summary of adult dependence analyses (1980-2021)

	Tier 1 (n = 7)								
	Dependence scales (n = 1)			Nicotine exposure (n = 5)			Nicotine PK (n = 1)		
Score	POS	No Effect	NEG	POS	No Effect	NEG	POS	No Effect	NEG
Strong	1 (0.5)	0	0	2 (0.9)	1 (0.5)	1 (0.5)	0	0	1 (0.5)
Moderate	0	0	0	1 (0.5)	0	0	0	0	0
Total	1 (0.5)	0	0	3 (1.4)	1 (0.5)	1 (0.5)	0	0	1 (0.5)

	Tier 2 (n = 144)											
	Dependence scales (n = 36)			TTFC (n = 30)			CPD (n = 58)			Other measures (n = 20)		
Score	POS	No Effect	NEG	POS	No Effect	NEG	POS	No Effect	NEG	POS	No Effect	NEG
Strong	0	6 (2.8)	0	5 (2.3)	7 (3.3)	1 (0.5)	0	5 (2.3)	7 (3.3)	4 (1.9)	2 (0.9)	0
Moderate	4 (1.9)	22 (10.3)	4 (1.9)	9 (4.2)	7 (3.3)	1 (0.5)	0	28 (13.1)	18 (8.4)	8 (3.7)	5 (2.3)	1 (0.5)
Total	4 (1.9)	28 (13.1)	4 (1.9)	14 (6.5)	14 (6.5)	2 (0.9)	0	33 (15.4)	25 (11.7)	12 (5.6)	7 (3.3)	1 (0.5)

Note. *Other measures include craving, frequency of use (daily vs. nondaily), night waking to smoke. Values represent n (%); POS= positive; NEG= negative

	Tier 2 (n = 47)					
	Nicotine exposure (n = 35)			Nicotine PK (n = 12)		
Score	POS	No Effect	NEG	POS	No Effect	NEG
Strong	6 (2.8)	10 (4.7)	3 (1.4)	1 (0.5)	7 (3.3)	1 (0.5)
Moderate	3 (1.4)	13 (6.1)	0	0	2 (0.9)	1 (0.5)
Total	9 (4.2)	23 (10.7)	3 (1.4)	1 (0.5)	9 (4.2)	2 (0.9)

Note. Values represent n (%); PK=pharmacokinetics

	Tier 3 (n = 16)								
	Behavioral measures (n = 9)			Nicotine exposure (n = 5)			Nicotine PK (n = 2)		
Score	POS	No Effect	NEG	POS	No Effect	NEG	POS	No Effect	NEG
Strong	7 (3.3)	1 (0.5)	1 (0.5)	2 (0.9)	1 (0.5)	1 (0.5)	0	0	0
Moderate	0	0	0	0	1 (0.5)	0	1 (0.5)	0	1 (0.5)
Total	7 (3.3)	1(0.5)	1 (0.5)	2 (0.9)	2 (0.9)	1 (0.5)	1 (0.5)	0	1 (0.5)

Note. Values represent n (%); PK=pharmacokinetics

Adolescent findings

Nineteen articles were reviewed for inclusion in the weight of evidence for dependence in adolescents. From these articles, 29 analyses of nicotine dependence across the 19 articles were conducted in youth populations or adolescent animals. Two analyses were Tier 1, 23 analyses were Tier 2, and four analyses were Tier 3. Of the analyses, thirteen found evidence of significant associations with menthol and increased dependence (Tier 1 = 1 strong, Tier 2= 5 strong, 5 moderate; Tier 3= 2 strong), three found that menthol in cigarettes was associated with lower dependence in adolescent smokers (Tier 2= 2 moderate; Tier 3= 1 strong), and thirteen analyses found that there was no significant difference in level of dependence between adolescent menthol and non-menthol smokers (Tier 1= 1 moderate, Tier 2= 11 moderate; Tier 3= 1 strong). Because dependence outcomes were analyzed as separate outcomes, even within the same study, some analyses represent findings from the same study populations within the same article (i.e., Curtin et al., 2014a; Curtin et al., 2014b; Collins & Moolchan, 2006; Denlinger-Apte, Kotlyar, et al., 2019). While all analyses were considered distinct outcomes for scoring, it was a consideration in the weight of the evidence that some findings represent independent assessments from different study populations and others represent different dependence assessments in the same population.

One Tier 1 and eight independent Tier 2 analyses (strong [n = 6] or moderate [n = 3]) (Azagba et al., 2020; A. M. Cohn et al., 2019; Cwalina et al., 2020; Hersey et al., 2006; Hersey et al., 2010; Muilenburg & Legge, 2008; Nonnemaker et al., 2013; Sawdey et al., 2020; Wackowski & Delnevo, 2007) and two strong Tier 3 analyses found an association between menthol in cigarettes and greater dependence in youth. The Tier 2 analyses included six strong and one moderate nationally representative finding from youth surveys (i.e., 2000 and 2002, 2004, 2006, 2011-2018, and 2017-2018 NYTS surveys; Wave 1 and Wave 2PATH study). Studies used scales of dependence and measures of craving and smoking frequency to determine that youth menthol smokers smoke more frequently than youth non-menthol smokers. Nicotine dependence symptoms are associated with smoking frequency among youth; youth who smoke more frequently display greater symptoms of nicotine dependence (O'Loughlin et al., 2003). Alternatively, seven of the Tier 2 analyses that found no effect or that reported lower dependence (n = 2) were from two different nationally representative survey populations (i.e., NHANES, TUS-CPS) that evaluated several dependence measures (i.e., HSI, TTFC, CPD) in youth; however, these analyses were presented across two publications that did not report sample sizes for the populations assessed and included participants aged 18-19 years in the youth category for both surveys (Curtin et al., 2014a, 2014b). Because 18-19 year olds could legally purchase and openly use tobacco at the time of the survey, patterns of use and accessibility differ from 12-17 year olds, the majority age group used for other nationally representative surveys of youth and tobacco dependence (e.g., NYTS and PATH). Incorporating this age range into studies of youth tobacco use may confound interpretation of results. These limitations influence the validity of the findings and resulted in moderate ratings for these nine analyses. Remaining analyses for youth that did not find an effect of menthol on dependence were from non-nationally representative studies (Collins & Moolchan, 2006; DiFranza et al., 2004; Denlinger-Apte, Kotlyar, et al., 2019), which also limits generalizability of the conclusions, or studies had small samples sizes for dependence outcomes due to restricting analysis to participants with new cigarette use at Wave 2 or 3 only (Villanti et al., 2021), which may reduce ability to detect significant between-group differences.

Based on the number and strength of the studies that support an association of menthol in cigarettes with greater dependence among youth and the limitations of the body of evidence that does not support an association of menthol in cigarettes with greater dependence in youth, the weight of the evidence from 1980-2021 supports the conclusion that **menthol in cigarettes is associated with greater dependence among youth**. This conclusion is supported by multiple strong studies, the majority of which are nationally representative and designed to collect survey data on tobacco use in youth populations.

The weight of evidence breakdown by tier, outcome, and analysis weight is presented in Figure 4. Table 2 presents each outcome, total number, and percentage of total analyses (in parentheses).

Figure 4. Summary of analyses on dependence in adolescents (1980-2021)
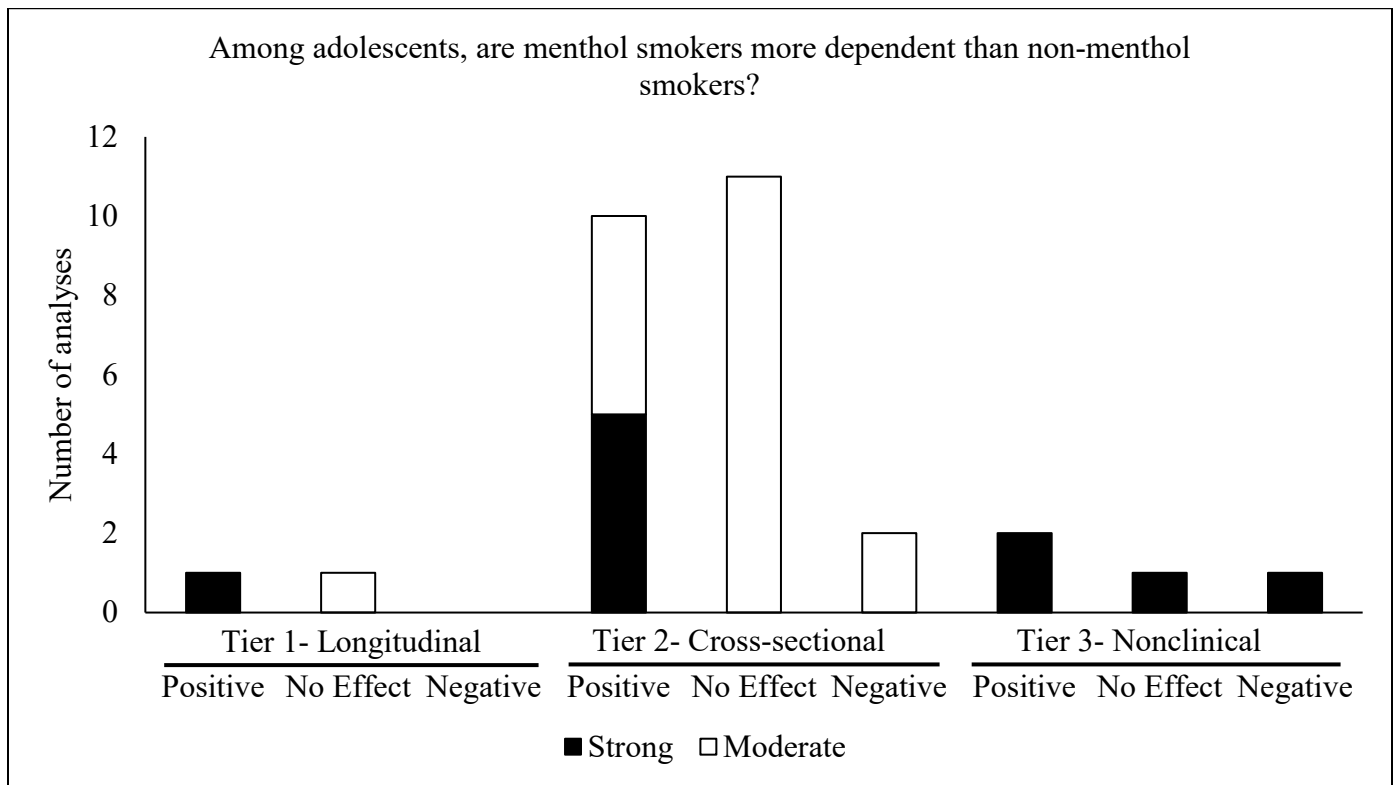
Table 2. Summary of adolescent dependence analyses (1980-2021)

	Tier 1 (n = 2)		
	Dependence scales (n = 2)		
Score	**POS**	**No Effect**	**NEG**
Strong	1 (3.4)	0	0
Moderate	0	1 (3.4)	0
Total	1 (3.4)	1 (3.4)	0

	Tier 2 (n = 23)											
	Dependence scales (n = 7)			**TTFC** (n = 4)			**CPD** (n = 6)			**Other measures*** (n = 6)		
Score	**POS**	**No Effect**	**NEG**	**POS**	**No Effect**	**NEG**	**POS**	**No Effect**	**NEG**	**POS**	**No Effect**	**NEG**
Strong	2 (6.9)	0	0	0	0	0	0	0	0	3 (10.3)	0	0
Moderate	1 (3.4)	4 (13.8)^	0	1 (3.4)^	1 (3.4)^	2 (6.9)^	2 (6.9)	4 (11.1)^	0	1 (3.4)	2 (6.9)	0 (6.9)^
Total	3 (10.3)	4 (13.8)	0	1 (3.4)	1 (3.4)	2 (6.9)	2 (6.9)	4 (13.8)	0	4 (13.8)	0	2 (6.9)^

Note. *Other measures include craving, frequency of use (daily vs. nondaily), night waking to smoke. Values represent n(%); POS= positive; NEG= negative
^Denotes that the number contains multiple analyses from a single publication.

	Tier 3 (n = 4)		
	Behavioral (n = 4)		
Score	**POS**	**No Effect**	**NEG**
Strong	2 (6.9)	1 (3.4)	1 (3.4)
Moderate	0	0	0
Total	2 (6.9)	1 (3.4)	1 (3.4)

XIII.   STRENGTH OF EVIDENCE: TOPOGRAPHY

Studies summarized in this section include at least one of the following measures:

- Studies comparing menthol and non-menthol cigarette smoking topography

A simple summary is provided for each study outcome, presented by measure and whether the outcome found a positive association, negative association, or no association with menthol.

Background

Industry documents suggest that the sensory effects of menthol may contribute to altered smoking behaviors (Yerger, 2011; Yerger & McCandless, 2011). Smoking topography provides a quantitative measure of smoking behaviors, which can include number of puffs; interval between each puff; volume, velocity, and duration of each puff; total smoking duration; length of cigarette smoked; depth, volume, and duration of respiratory inhalation; and breath holding. Differences in smoking topography can affect smoke exposure (e.g., CO, nicotine exposure, harmful and potentially harmful constituents [HPHCs]) and subsequent nicotine dependence as well as reveal compensatory behaviors (e.g., smoking intensity) (e.g., (Hammond, Fong, Cummings, & Hyland, 2005; Krebs et al., 2016; Lee, Malson, Waters, Moolchan, & Pickworth, 2003)).

Topography can be measured during prescribed smoking, which may restrict puff timing or volumes to standardize between-subject comparisons, or *ad libitum* smoking, which represents more naturalistic smoking behavior. Additionally, studies using own-brand cigarettes collect topography data that may reflect more naturalistic behavior, however they are unable to control for differences in cigarette ingredients or characteristics, such as tar or nicotine yield, that may affect topography. Finally, topography may be influenced by participant experience with, or preference for, the cigarette type(s) used in the study as well as the topography device/apparatus. This review places a higher weight on within-subject studies that include menthol smokers, who would be most affected by the removal of menthol products from the market. Additionally, *ad libitum* (compared to prescribed use) studies received a greater weight due to a measuring more naturalistic behavior.

In this review of topography, self-reported measures of puffing behavior were not included due to low validity (Shahab et al., 2008; Tobin, Jenouri, & Sackner, 1982); instead, quantitative measures were evaluated. Smoking behavior is dynamic, and may be affected by the internal (e.g., withdrawal) and external (e.g., cigarette characteristics, smoking topography device) environments (Hammond et al., 2005; Lee et al., 2003; Zacny & Stitzer, 1996). Puffing behavior has been shown to have a high degree of stability within the same subject over time but considerable variability between smokers; therefore, this review considers within-subject designs to be more powerful (Hammond et al., 2005).

Summary of Within-Subject Studies on Topography

Longitudinal analyses (Tier 1)

Ad libitum **Smoking**

Two longitudinal analyses suggest that menthol increases smoking topography

Brinkman et al. (2012) conducted a cross-over study in menthol (n = 1) and non-menthol (n = 8) smokers aged 18-30 who smoked ≥20 CPD for ≥6 months and used no other forms of nicotine. Acceptability of both non-menthol and menthol test cigarettes was confirmed during a preliminary visit. Participants were randomly assigned to smoke cigarettes (menthol or non-menthol) for one week each and given the other product to take home for week two. At the end of each week, participants completed a laboratory session where they smoked four test cigarettes. *Ad libitum smoking* topography (puff volume, puff duration, average and peak flow, interpuff interval, number of puffs per cigarette) and post puff inhalation data (peak inspiratory flow, peak expiratory flow, inspiration time, expiration time, inspiration volume, expiration volume) were measured using the SPA-D device and inductive plethysmography. The study found that smoking menthol cigarettes was associated with significantly greater inhaled smoke volume per cigarette (p = 0.027), longer puff duration (p < 0.0001), and longer smoking time (p = 0.045) compared to non-menthol cigarettes. Additionally, average flow and peak flow rates were significantly lower for menthol compared to non-menthol cigarettes (p's < 0.0001). Inhalation data showed significantly higher peak inspiratory flow (p < 0.0001) and expiratory flow (p = 0.017) as well as greater inspiration volume (p < 0.0001) and expiration volume (p = 0.037) for non-menthol cigarettes; expiration time was longer for menthol cigarettes (p = 0.004). Study limitations include potential non-menthol related differences between study cigarettes and small sample size (cannot test hypotheses, cannot control for racial differences, cannot control for menthol/non-menthol preferences). The sample has low generalizability due to consisting of primarily non-menthol preferring smokers. (Moderate)

Watson et al. (2017) conducted a 2-part cross-over study design where 42 adult smokers (>6 CPD, smoking >3 years; 60% Caucasian/40% African American; 62% menthol preference) alternated between two weeks of exclusively smoking a menthol (Benson & Hedges Light 100) or non-menthol (Kent 100 soft pack) study cigarette. Study cigarettes were selected based on similarity of mainstream smoke constituent levels and were matched for length, circumference, and tobacco weight. Participants completed three laboratory visits where *ad libitum* smoking topography was measured using the CReSS device. During the first visit, they smoked their own-brand cigarette and after 30 minutes a study cigarette (randomly assigned to menthol or non-menthol). During visits two and three, participants smoked the test cigarette they had been smoking for the previous two weeks, and after 30 minutes smoked the other test cigarette. Analyses showed significantly higher puff volumes (p = 0.04) and longer puff duration (p = 0.04) for menthol compared to non-menthol cigarettes, but no difference in number of puffs or peak puff volume; the authors concluded that "participants found it easier to take bigger and longer puffs when smoking a menthol cigarette." Analysis of topography by menthol (n = 26) vs. non-menthol (n = 16) preference was not reported. The small sample of African American non-menthol smokers precluded an analysis for race effects. The study faced challenges of participant retention and non-compliance in using study cigarettes at home. (Strong)

Three longitudinal analyses suggest that menthol decreases smoking topography

Gunawan and Juliano (2020) investigated differences between menthol and non-menthol smokers in smoke exposure, smoking topography, and subjective rewarding and sensory effects of smoking. Adult, daily smokers (n = 100) participated in two laboratory sessions over two days, during which participants smoked their usual brand cigarette *ad libitum* via a CReSS topography device (puff count, puff volume, puff duration, mean and peak puff flow, and interpuff interval) and under natural smoking conditions. Data from 16 participants were excluded due to improper use or malfunction of the CReSS device; first and last puffs were excluded from analyses and data were screened for outlying and implausible values. The authors found that use of the CReSS device had no impact on smoking behavior or exposure compared to naturalistic smoking. After controlling for baseline differences among menthol and non-menthol smokers, analyses showed that menthol smokers took significantly shorter (p = .007) and smaller volume (p = .018) puffs. However, there were no differences in puff count, smoking duration, total puff volume, or carbon monoxide exposure between menthol and non-menthol smokers. Finally, while this study was balanced on race (44 African American smokers [n = 27 preferred menthol] and 56 White smokers [n = 27 preferred menthol]), there were significant effects of race or race x menthol interactions for puff duration, mean puff flow, and mean peak flow topography. (Strong)

Jarvik et al. (1994) used a factorial design to measure the effects of race and cigarette preference on topography in male smokers recruited from the community and the West Los Angeles Veterans Administration Medical Center. Adult menthol (n = 10) and non-menthol (n = 10) smokers completed two sessions where they smoked each cigarette type. Participants smoked ≥15 CPD and were not overnight abstinent (asked to refrain for smoking for 30 minutes prior to testing). Participants smoked their own-brand cigarette, and then a study-supplied cigarette thirty minutes later. Topography (number of puffs, puff volume, puff duration, mean puff flow, interpuff interval) was measured using a Fleisch pneumotachygraph attached to differential pressure transducer. Participants were instructed to smoke the study cigarette *ad libitum* ("in a manner as similar as possible to their usual pattern of smoking"). ANOVA found that smoking menthol cigarettes was associated with significantly smaller average puff volume (p < 0.0001), smaller total puff volume (p < 0.01), shorter puff duration (p < 0.05), and fewer puffs (p < 0.05) compared to non-menthol cigarettes. Additionally, mean puff flow rate was significantly lower during menthol cigarette smoking than non-menthol cigarette smoking (p < 0.01). Inhaled volume (smoke mixed with inspired air) did not differ between the menthol and non-menthol cigarette condition, and there were no significant differences for peak puff flow, interpuff interval, or lung retention time. Race had a significant effect on topography and respiration measures; however, the small sample size precludes a firm conclusion regarding racial differences. (Moderate)

Strasser et al. (2013) conducted a randomized, open-label, laboratory study in menthol smokers (smoke menthol cigarettes ≥80% of the time) aged 21-65 who smoked ≥10 CPD for ≥5 years. After a five-day baseline period using their own brand cigarettes, participants were randomized to the experimental group (n = 22) to smoke menthol cigarette (Camel Crush) for 15 days, followed by a non-menthol cigarette (non-menthol Camel Crush) for 15 days, whereas control group participants (n = 10) smoked their own brand cigarette across all periods. Sixty participants completed at least up to session two, day five, and were included in the analysis. *Ad libitum* smoking topography was measured using the CReSS device every five days; total puff

volume was considered the primary outcome measure, but number of puffs, puff duration, and interpuff interval were also measured. During each session, participants smoked two cigarettes using a smoking topography device, with a 45-minutes break in between each bout. The study found that the experimental group had significantly longer puff duration (p = 0.03) and marginally increased total puff volume (p = 0.06) in the non-menthol condition than the menthol condition. The authors concluded that there were no meaningful changes in consumption behavior when menthol was removed from the cigarettes; there were no changes in CPD or BOE, and total puff volume increased by an average of 65 mL (11% increase). The study is strengthened by using cigarettes that differed only in menthol content and by allowing participants over two weeks of use experience with cigarettes that were not the participants' usual brand. Sex, race, and nicotine dependence score were included as covariates in all models. (Strong)

Prescribed Smoking

One longitudinal analysis suggests that menthol decreases smoking topography

McCarthy et al. (1995) used a repeated measures, cross-over design in male menthol (n = 11) and non-menthol (n = 18) adults who smoked ≥10 CPD and were inpatients for drug and alcohol treatment Participants completed two sessions where they smoked each cigarette type. In each session, participants were asked to take one puff every 15 seconds and were limited to a maximum volume of 100 cc per puff. One participant's puff volumes consistently reached the maximum. Participants were asked "to smoke until you are no longer able to do so." Menthol and non-menthol cigarettes were commercially available and selected for comparable delivery of tar, nicotine, and CO delivery based on 1991 FTC ratings. Analyses found significantly more puffs-to-stopping (p = 0.03) and higher mean volumes per puff (p = 0.001) for the non-menthol cigarette smoking condition compared to menthol cigarette smoking. Limitations of this study include the prescribed method of rapid smoke inhalation, racial differences, and inclusion of only male veterans in addiction treatment. Although the non-menthol preferring smokers were balanced on race (56% White), only 28% of the menthol-preferring smokers were White. (Moderate)

One longitudinal analysis suggests no significant impact of menthol on smoking topography

Miller et al. (1994) used a repeated measures cross-over design in male African American menthol (n = 6) and non-menthol (n = 6) adults who smoked ≥15 CPD and were inpatients for drug and alcohol dependence treatment. Participants completed three sessions where menthol content varied (0, 4, 8 mg menthol). They were instructed to draw puffs at 30-second intervals until they had drawn a total of 600 cc of smoke. Then, participants repeated the smoking protocol to draw in another 600 cc of smoke. A maximum of 100 cc per inhalation was possible. Menthol content was not found to effect number of puffs to reach 1,200 cc of smoke or per-puff volume. Limitations of this study include the prescribed method of smoke inhalation and a small sample of male veterans in addiction treatment. (Moderate)

Summary of Between-Subject Studies on Topography

Longitudinal analyses (Tier 1)

Ad libitum **Smoking**

One longitudinal analysis suggests no significant impact of menthol on smoking topography

Jarvik et al. ([1994](#)) used a factorial design to measure topography in male menthol (n = 10) and non-menthol (n = 10) adult smokers recruited from the community and the West Los Angeles Veterans Administration Medical Center. Participants completed two sessions where they smoked each cigarette type. There was no main effect of preferred cigarette type on topography and respiration measures. Study design and limitations are described above. (Moderate)

Prescribed Smoking

Two longitudinal analyses suggest no significant impact of menthol on smoking topography

McCarthy et al. ([1995](#)) used a repeated measures, cross-over design in male menthol (n = 11) and non-menthol (n = 18) adult smokers. Participants completed two sessions where they smoked each cigarette type. There was no main effect of preferred cigarette type on these topography measures of number of puffs-to-stopping and puff volume. Study design and limitations are described above. (Moderate)

Miller et al. ([1994](#)) used a repeated measures, cross-over design in male African American menthol (n = 6) and non-menthol (n = 6) adult smokers. Participants completed three sessions where they smoked cigarettes of different menthol content (0, 4, 8 mg menthol). Repeated measures ANOVA found no differences in the number of puffs to reach 1,200 cc of smoke or per-puff volume for menthol and non-menthol smokers. Study design and limitations are described above. (Moderate)

Cross-sectional analyses (Tier 2)

***Ad libitum* Smoking**

One cross-sectional analysis suggests that menthol increases smoking topography

Ahijevych et al. ([2018](#)) conducted an in-patient study among adult, daily menthol (n = 35 White, 36 Black) and non-menthol smokers (n = 35 White, 30 Black), aged 18-50 years old. Analyses were stratified by race and cigarette type. Puff volume was assessed via CReSS topography device during *ad libitum* smoking of own-brand cigarettes throughout the day; other topography outcomes were not reported. Measures of dependence and biomarkers of nicotine, menthol, and other HPHCs were also collected. Trend plots were used to visually illustrate the trajectories of puff volume throughout the day, stratified by race and cigarette type. Additionally, the effect of cigarette type on puff volume was analyzed using mixed effect to account for repeated measures. Puff volume was lowest for Black, non-menthol smokers; no significant effect of puff volume was found by cigarette type. However, total menthol was significantly associated with greater puff volume ($p < 0.05$; "each unit increase in total menthol was associated with 4.23 mL greater puff volume"). (Moderate)

Five cross-sectional analyses suggest no significant impact of menthol on smoking topography

Ahijevych et al. ([1996](#)) used a between-subject design to measure topography in Black and White, adult women who preferred menthol (n = 18) or non-menthol (n = 19) cigarettes, smoked at most 20 CPD (average = 14.7 CPD), and did not use other forms of nicotine. To avoid 25% loss of menthol that can happen within one day of pack opening, the investigators provided

unopened packs of own-brand cigarettes to the participants. Participants were not overnight abstinent and time since last cigarette did not differ by race or cigarette type preference. *Ad libitum* smoking topography was measured using a flow-meter cigarette holder attached to a differential pressure transducer. No significant differences were found for topography (puff duration, puff volume, interpuff interval, number of puffs) or respiratory (inhalation duration/volume, exhalation duration/volume) measures by cigarette type preference; no effect of race was found on topography and respiratory parameters. These findings have limited generalizability because the study was conducted in women only; used cigarettes that vary in nicotine, tar, and CO delivery; and did not include a cross-over component for cigarette type. (Moderate)

Hsu et al. (2017a) reported on topography data from a cross sectional study (Hsu et al., 2017b) measuring biomarkers and smoking behavior in 105 current, adult smokers (>10 CPD, smoking ≥ 5 years) of menthol (n = 71) and non-menthol (n = 34) cigarettes. Participants smoked two usual brand cigarettes, one hour apart: the first was smoked *ad libitum* and the second smoked using the CReSS topography device. Two-sample *t*-tests found no difference between menthol and non-menthol smokers on measures of topography (i.e., maximum puff velocity, average puff volume, average puff duration, average interpuff interval, total number of puffs, and total smoke exposure [puff number x puff volume]). However, the authors report that change in menthol-glucuronide boosts for menthol smokers was related to smoking topography; including this biomarker provides a biochemical measure of menthol exposure, beyond self-report, in a sample of self-reported menthol smokers. Participants in this study were predominantly male (63.8%) and African American (60%). African American smokers made up 81.7% of menthol users and 14.7% of non-menthol users; however, race was not a covariate or stratification factor for topography analysis. (Strong)

Pickworth et al. (2002) conducted a study in menthol (n = 18, 94.4% African American) and non-menthol (n = 18, 16.6% African American) adults who smoked ≥15 CPD and had been smoking for ≥2 years. Participants smoked three study cigarettes of their preferred type with different nicotine yields (random order: 0.2 mg, 1.2 mg, 2.5 mg) in a single session, 45 minutes apart. Participants were not overnight abstinent, and time since last usual brand cigarette was approximately 45 minutes. *Ad libitum* smoking topography measures were time to smoke to a defined length (50 mm of tobacco rod) and number of puffs. The two topography measures did not differ between menthol and non-menthol smokers. The authors note that although African American smokers frequently choose menthol cigarettes, whereas White smokers frequently choose non-mentholated cigarettes, the overrepresentation of African American smokers in the menthol group may have impacted the study results. (Moderate)

Strasser et al. (2007) collected baseline topography data from treatment-seeking, menthol (n = 43) and non-menthol (n = 73) adults who smoked ≥ 10 CPD for at least the past 12 months. Participants used own-brand cigarettes (62% menthol) brought from home and were instructed to "smoke as usual." Participants (52.6% female, 63.8% White) were abstinent from smoking for 45-60 minutes before the topography session. In this between-subjects analysis, smoking topography variables (number of puffs, puff volume) did not differ significantly by cigarette mentholation, but there were gender and race/ethnicity differences for topography measures. Topography measures were not controlled for race/ethnicity, which may be significant given that 80% of menthol smokers were non-White. (Strong)

Conclusions on Menthol and Topography

Twelve articles examining the effect of menthol on topography were reviewed. Overall, results were mixed. Two strong within-subject study found that menthol is associated with some decreased topography metrics; however, these differences were not associated with changes in cigarette consumption or BOE (Gunawan & Juliano, 2020; Strasser et al., 2013). In contrast, another strong within-subject study found that menthol was associated with increased topography for some smoke metrics (Strasser et al., 2013). Additional studies reviewed in this section have found that menthol both did and did not have an impact on smoke topography. Differences in study methodology and design (i.e., using different topography metrics, including recruiting only male or female smokers, adults vs. youth, *ad libitum* or prescribed smoking instructions, time since last cigarette, smoking own-brand or study cigarettes, single or multiple exposures, using preferred or non-preferred flavor cigarettes, and within- or between-subjects analysis) limit the comparison of outcomes across studies and conclusive support for menthol's role in smoking topography. The overall breakdown of strong and moderate articles, tier, outcome, and analysis weight is presented in Figure 5.

Figure 5. Summary of analyses on smoking topography (1980-2021)
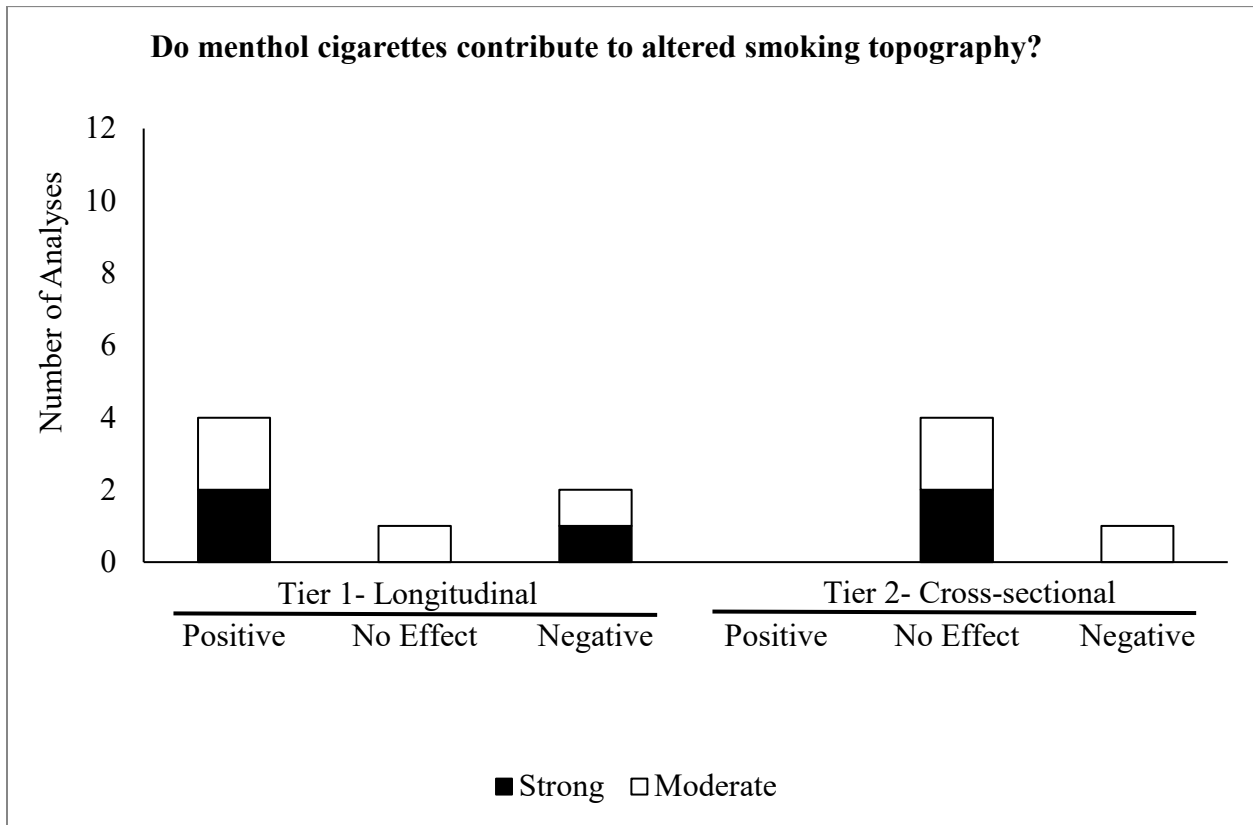
Based on the weight of evidence spanning 1980-2021, **the evidence is not sufficient to support a conclusion of an association of menthol in cigarettes with altered smoking topography**. A relationship cannot be determined between menthol and smoking topography due to the inconsistency of findings across individual studies.

XIV. STRENGTH OF EVIDENCE: CESSATION

Studies summarized in this section include the following measure used to evaluate cessation from an addiction perspective:

- Self-report and/or biochemical confirmation of cessation rates

In the case of cessation, the following study-specific criteria were used to evaluate weight of evidence:

- Longitudinal (Tier 1) and cross-sectional (Tier 2) analyses are scored as distinct groups, with the Tier 1 analyses given the most weight.
- Greater weight is given to studies with long-term (6 months or longer) compared to short-term follow-up periods.
- Greater weight is given to studies with continuous compared to point-prevalence abstinence rates.
- Greater weight is given to studies with biochemically-confirmed abstinence compared to self-report.
- Greater weight is given to longitudinal (including randomized controlled trials) compared to cross-sectional studies.
- Studies with cessation rates are given greater weight than studies reporting length of longest quit attempt in current smokers only (cross-sectional).

A brief summary is included for each analysis, presented by design (longitudinal or cross-sectional) and whether the analysis found a positive, negative, or no association with menthol and reduced cessation success. Note that some studies evaluated multiple populations within the same study and had divergent results by population. Therefore, studies that found a positive association with menthol in at least one population were scored as having a positive association with menthol and reduced cessation success and are discussed in the corresponding section.

Background

Quitting smoking, even at later ages, may result in a significant reduction in disease risk and years of life lost (Doll, Peto, Boreham, & Sutherland, 2004). Therefore, any impact that menthol in cigarettes may have on smoking cessation has the potential to substantially impact public health.

Smoking cessation is best measured by longitudinal studies examining successful cessation (including cessation treatment trials) because they allow for within-subject comparisons on related smoking trajectories and allow for a more reliable analysis of causal effects. Cross-sectional studies may be subject to recall bias, but can offer insight into self-reported cessation behaviors.

Definitions of successful cessation vary widely -- from self-report to biochemically-confirmed abstinence, past seven-day quitting to sustained quitting in the past six months, and short- or long- term follow-up periods. While longest duration of smoking abstinence on a recent quit attempt (among relapsed smokers) is not a direct measure of cessation success, it has been shown

to predict cessation success (Ferguson et al., 2003) and provides a relative measure of cessation success. Therefore, we have reviewed the literature for successful cessation measures and duration of smoking abstinence on the most recent quit attempt.

Although quit intentions and quit attempts are precursors to quitting smoking and have been shown to be predictors of cessation success (Hyland et al., 2006), we did not include these measures in our review, given the focus on direct measures of cessation success and outcomes that inform addiction potential. We did not include one publication (Lewis, Wang, & Berg, 2014) that assessed smoking cessation indirectly through purchasing behaviors because this study did not directly measure actual cigarette use or cessation outcomes in participants, and instead relied on purchasing behavior as a proxy for these outcomes. Several studies performed analyses using the same sample population (i.e., clinical trial, survey); if statistical methods and results were similar one analysis was omitted so as not to conflate findings. Otherwise, we considered all analyses to be distinct, unless otherwise indicated.

Because we include cross-sectional analyses and self-reported cessation outcomes, some findings (and therefore our conclusions) are subject to recall bias. To partially address these concerns, Tier 2 (human cross-sectional analyses) were scored separately and generally ranked lower than Tier 1 (human longitudinal analyses). Longitudinal analyses with self-report outcomes were scored lower than those with biochemically confirmed outcomes. For instances where one article evaluated more than one measure of cessation or included both longitudinal and cross-sectional assessments of cessation, each outcome was counted as a separate analysis.

Summary of Studies on Cessation Success

Longitudinal analyses (Tier 1)

Thirteen longitudinal analyses found a relationship between menthol and reduced cessation success

Bover et al. (2008) conducted an analysis designed to investigate the impact of tobacco dependence symptoms on smoking cessation, and reported that in univariate associations, menthol smokers (n = 1,048) had significantly lower self-reported cessation rates (20.1%) than non-menthol smokers (n = 1,226; 29.3%; p < 0.0001) 26 weeks after their target quit date. All study participants were smokers seeking treatment at a specialist tobacco-dependence clinic. Because the study objectives did not include menthol cigarette smoking and associations with cessation, proper consideration of covariates was not accounted for in statistical modeling, limiting the study interpretation. (Moderate)

Faseru et al. (2009) performed a secondary analysis to evaluate predictors of cessation from a clinical study designed to evaluate the effectiveness of bupropion and health education on smoking cessation in African American light smokers. Participants (menthol n = 88, non-menthol n = 452) were followed for six months and cessation was defined at the end of treatment (week 7) and week 26 as biochemically confirmed (salivary cotinine <15 ng/mL) seven-day point prevalence. In unadjusted analyses, compared to continuing smokers, participants who were abstinent at week 7 (p = 0.001) and week 26 (p = 0.005) were more likely to smoke non-menthol cigarettes. Smoking non-menthol cigarettes increased the likelihood of quitting at week

7 (OR = 1.84; 95% CI: 1.01-3.36; p = 0.05), but not week 26. As is standard, participants lost to follow-up were included in the analyses and counted as continuing to smoke. (Strong)

Gandhi et al. (2009) reported lower quit rates among African American and Latino menthol smokers from a diverse cohort of smokers attending a smoking cessation service,. Cessation was defined as seven-day point prevalence abstinence, biochemically confirmed with exhaled CO (< 10 ppm) and assessed at four weeks and six months after the quit date. The study enrolled 778 menthol smokers and 910 non-menthol smokers. In unadjusted analyses, African American and Latino menthol smokers were significantly less likely to have quit at four weeks (p < 0.001, p = 0.001, respectively) and six months (p = 0.001, 0.009, respectively) than non-menthol smokers. Among White individuals, menthol smokers were less likely to have quit at four weeks (p = 0.031) compared to non-menthol smokers. Among African American individuals, in logistic regression analyses, menthol smokers were significantly less likely to have quit smoking than non-menthol smokers at four weeks (OR = 0.34, 95% CI: 0.17-0.69) and six months (OR = 0.48, 95% CI: 0.25-0.9). Latino menthol smokers were significantly less likely to have quit smoking (OR = 0.32, 95% CI: 0.16-0.62) than non-menthol smokers at four weeks; the differences were not significant at six months. No associations were found for White smokers. The model included some measures of dependence including CPD day, age smoked for the first time, awaken at night to smoke, TTFC, and previous attempts to quit smoking. As is standard, participants lost to follow-up were included in the analyses and counted as continuing to smoke. (Strong)

Harris et al. (2004) evaluated predictors of smoking cessation among African American menthol and non-menthol smokers who received bupropion therapy for seven weeks in a secondary analysis. However, the study was originally designed to assess the efficacy of bupropion on smoking cessation at six weeks and six months following the quit date; these data are presented in Okuyemi et al. (2003). Self-reported seven-day point prevalence smoking cessation was biochemically confirmed (expired CO < 10 ppm and salivary cotinine upon discrepancy < 20 ng/mL). As reported in that study, only 28.3% of menthol smokers (n = 417) had quit at the six-week follow-up, compared to 41.5% of non-menthol smokers (p < 0.006; n = 118). Menthol smoking was not a predictor of cessation in multivariable models. As in Okuyemi et al. (2003), analyses only included participants who completed all follow-up visits. We note that this study represents duplicative findings as described in Okuyemi et al. (2003). (Strong)

Mills et al. (2020)conducted a longitudinal study using Waves 1-4 of the PATH survey to examine relations between menthol cigarette use, cessation, and relapse among adult smokers aged 18+ years. Generalized estimating equations models were used to prospectively examine the relationship between menthol cigarette use, cessation (self-reported no smoking in the past 30 days), and relapse (self-reported smoking in the past 30 days following cessation) among both daily and non-daily smokers. Adjusted regression models indicated that among daily smokers, menthol smokers had a 24% lower odds of quitting than non-menthol smokers (OR = 0.76, 9–% CI: 0.63 - 0.91). This relationship existed among both African American (OR: 0.47, 95% CI: 0.24.- 0.91) and White (OR = 0.78, 95% CI: 0.63-0.97) daily smokers, but not among individuals of Hispanic and other races/ethnicities. Among non-daily smokers, there were no significant differences in quit rates as a function of menthol status. Moreover, there were also no differences in relapse rates between menthol and non-menthol smokers. Numbers of menthol and non-menthol participants were not reported, but the overall sample size was 17,318. (Strong)

Muench and Juliano ([2017](#)) evaluated predictors of smoking lapse in a laboratory-based study designed to imitate smoking cessation attempts. The experimental method required that participants (menthol, n = 60; non-menthol, n = 21) come into the lab for baseline measures and smoke a last cigarette. Participants were instructed on methods to help them quit smoking and returned to the lab 24 and 48 hours after their last cigarette. Smoking lapse was determined via self-report and biochemical confirmation (exhaled CO > 7ppm). Predictors of smoking lapse were determined via Cox proportional hazard models. Preference for menthol cigarettes was related to a greater relapse rate (OR = 3.747, p = 0.034) within 48 hours, indicating that menthol cigarettes may make it more difficult to successfully quit smoking compared to non-menthol smokers. (Strong)

Okuyemi et al. ([2003](#)) evaluated differences in cessation rates between African American menthol (n = 417) and non-menthol (n = 118) smokers. The study was designed to assess the efficacy of bupropion (seven weeks of treatment) on smoking cessation at six weeks and six months following the quit date. Self-reported seven-day point prevalence smoking cessation was biochemically confirmed (expired CO < 10 ppm and salivary cotinine upon discrepancy <20 ng/mL). Cessation rates were significantly lower among menthol (28.3%) compared to non-menthol (41.5%) smokers at six weeks (p = 0.006) and non-significantly lower at 26 weeks (potentially due to low overall abstinence at 26 weeks). When separated by treatment in logistic regression models, the effect at six weeks was consistent among participants who received bupropion, but not placebo, treatment. Cessation rates were also significantly lower at six weeks for menthol smokers (OR = 2.02, 95% CI: 1.03-3.95) among participants aged ≤50 years. Analyses only included participants who completed all follow-up visits. The same data were used in the secondary analysis conducted by Harris et al. ([2004](#)), described above. (Strong)

Okuyemi et al. ([2007](#)), measured biochemically-confirmed (salivary cotinine ≤ 20ng/mL and exhaled CO ≤ 10 ppm), seven-day point prevalence cessation at eight and 26 weeks after randomization in a secondary analysis of a study in African American light smokers. The study was designed to measure the impact of pharmacotherapy, health education, and motivational interviewing on smoking cessation. In logistic regression models, menthol smokers (n = 615) were less likely to be quit than non-menthol smokers (n = 138) at week 26 (p = 0.015), but not week 8. In stepwise regression, non-menthol smokers had higher abstinence rates than menthol smokers within the nicotine gum and health education groups, but not motivational interviewing or placebo gum groups. (Strong)

Pletcher et al. ([2006](#)) prospectively measured smoking cessation behaviors in menthol and non-menthol smokers using the longitudinal CARDIA Study. Participants were enrolled in 1984 and were followed for 15 years. Cessation was defined as self-reported not currently smoking among participants who reported a recent quit attempt. Sustained cessation was evaluated by participants who self-reported not currently smoking during two consecutive follow-ups. In unadjusted analyses, menthol smokers (n = 563) were significantly less likely to have achieved cessation than non-menthol smokers (n = 972; OR = 0.61, 95% CI: 0.49-0.76); but when stratified by race, this difference was no longer significant. In longitudinal analyses, menthol smokers tended to be less likely to achieve sustained cessation than non-menthol smokers (AOR = 0.71, 95% CI: 0.49-1.02; p = 0.06). Menthol smokers were also significantly more likely to have relapsed (AOR = 1.89, 95% CI: 1.17-3.05; p = 0.009) than non-menthol smokers. These findings for sustained cessation and relapse remained significant among African American and European American individuals as well as in models that adjusted for CPD at baseline. (Strong)

Reitzel et al. (2011) examined continuous smoking abstinence in a population of female smokers who quit smoking within two months of becoming pregnant or during pregnancy. Abstinence was defined as continuous abstinence at eight- and 26-weeks post-partum and was biochemically confirmed with exhaled CO and/or cotinine levels. In longitudinal analyses, menthol smokers (n = 123) did not have different rates of continuous abstinence than non-menthol smokers (n = 12). However, in subgroup analyses, menthol smoking predicted abstinence among White individuals (p = 0.03). Findings only trended toward significance among African American individuals (p = 0.08). (Strong)

Reitzel et al. (2013) analyzed short-term cessation rates among menthol (n = 83) and non-menthol (n = 100) smokers in a secondary analysis of a longitudinal study evaluating changed risk perceptions in smokers motivated to quit,. Continuous cessation was determined based on self-report of not smoking any cigarettes since the quit date and was biochemically confirmed with exhaled CO (<10 ppm) at every follow-up visit; the study followed participants for three weeks past their quit date. Analyses were not controlled for dependence measures. By week 3, 12.1% of menthol smokers and 19% of non-menthol smokers achieved continuous short-term abstinence; these differences were not statistically significant. However, when stratified by race, White menthol smokers were about five times less likely to achieve continuous short-term abstinence than White non-menthol smokers (OR = 0.21, 95% CI: 0.05-0.98; p = 0.05); there were no significant effects of menthol among non-Hispanic Black individuals. Exploratory analyses examined completers-only continuous abstinence and seven-day point prevalence abstinence. Among completers-only, White menthol smokers were significantly less likely to maintain short-term abstinence than White non-menthol smokers (p = 0.04). Among White individuals, menthol smoking was also associated with significantly lower seven-day point prevalence abstinence at week 3 (p = 0.02) than non-menthol smokers. (Strong)

Rojewski et al. (2014) conducted a secondary analysis of a smoking cessation pharmacotherapy RCT in weight-concerned smokers to examine the effect of menthol smoking on cessation and latency to smoking lapse. Cessation was defined as biochemically confirmed (exhaled CO < 10 ppm) seven-day point prevalence abstinence at weeks 14 and 26 after the quit date. Age was included in the final regression models. At weeks 14 (OR = 2.10, 95% CI: 1.04-5.55; p = 0.04) and 26 (OR = 2.47, 95% CI: 1.04-5.90; p = 0.04), logistic regression analyses showed that menthol smokers (n = 61) were significantly less likely to have quit than non-menthol smokers (n = 105). However, there were no differences in latency to smoking lapse between menthol and non-menthol smokers. The study population was predominately White individuals, and race was not included in regression models. (Strong)

Smith and colleagues (2014) assessed biochemically confirmed (expired CO < 10 ppm) abstinence for 26 weeks post-quit date using data from a large comparative effectiveness trial of several smoking cessation pharmacotherapies. All participants were motivated to quit smoking. At 26 weeks, unadjusted analyses showed that menthol smokers (n = 648) had approximately 6% lower cessation rates than non-menthol smokers (n = 847). In longitudinal analyses that controlled for cessation treatment, menthol smokers were associated with reduced likelihood of successful cessation at all follow-up visits (4, 8, and 26 weeks) compared to non-menthol smokers (OR = 0.72, 95% CI: 0.60-0.87). In additional models where several covariates (including FTND) were included, the effect remained significant (OR = 0.8, 95% CI: 0.66-0.97; p = 0.0236). Further analyses showed a significant effect of menthol smoking and reduced cessation success among African American females vs. White females (p < 0.0001). Of note, this

study did not include African American non-menthol smokers in the analyses due to an insufficient population size. (Strong)

Thirteen longitudinal analyses did not find a relationship between menthol and cessation success

Blot et al. (2011) examined self-reported quit rates between menthol and non-menthol smokers enrolled in the SCSS. This study was designed to evaluate disparities in cancer and other chronic diseases. Participants were enrolled between 2002 and 2009 and completed a follow-up questionnaire. Cessation was defined prospectively by computing quit rates from the follow-up interviews for participants who enrolled as current smokers. The odds of quitting smoking at follow-up was similar among menthol (n = 7,886) and non-menthol smokers (n = 4,487). As a cross-sectional analysis, retrospective quit rates were also assessed based on information provided at entry into the cohort (described as Tier 2 analysis). (Moderate)

Brunette et al. (2018) evaluated the prevalence of menthol cigarette smoking in a young adult population with severe mental health illness. Participants (menthol n = 47, non-menthol n = 34) were recruited into a pilot study of brief cessation interventions. At the three-month follow-up visit, cessation outcomes included self-reported ≥ seven days abstinence and biochemically confirmed (CO < 9 ppm) abstinence. Menthol smoking was not associated with self-reported ≥ seven days abstinence (menthol 16.7%, non-menthol 10%) or biochemically confirmed abstinence (menthol 4.8%, non-menthol 6.7%). (Moderate)

Cropsey et al. (2009) performed a secondary analysis of a smoking cessation RCT in female prisoners and reported that menthol smoking was not associated with quit rates. The original study randomized participants to receive either behavioral and pharmacological intervention or no treatment, but this analysis only included participants enrolled in the active treatment arm. Participants (menthol n = 143; non-menthol n = 36) were encouraged to set a quit date after 3-4 weeks of starting the intervention. Cessation at 12 months from randomization was defined as seven-day point prevalence with expired CO (≤ 2 ppm) biochemical confirmation. In generalized estimating equations, menthol smoking and the interaction of menthol smoking and race were not associated with smoking cessation. As is standard, participants lost to follow-up (of those who remained at the site, >50%) were included in the analyses and counted as continuing to smoke. Of note, analyses controlled for CPD. (Moderate)

D'Silva et al. (2012) assessed self-report 30-day point prevalence abstinence rates seven months after participants called a quitline and registered in a cessation program.. There were no significant differences in abstinence for menthol (n = 1,172) compared to non-menthol (n = 5,085) smokers when the analysis was conducted on an ITT population or in responders only. Likewise, there were no significant differences with alternative definitions of abstinence, including 24-hour abstinence, prolonged abstinence, or relapse rates. In logistic regression models, menthol smoking was not associated with 30-day point prevalence abstinence. (Strong)

Fu et al. (2008) examined the effect of menthol cigarette smoking on cessation using data from a study evaluating cessation rates among participants randomized to receive either intervention or usual care. Cessation was defined as self-reported seven-day point prevalence abstinence six months after study randomization. Unadjusted models found no significant differences in cessation rates among menthol (n = 342) and non-menthol (n = 1,001) smokers. Several multivariate analyses found no differences in cessation rates between menthol and non-menthol

smokers. Analyses did not include participants who were lost to follow-up. Of note, analyses controlled for TTFC and ethnicity. (Moderate)

Hyland et al. (2002) analyzed self-reported cessation rates in smokers who enrolled in the telephone-based smoking intervention COMMIT study and who were re-interviewed five years later. Cessation was defined by asking participants if they had smoked any cigarettes in the past six months. There were no significant differences in cessation rates between menthol (n = 3,188) and non-menthol (n = 10,080) smokers overall, or when stratified by race/ethnicity. (Strong)

Jao and colleagues (2017) performed a secondary analysis (n = 474) on a RCT of smoking cessation with the transdermal nicotine patch to evaluate whether menthol smoking moderates the established relationship between NMR and smoking cessation. For this analysis, seven-day point prevalence smoking abstinence at eight weeks was biochemically confirmed with exhaled CO ($\leq$ 10 ppm). There were no significant differences in smoking cessation between menthol (31%) and non-menthol (29%) smokers. Furthermore, menthol smoking did not moderate the effect of NMR on smoking cessation. The effect of race was not evaluated. (Strong)

Kumar et al. (2021) examined whether the relationship between menthol cigarette use and increased difficulty quitting smoking extended to participants receiving methadone treatment for opioid use disorder (OUD). Participant data were pooled from three randomized controlled trials examining varenicline for smoking cessation among individuals with OUD. Cessation-related outcomes included whether participants achieved a 24-hour quit attempt at any time during the 12-week intervention, total number of quit attempts during the intervention, and whether participants achieved 7-day point prevalence abstinence during the intervention. Only 12.7% of menthol smokers (n = 237) achieved 7-day point prevalence abstinence during the intervention vs. 22.6% of non-menthol smokers (n = 31), although this difference did not reach statistical significance. (Strong)

Murray et al. (2007) conducted a secondary analysis of the Lung Health Study of smoking cessation and active treatment of chronic obstructive pulmonary disease. All participants showed early signs of lung impairment and were contacted for follow-up annually for five years. Sustained quitters had five years of self-reported and biochemically confirmed (exhaled CO < 10 ppm) abstinence; intermittent quitters had at least one visit with biochemically confirmed abstinence, but were smoking at other visits; continued smokers had no successful abstinence. Unadjusted analysis did not show a significant effect of menthol (n = 1,216) vs. non-menthol (n = 4,667) smoking in the three smoking categories. (Strong)

Steinberg et al. (2011), in a retrospective cohort study of participants with significant medical and psychiatric comorbidity who were evaluated at a tobacco dependence clinic from 2006-2008, measured self-report (by phone) or biochemically confirmed (in clinic, expired CO < 10 ppm) seven-day point prevalence quit rates six months after their quit date. Participants received behavioral therapy and FDA-approved smoking cessation medication on an individual basis. At six months, unadjusted analyses indicated that menthol smokers (n = 331) tended to have lower cessation rates than non-menthol smokers (n = 361; p = 0.06). When participant demographics (including race) and dependence were controlled for, the adjusted odds ratio suggested no association. (Strong)

Schneller et al. (2020a) used data from Waves 1 and 2 of the PATH Study to examine associations between delivery method of menthol and outcomes including cessation, nicotine

dependence, and quit attempts among 8,292 current adult cigarette smokers who completed both Wave 1 and Wave 2 PATH surveys. Menthol delivery method was categorized into four groups: non-menthol, menthol in tobacco only, menthol using a crushable capsule in the cigarette's filter only, and menthol in both the tobacco and crushable filter capsule. Cessation was defined as self-reported smoking daily or some days in Wave 1 but not at Wave 2. After adjustment, neither regression models nor pairwise comparisons indicated any association between menthol delivery method at Wave 1 and cessation Wave 2. (Moderate)

Tanner et al. (2020) conducted an analysis of secondary data from 14,123 current and former smokers in the National Lung Screening Trial to assess the association between cigarette type and nicotine dependence. Smoking abstinence was also evaluated in the study. Participants were defined as abstinent from smoking when they answered "no" to the smoking status question, "In the past 6 months, have you smoked any cigarettes?" in their final questionnaire response. There was no significant difference in adjusted smoking abstinence for menthol cigarette smokers compared with those who smoked non-menthol cigarettes. (Moderate)

Winhusen and colleagues (2013) assessed whether menthol cigarette smoking was associated with smoking cessation 10 weeks following the quit date. in a secondary analysis of a randomized trial of smoking cessation therapies in cocaine- and methamphetamine-dependent participants, Study participants were randomized to receive smoking cessation treatment (bupropion, nicotine inhaler, and counseling) in combination with usual care for substance use disorders or the substance abuse care alone. Cessation was biochemically confirmed via exhaled CO < 4 ppm. In logistic regression models, there was no association between cigarette type and smoking cessation in either cocaine-dependent (menthol, n = 201; non-menthol, n = 100) or methamphetamine-dependent (menthol, n = 33; non-menthol, n = 176) participants. Of note, analyses controlled for race/ethnicity. (Moderate)

Cross-Sectional analyses (Tier 2)

Current and former smokers

Six cross-sectional analyses in current and former smokers found a relationship between menthol and reduced cessation success

Delnevo and colleagues (2011) evaluated the odds of being a former smoker using data from the 2003 and 2006/7 TUS-CPS in current and former smokers. Various sample restrictions were made based on types of tobacco products used and quit attempts. Former smokers were defined as those who had quit smoking in the past five years and current smokers were defined as those who reported current smoking (currently reporting smoking "everyday" or "some days"). Overall, menthol smokers were less likely to be former smokers (AOR = 0.90, 95% CI: 0.88-0.98) than were non-menthol smokers. When stratified by race/ethnicity, the associations remained among Black smokers (AOR = 0.81, 95% CI: 0.67-0.98) and Puerto Rican smokers (AOR = 0.63; 95% CI not reported), and in some sample restriction groups for White (AOR = 0.93, 95% CI: 0.88-0.98) and Mexican (AOR = 1.34, 95% CI: 1.04-1.72) individuals. No significant effects were seen for Hispanic individuals overall. The number of menthol and non-menthol participants was not reported, but the sample size ranged from 24,465 to 71,193, depending on the sample restrictions. (Strong)

Gunderson et al. (2009)analyzed data from the nationally-representative 2005 NHIS to explore the relationship between menthol smoking and cessation. The population (n = 7,815) included current and former cigarette smokers who did not use other tobacco products and had made a quit attempt. Overall and among Black and Hispanic participants, menthol smokers were significantly less likely than non-menthol smokers to be former smokers (AOR = 0.55, 95% CI: 0.43-0.71; p < 0.01). In regression models, there were no overall associations between menthol smoking and being a former smoker, but Hispanic menthol vs. non-menthol smokers were significantly less likely to be former smokers (AOR = 0.61, 95% CI: 0.39-0.97; p = 0.04), and White menthol vs. non-menthol smokers were significantly more likely to be former smokers (AOR = 1.17, 95% CI: 1.00-1.36; p < 0.05). When Black and Hispanic individuals were collapsed, menthol smokers were less likely to have quit relative to non-menthol smokers (AOR = 0.55, 95% CI: 0.43-0.71; p = 0.01). Of note, analyses controlled for CPD. (Strong)

Levy et al. (2011) , reported quit rates among menthol and non-menthol smokers using data from the 2003 and 2006/7 TUS-CPS. Among former smokers, cessation was categorized by duration: recent quitters had quit within the year and had been quit for ≥3 months; long-term quitters had quit in the past five years and had been quit ≥3 months. Cessation <3 months was not considered in this analysis due to high relapse rates within the first three months of a quit attempt. In 2003 and 2006/7, menthol smokers were 4% and 12% (respectively) less likely to have quit successfully during the past year than non-menthol smokers. In 2003 and 2006/7, quit rates in menthol smokers were 11% and 14% (respectively) lower than in non-menthol smokers. In logistic regression models with pooled 2003 and 2006/7 data, menthol smokers were significantly less likely than non-menthol smokers to have quit for less than one year (approximately 3.5%; AOR = 0.92-0.97; p's < 0.001). Among non-Hispanic Black individuals (AOR = 1.24, 95% CI: 1.23-1.25; p < 0.001) and among participants aged 18-24 years (AOR = 1.14, 95% CI: 1.13-1.15; p < 0.001), menthol smokers had higher quit rates than non-menthol smokers. Menthol smokers also had statistically significant lower quit rates (approximately 6%; p's < 0.001) within the past five years than non-menthol smokers; these results were consistent among non-Hispanic Black individuals (AOR = 0.97, 95% CI: 0.97-0.97; p < 0.001) and participants aged 18-24 years (AOR = 0.94, 95% CI: 1.15-1.16; p < 0.001). Controlling for dependence did not affect outcomes. Numbers of menthol and non-menthol participants were not reported, but the 2003 and 2006/7 sample sizes were 34,206 and 31,250, respectively. (Strong)

Stahre et al. (2010) conducted a secondary data analysis of the 2005 NHIS Cancer Control Supplement to identify the population quit ratio. The population quit ratio was calculated by dividing the total number of former smokers by the total number of participants who had reported smoking during their lifetime (current [menthol n = 1,700, non-menthol n = 4,355] and former [menthol n = 1,515, non-menthol n = 4,434] smokers). Former smokers were restricted to those who quit within the past year. Among African American individuals, menthol smokers (34%) had lower population quit ratios than non-menthol smokers (49%; AOR = 0.72, 95% CI: 0.53-0.97; p = 0.031). There were no significant differences in quit ratios among White, Asian American, American Indian/Alaskan Native, or Hispanic individuals. Of note, analyses controlled for CPD. (Strong)

Sulsky et al. (2014) analyzed data from the nationally representative 2005 and 2010 NHIS and evaluated the impact of menthol smoking on the likelihood of being a former (long-term and short-term) or current (regular or daily) smoker (unweighted sample size not reported). The associated corrigendum (Sulsky et al., 2015) is also considered here. NHIS defined long-term

former smokers as those who smoked ≥ 100 lifetime cigarettes, but with a quit duration of ≥1 year. In regression models of NHIS data, there were no significant associations between menthol smoking and being a long-term or short-term former smoker vs. current smoker. When duration of smoking was substituted for current age in the models, non-Hispanic Black menthol smokers, compared to non-menthol smokers, were significantly less likely to be long-term former smokers (regular smoker: AOR = 0.56, 95% CI: 0.45-0.69; daily smoker: AOR = 0.54, 95% CI: 0.44-0.68). (Strong)

Sulsky et al. (2014) also analyzed 2010/11 TUS-CPS data and evaluated the impact of menthol smoking on the likelihood of being a short-term former or current (regular or daily) smoker (unweighted sample size not reported). The associated corrigendum (Sulsky et al., 2015) is also considered here. TUS-CPS defined short-term smokers as those smokers who smoked ≥ 100 cigarettes, but had a quit duration of 1-3 years. In TUS-CPS analyses, regression models showed a statistically significant inverse association between menthol smoking (vs. smoking non-menthol cigarettes) and being a short-term former smoker among non-Hispanic White individuals (regular smoker: AOR = 0.90, 95% CI: 0.84-0.96; daily smoker: AOR = 0.90, 95% CI: 0.84-0.96) and non-Hispanic Black individuals (regular smoker: AOR = 0.77, 95% CI:0.62-0.96; daily smoker: AOR = 0.79, 95% CI: 0.63-0.99) irrespective of whether HSI or night waking to smoke were included in the models. The authors noted that TUS-CPS provides more data on smoking dependence than NHIS (also analyzed for similar outcomes in the same publication), so they performed additional regression analyses on TUS-CPS data with only those variables provided by NHIS, including CPD, duration of smoking, and smoking initiation age. In these models, non-Hispanic White menthol smokers were significantly less likely to be short-term former smokers (regular smoker: AOR = 0.9, 95% CI 0.84-0.96; daily smoker: AOR = 0.89, 95% CI: 0.84-0.95) than non-menthol smokers. Other associations were not significant. (Strong)

Five cross-sectional analyses in current and former smokers did not find a relationship between menthol and cessation success

Blot et al. (2011) examined self-reported quit rates between menthol and non-menthol smokers enrolled in the SCSS as part of an analysis on prospective cessation rates. This study was designed to evaluate disparities in cancer and other chronic diseases. Participants were enrolled between 2002 and 2009, and retrospective quit rates were assessed based on information provided at entry into the cohort. After adjustment for covariates, in cross-sectional analysis, the odds of quitting were similar between menthol (n = 10,683) and non-menthol (n = 7,252) smokers. Black menthol and non-menthol smokers had equal prevalence of having quit smoking, but White menthol smokers were more likely than White non-menthol smokers to have quit smoking (AOR = 1.55, 95% CI: 1.41-1.70). (Moderate)

Delnevo and colleagues (2016) examined quit patterns in current and former young adult smokers (aged 18-34 years) enrolled in the 2011 NYAHS. Participants smoking at least 100 cigarettes in their lifetime reported their current cigarette use as well as cigarette use one year ago. Successful quitting was defined as smoking one year ago but not smoking currently. Although statistical analyses were not conducted on percent quit, 9.8% (95% CI: 5.6-16.5) of menthol (n = 355) and 7.2% (95% CI: 4.7-10.8) of non-menthol (n = 554) smokers reported quitting. Furthermore, 19% (95% CI: 13.9-25.6) of menthol smokers remained quit (not smoking one year ago and not currently smoking), whereas 25.5% (95% CI: 20.7-31.0) of non-menthol

smokers remained quit. Although not reported in the publication, p-values were converted from the summary statistics in the published report and confirmed that the difference in quitting behavior between menthol and non-menthol smokers was not statistically significant. (Moderate)

Keeler et al. (2017) evaluated smoking cessation rates using 2006/07 and 2010/11 TUS-CPS data on current and former smokers who quit within the last 12 months. Successful cessation was defined as no smoking for at least three months. The annual rates of successful cessation were 5.4% for menthol smokers (n = 16,871) and 6.0% for non-menthol smokers (n = 41,333); this finding was not statistically significant. In multiple regression models, there were no significant differences in successful cessation between menthol and non-menthol smokers, or when stratified by race/ethnicity. (Strong)

Keeler and colleagues (2018) evaluated the effects of cigarette price on cessation outcomes using data from the 2006-2007 and 2010-2011 TUS-CPS data. Successful cessation was defined as self-reported cessation for at least three months. Cessation in non-Hispanic African American (n = 3,096 menthol, n = 997 non-menthol) and non-Hispanic White (n = 3,324 menthol, n = 31,079 non-menthol) individuals was analyzed. Menthol cigarette smoking was not associated with successful cessation compared to non-menthol smoking in either population. (Strong)

Muscat et al. (2002) assessed cessation among menthol (n = 3,005) and non-menthol (n = 16,540) current and former smokers from a cross-sectional case-control study of tobacco-related cancers conducted between 1981 and 1999. Former smokers did not smoke at least one CPD for the prior year. In unadjusted analyses, Black and White menthol smokers were more likely to be former than current smokers. Unconditional logistic regression models did not show an association between continued smoking and menthol (vs. non-menthol) smoking for Black or White individuals. Of note, analyses were adjusted for years of smoking and CPD. (Moderate)

Current (Relapsed) Smokers

One cross-sectional analysis in current smokers did not find a relationship between menthol and cessation success

Fagan and colleagues (2010) compared length of smoking abstinence in the past year between menthol (n = 11,671) and non-menthol (n = 33,644) cigarette smokers who reported one or more quit attempts by pooling data from the nationally representative 2003 and 2006/07 TUS-CPS,. Duration of abstinence was categorized as greater or less than two weeks. In multivariate logistic regression models, there were no associations between menthol smoking and duration of abstinence greater than two weeks in models stratified by CPD. Age of smoking onset and total years smoked daily were included as covariates in these models. (Moderate)

Former smokers

One cross-sectional analysis in former smokers found a relationship between menthol and reduced cessation success

Trinidad et al. (2010) used data from the 2003 and 2006/7 TUS-CPS to examine racial/ethnic differences in the relationship between using cessation. Among former smokers, across racial/ethnic groups, those who smoked menthol (n = 3,826) cigarettes (vs. non-menthol (n = 12,722) were significantly less likely to have successfully quit for at least six months: African

American (OR = 0.23, 95% CI: 0.17–0.31), Asian Americans/Pacific Islander (OR = 0.22, 95% CI: 0.11–0.45), Hispanic/Latino (OR = 0.48, 95% CI: 0.34–0.69) and Non-Hispanic White (OR = 0.28, 95% CI: 0.25–0.33) individuals. (Moderate)*One cross-sectional analysis in former smokers found no relationship between menthol and cessation success*

Cubbin et al. (2010) used data from the NHIS-CCS (2005) (n = 31,428) to examine relationships between menthol cigarette smoking and initiation, smoking rate, and cessation. After adjusting for other sociodemographic characteristics, all analyses evaluating menthol and cessation success found no relationship except among White women, where menthol smokers reported significantly longer cessation compared with non-menthol smokers. (Moderate)

Meta-Analyses

Two Meta-analyses found a relationship between menthol and reduced cessation success

Sanders et al. (2017) conducted a meta-analysis of 29 published cessation analyses and found that menthol smoking is associated with decreased cessation success (random effects OR = 0.87, 95% CI 0.80–0.96); the relationship was consistent among African American (n = 14 estimates; random effects OR = 0.76, 95% CI 0.62–0.92), but not Caucasian (n = 10 estimates; random effects OR = 1.02, 95% CI 0.87–1.19) individuals. While large studies (n = 13; random effects OR = 0.98, 95% CI 0.89–1.09) did not find an association between menthol smoking and decreased cessation success, randomized controlled trials (n = 17; random effects OR = 0.7, 95% CI 0.60–0.82) did. It is important to note that cessation estimates that were adjusted for nicotine dependence were not included in the meta-analysis to avoid over-adjustment. (Not scored)

Smith et al. (2020) conducted a meta-analysis summarizing the state of evidence regarding the association between menthol cigarette use and the likelihood of smoking cessation. The search strategy involved searching Medline, PsychINFO, and Embase for prospective and cross-sectional studies of the association between menthol cigarette use and cigarette smoking cessation. Twenty-two reports met criteria for inclusion in the review, of which 21 included only U.S. smokers, and one included both U.S. and Canadian smokers. Results overall did not demonstrate a significant association between menthol use and cessation. However, among African American smokers, menthol users were significantly less likely to quit cigarette smoking than non-menthol cigarette smokers (OR = 0.88). Across studies, approximately half of the variance in the association between menthol cigarettes and smoking cessation was attributable to explainable heterogeneity. More specifically, race/ethnicity accounted for roughly 47% of this heterogeneity, in that among African American smokers, menthol cigarette use was associated with 12% lower odds of smoking cessation (p = 0.04), whereas among White smokers there was no association between cigarette type and the likelihood of cessation. Among studies that did not report results for racial/ethnic subgroups, menthol smokers had 14% lower odds of successfully quitting smoking compared to non-menthol smokers (p = 0.03). (Not scored)

Conclusions on Menthol and Cessation Success

Forty-three articles and two meta-analyses that evaluated the impact of menthol on cessation rates or duration of the longest quit attempt were reviewed. Forty-five analyses were identified across the included articles; one article included results from two nationally representative surveys (Sulsky et al., 2014) and another included both a longitudinal and a cross-sectional analysis (Blot et al., 2011) , with respective outcomes were scored as Tier 1 or Tier 2 analyses. After review, five analyses were scored as weak and are described in Appendix F; these analyses and one analysis that represented duplicative findings (Harris et al., 2004) were not considered in the weight of the evidence. Therefore, 39 analyses were determined to be of strong or moderate quality considered in the weight of evidence for cessation across the 37 articles, and were either longitudinal (Tier 1, n = 25) or cross-sectional (Tier 2, n = 14) in nature.

Of note, we additionally identified a pilot study by Kotlyar et al. (2020) that examined if switching to non-menthol cigarettes was an effective first step towards cessation for menthol smokers interested in quitting. However, this study was not included in this review because it did not evaluate differences between menthol and non-menthol smokers for cessation success (i.e., some menthol smokers were switched to non-menthol cigarettes and their cessation outcomes were compared to menthol smokers who continued to smoke menthol cigarettes).

After scoring individual analyses, the breakdown of strong and moderate analyses by tier, outcome, total number, and percentage of total analyses were evaluated. There was a large amount of variability across the different studies in this body of literature. For example, across menthol and cessation studies, populations varied by sociodemographic factors such as race/ethnicity, gender, and geographic region; studies ranged from large nationally representative samples to small clinical trials of cessation; studies varied by the follow-up timepoints at which they assessed cessation, ranging from 48 hours to 15 years; studies did not use the same methods or definitions to measure cessation; and studies did not control for the same factors that may influence cessation outcomes (e.g., demographics, nicotine dependence, use behaviors). Due to this study heterogeneity, analyses were separated into two categories to better understand the potential relationship between menthol smoking and cessation success: the general population and Black individuals specifically.

General Population

This category included all strong and moderate analyses reviewed that analyzed cessation rates in the general population. Therefore, analyses in female prisoners and vulnerable populations with mental health or substance use disorders were not included in this category. Although these findings are important to understand in the context of menthol's effects on vulnerable populations, the altered smoking environments of prison populations and the smoking behaviors of smokers with comorbid substance use or mental health disorders (given the generally greater smoking prevalence, nicotine dependence, and difficulty quitting in these populations) (Centers for Disease Control, Prevention, 2020)) have limited generalizability to the general smoking population. As a result, five analyses were excluded from the general population category (Brunette et al., 2018; Cropsey et al., 2009; Kumar et al., 2021; Steinberg et al., 2011; Winhusen et al., 2013).

If an analysis found a significant effect of menthol on smoking cessation in one population (e.g., Black individuals), but not others (e.g., Hispanic individuals), it was included in the "Positive" category. It should be noted that two cross-sectional analyses found that menthol may augment quit rates in White smokers (Blot et al., 2011) and White female smokers (Cubbin et al., 2010). Another cross-sectional analysis found that among non-Hispanic Black individuals, menthol smokers had higher quit rates than non-menthol smokers (Levy et al., 2011). Although these findings are important to consider in the context of the associated analyses, the analyses were not considered in the weight-of-evidence (i.e., a separate category for analyses finding that menthol augments cessation success) given that other analyses have not replicated such findings in the same populations. These results, however, are described in the summaries.

Of 34 strong and moderate analyses that evaluated the general population of smokers, 12 Tier 1 analyses concluded that menthol smokers have a more difficult time quitting smoking than non-menthol smokers; in contrast, eight Tier 1 analyses concluded that menthol smokers do not have a more difficult time quitting smoking than non-menthol smokers. Among Tier 2 analyses, an equivalent number of analyses (n = 7) concluded either that menthol smokers have a more difficult time quitting smoking or that there was no effect of menthol on cessation success (n = 7). Of note, analyses of the general population are not necessarily analyses of a nationally representative population, given that the majority of Tier 1 analyses identified were not nationally representative. The weight of evidence breakdown by tier, outcome, and analysis weight is presented in Figure 6. The breakdown of each outcome, total number, and percentage of total analyses (in parentheses) is presented in Table 3.

Figure 6. Summary of analyses on cessation in the general population (1980-2021)
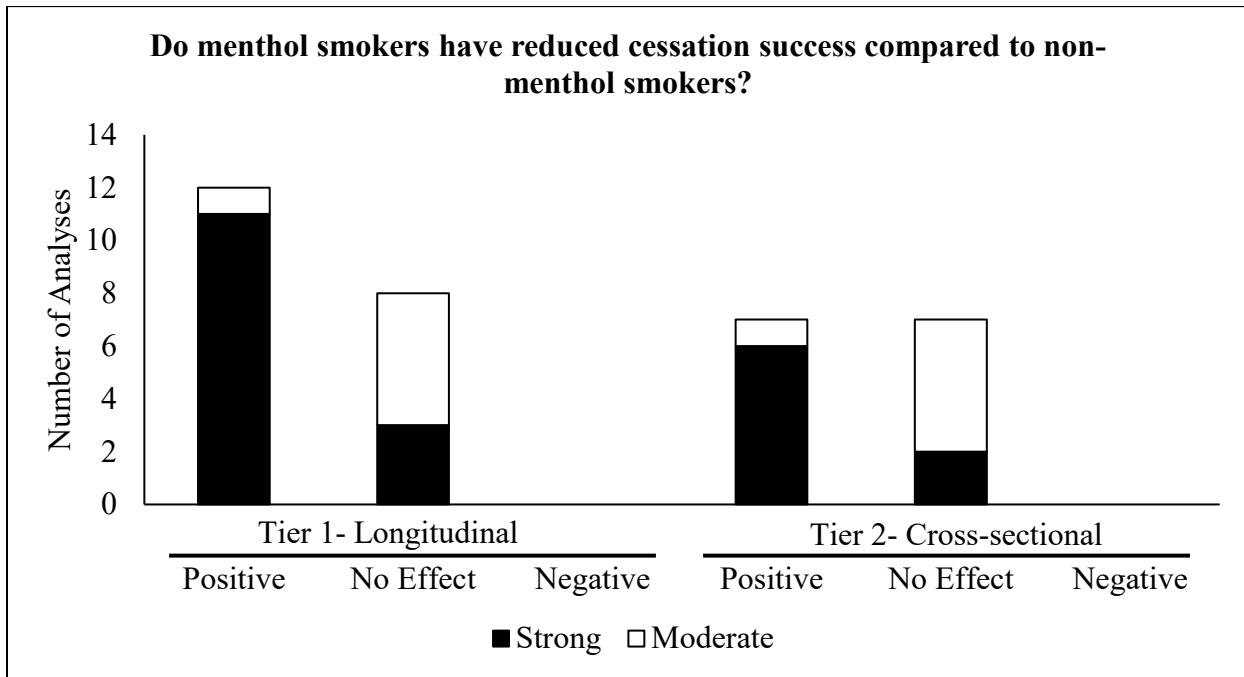
Table 3. Summary of cessation analyses in the general population (1980-2021)

Score	Tier 1 (n = 20)			Tier 2 (n = 14)		
	POS	**No Effect**	**NEG**	**POS**	**No Effect**	**NEG**
Strong	11 (32.4)	3 (8.8)	0	6 (17.6)^	2 (5.9)^	0
Moderate	1 (2.9)	5 (14.7)	0	1 (2.9)	5 (14.7)	0
Total	*12 (35.3)*	*8 (23.5)*	*0*	*7 (20.6)*	*7 (20.6)*	*0*

Note. Values represent n(%) POS= Positive ; NEG= Negative
^Two analyses present findings from the same cross-sectional surveys but populations were defined differently.

These data are heterogeneous, likely given the different study populations, study designs, outcome measures, and follow-up periods. However, of 14 strong Tier 1 analyses, a greater proportion (n = 12, 86%) found that menthol is associated with reduced cessation success in the general population. This includes a longitudinal PATH study that evaluated smoking cessation outcomes among smokers at a 12 month follow-up (Mills et al., 2020). Nine of the 12 Tier 1 analyses that found an association of menthol with reduced cessation success also biochemically-verified cessation and had follow-up periods of up to six months, thereby strengthening the weight of this body of evidence. Of the eight Tier 1 analyses that did not find an association, only three biochemically-verified cessation. As such, of Tier 1 studies that biochemically-verified cessation with follow-up periods of up to six months, the majority were strong analyses that found an association with menthol and reduced cessation success. Additionally, while one analysis that had a follow-up of 5 years did not find an effect of menthol on cessation success (Hyland et al., 2002), the study with the longest follow-up period (15 years) found that menthol is associated with reduced cessation success among young adult smokers (Pletcher et al., 2006).

Among Tier 2 (cross-sectional) studies, an equivalent proportion of nationally representative studies found that menthol either is or is not associated with reduced cessation success; all studies that found an effect of menthol were nationally representative (n = 7) while five of the seven studies that did not find an effect of menthol were nationally representative. The majority of strong Tier 2 analyses found that menthol was associated with reduced cessation success. These analyses received greater weight in the totality of evidence because: they were more likely to be in populations of current and former smokers (vs. current relapsed smokers or only former smokers); they evaluated cessation rates (vs. longest quit attempt in current smokers); and they evaluated continuous abstinence (vs. point-prevalence abstinence).

Based on the weight of evidence from the majority of strong longitudinal and nationally representative analyses reviewed from 1980 through 2021, **menthol in cigarettes is likely associated with reduced cessation success among the general population.**

Black Individuals

Due to the high rates of menthol smoking among Black individuals and because several Tier 1 analyses evaluated the effects of menthol on cessation in Black smoking populations exclusively, we also evaluated the effects of menthol in this population separately.

Analyses conducted in Black smokers only and those that stratified by race/ethnicity were also evaluated independently. Two strong analyses evaluated the impacts of menthol on cessation in Black individuals based on the same bupropion clinical trial data (Harris et al., 2004; Okuyemi et al., 2003); because they provided duplicative results, Harris et al. (2004)was not included in the weight of evidence. Of these 22 analyses, six strong Tier 1 and six strong and one moderate Tier 2 analyses concluded that Black menthol smokers have a more difficult time quitting cigarette smoking than non-menthol smokers (n = 13 total; 59.1% of analyses). In contrast, three strong and one moderate Tier 1 and two strong and three moderate Tier 2 analyses concluded that Black menthol smokers do not have a more difficult time quitting cigarette smoking than non-menthol smokers (n = 9 total; 40.9% of analyses). The weight of evidence breakdown by tier, outcome, and analysis weight is presented in Figure 7. The breakdown of each outcome, total number, and percentage of total analyses (in parentheses) is presented in Table 4.

Figure 7. Summary of analyses on cessation among Black individuals (1980-2021)
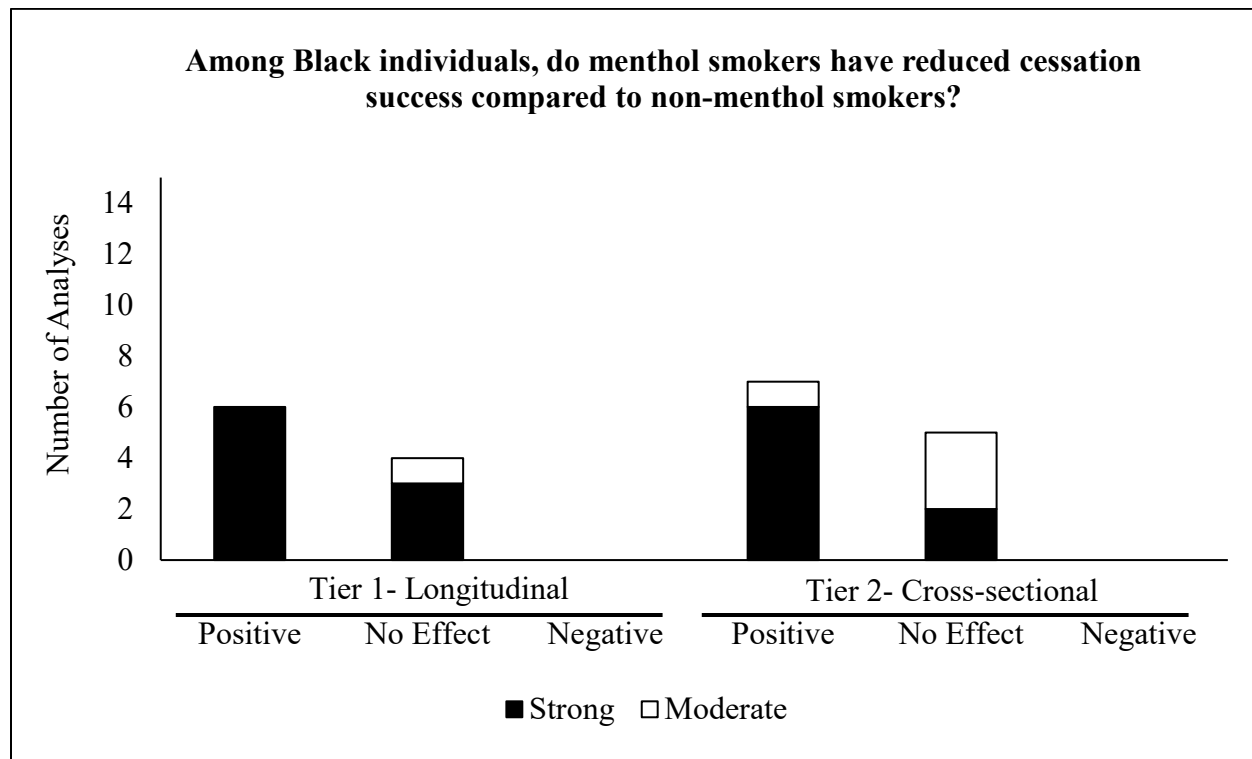
Table 4. Summary of analyses on cessation among Black individuals (1980-2021)

Score	Tier 1 (n = 10)			Tier 2 (n = 12)		
	POS	**No Effect**	**NEG**	**POS**	**No Effect**	**NEG**
Strong	6 (27.3)	3 (13.6)	0	6 (27.3)^	2 (9.1)^	0
Moderate	0	1 (4.5)	0	1 (4.5)	3 (13.6)	0
Total	*6 (27.3)*	*4 (18.2)*	*0*	*7 (31.8)*	*5 (22.7)*	*0*

Note. Values represent n(%) POS= Positive ; NEG= Negative
^Two analyses present findings from the same cross-sectional surveys but populations were defined differently.

A greater proportion of strong Tier 1 analyses (60%) found an effect of menthol on reduced cessation success in Black individuals, including one nationally representative longitudinal study that evaluated cessation success after 12 months (Mills et al., 2020). Analyses were conducted among current or treatment seeking smokers; the majority, which were RCTs, also biochemically verified cessation and had follow-up periods of up to six months. Of Tier 1 analyses that did not find an association, the majority also biochemically verified cessation, but half the analyses were in populations that are not generalizable to the population of smokers (i.e., pregnant women, female prisoners), which resulted in lower weight for these analyses. As such, of Tier 1 studies that biochemically verified cessation with follow-up periods of four weeks to six months and that were generalizable to the smoking population, the majority were strong analyses that found an association with menthol and reduced cessation success. The study with the longest follow-up period of 15 years also found that Black menthol smokers have reduced cessation success compared to Black non-menthol smokers (Pletcher et al., 2006). Across Tier 2 analyses that were nationally representative (n = 10), a greater proportion of strong studies (70%) found that menthol was associated with reduced cessation success compared to 30% of analyses that did not find an association.

Based on the weight of evidence spanning 1980-2021, **menthol in cigarettes is associated with reduced cessation success among Black individuals**. While not considered in the weight of the evidence, these conclusions of reduced cessation success among Black smokers are supported by results from two meta-analyses of the cessation literature (Sanders et al., 2017; Smith et al., 2020).

XV.   SUMMARY OF EVIDENCE

Sensory Effects

Evaluation of the sensory effects of menthol found that menthol in cigarettes contributes to positive smoking experiences among menthol smokers. This conclusion was based on findings from the majority of Tier 2 (human cross-sectional) and Tier 3 (nonclinical) analyses (75%), which provided strong support for the sensory effects of menthol in reducing irritation produced by cigarette smoke and enhancing nicotine consumption. A small percentage of analyses (25%) indicated no difference in sensory effects of menthol compared to non-menthol cigarettes; however, other factors, such as differences in cigarette nicotine content in the study cigarettes, may have affected interpretation of the results in the context of menthol's sensory effects.

The sensory effects of menthol make cigarettes more palatable by masking the harsh taste of tobacco and reducing aversive responses associated with initial smoking experiences (e.g., throat irritation, coughing) that can deter new and inexperienced users from repeated experimentation. Because studies support a likely effect of menthol on progression to regular cigarette smoking in youth and young adults, the sensory effects of menthol likely contribute to this effect. Repeated exposure to nicotine, particularly during adolescence, increases the likelihood of addiction (Benowitz, 2010; Yuan, Cross, Loughlin, & Leslie, 2015). Consequently, youth who initiate smoking with menthol cigarettes may be at greater risk for progression from experimentation to established smoking and nicotine dependence than youth who initiate with non-menthol cigarettes (Delnevo et al., 2016; Nonnemaker et al., 2013).

Progression to Regular Cigarette Use

The weight of evidence supports that menthol in cigarettes is associated with progression to regular smoking among youth and young adults. The six analyses reviewed were all strong studies that compared menthol and non-menthol smokers, and the majority (n = 4, 66.7%) were categorized under Tier 1 (human longitudinal). Therefore, this conclusion is supported by multiple, strong, longitudinal and cross-sectional, nationally representative studies of tobacco use among youth and young adults.

Dependence

When evaluating the totality of evidence across studies in adult subjects (human and animal), the strength of evidence is not sufficient to support conclusions of an association between menthol cigarettes and dependence among adults. Dependence was evaluated based on several measures, including individual scales of nicotine dependence (e.g., FTND, NDSS, WISDM), TTFC, CPD, night waking to smoke, smoking frequency, craving, and nicotine BOE and nicotine pharmacokinetics. It is noted that a number of analyses were conducted as comparisons of baseline characteristics, and as such, did not generally control for confounding variables (e.g., race, sex, age).

The evidence for this conclusion was based on the inconsistency of findings across analyses. The majority of analyses found no significant difference in level of dependence between adult menthol and non-menthol smokers based on various dependence outcomes. However, several strong and moderate analyses have identified an association with menthol and increased dependence, and this body of evidence cannot be negated.

Studies were conducted across multiple heterogenous populations and a variety of different dependence measure were used across studies. Therefore, evaluations of individual nicotine dependence outcomes in adults were conducted. In weighing the evidence based on analyses of scales of dependence (e.g., FTND, HSI), the majority of analyses indicated no significant difference between menthol and non-menthol smokers in level of dependence. Although TTFC was the single item measure that most frequently identified significant differences between menthol and non-menthol smokers, results for this measure are mixed, such that the evidence is not sufficient to support an association of menthol in cigarettes with effects on TTFC. It is noted that different studies measured TTFC using different time categories. For example, some studies evaluated TTFC as a dichotomized variable (e.g., do you smoke within 5-30 min of waking [yes/no]), whereas other studies used a continuous variable (i.e., ≤ 5, 6-30, 31-60, and > 60 minutes) or author-generated time categories. For this review, studies measuring TTFC were evaluated based on the measure as a whole and were not separated based on the different time brackets. As such, it is possible that different results may have been identified for specific time points (e.g., differences identified in the < 5 minutes time point vs. < 30 minutes time point). Indeed, a meta-analysis identified found that comparison of studies that determined TTFC within 5 min found that menthol smokers were more likely than non-menthol smokers to smoke within the first 5 min of waking (Sanders et al., 2017). Differences were not significant when comparing studies that evaluated TTFC within 30 min of waking.

Studies evaluating nicotine BOE and/or nicotine pharmacokinetics were also inconsistent. Analyses show mixed results regarding menthol's effect on nicotine exposure or pharmacokinetics. Thus, the evidence is not sufficient to support conclusions of an association of menthol in cigarettes with effects on nicotine exposure or pharmacokinetics. Of note, racial/ethnic, gender, and genetic differences in the rate of nicotine metabolism have been observed across smokers (Benowitz et al., 2011; Caraballo et al., 2011). Therefore, although we examined individual dependence outcomes, dependence in general may be influenced by these differences in nicotine metabolism that may not have been accounted for across dependence studies.

Alternatively, youth analyses support that menthol in cigarettes is associated with greater dependence, i.e., among youth, menthol smokers are more nicotine dependent than non-menthol smokers. This relationship was observed in multiple strong, nationally representative studies in youth and in animal adolescent studies of nicotine's abuse liability. Although some studies did not find a relationship between menthol cigarettes and dependence in youth, the limitations of these studies resulted in lower weight for these analyses in the totality of evidence. The weight of the evidence from the strongest nationally representative studies on youth supports that menthol is associated with increased dependence among youth.

The nonclinical studies reviewed in this section indicate that the effects of menthol extend beyond sensory. Findings demonstrate that menthol has pharmacological effects in the brain that alter the effects of nicotine and subsequently affect addiction outcomes. Nonclinical studies identified in this review demonstrate that menthol alone upregulates nAChR in the brain (Alsharari et al., 2015; Henderson et al., 2016). Menthol also enhances nicotine-induced nAChR upregulation to a greater extent than nicotine alone in brain regions implicated in addiction (Alsharari et al., 2015; Henderson et al., 2017; Henderson et al., 2016). Enhanced receptor upregulation was accompanied by greater intensity of nicotine withdrawal signs in rodents treated with nicotine and menthol compared to those treated with nicotine alone (Alsharari et al.,

2015). These findings from animal studies are consistent with clinical data, which indicate that menthol cigarette smokers have higher levels of brain nicotinic receptors compared to non-menthol smokers (Brody et al., 2013). Smokers with greater nicotinic receptor levels in the brain have a decreased likelihood of successful quitting than smokers with lower nicotinic receptor levels (Brody et al., 2014).

Menthol also enhances nicotine-induced dopamine release in the nucleus accumbens shell (Zhang et al., 2018) and enhances nicotine-induced increases in midbrain dopamine neuron function and activity to a greater extent than nicotine alone (Henderson et al., 2017). Changes in midbrain dopamine function were associated with differences in behavioral responses to the rewarding effects of nicotine, where menthol-treated rodents exhibited greater reward for nicotine than those treated with nicotine alone.

These findings suggest a mechanism by which menthol interacts with nicotine in the brain at the receptor level to enhance nicotine addiction. Youth and young adults who experiment with smoking are at greater risk of becoming addicted to nicotine and maintaining tobacco product use into adulthood (U.S. Department of Health and Human Services, 2012; Yuan et al., 2015).Therefore, due to the combined effects of nicotine and menthol in the developing brain, youth who smoke menthol cigarettes are particularly vulnerable to the effects of menthol on dependence.

Smoking Topography

Evidence is not sufficient to support a conclusion of an association between menthol in cigarettes and altered smoking topography. This conclusion is based on the overall findings from Tier 1 studies that measured within and/or between subject differences between cigarette types, as well as Tier 2 studies that measured differences between menthol and non-menthol smokers. The Tier 1 studies were more supportive of an existing effect of smoking menthol on topography. However, of the strong Tier 1 studies, two concluded that topography differences in menthol and non-menthol smoking did not result in a meaningful change in behavior (e.g., CPD, BOE) (Strasser et al., 2013) and another conducted analyses by cigarette type, but did not analyze the effects of participant menthol preference (Watson et al., 2017). The majority of Tier 2 studies found no effect of menthol on smoking topography. Differences in study designs and small sample size limit the comparison of outcomes across studies. Differences in methodology across studies also limit conclusive support for menthol's role in affecting topography.

Cessation

The weight of evidence supports that menthol in cigarettes is likely associated with reduced cessation success in the general population and that menthol is associated with reduced cessation success among Black smokers.

Because the study populations assessed for cessation outcomes in the literature were highly variable, we analyzed the weight of evidence in studies that evaluated the general population of smokers. While results from studies among smokers with comorbid substance use or mental health disorders are important to understand in the context of menthol's effects on vulnerable populations, these studies, as well as studies in female prisoners who smoke, have limited generalizability to the general smoking population. Of twenty-three strong Tier 1 and Tier 2

cessation studies, the majority (n = 18, 78.3%) indicated that menthol cigarettes are associated with decreased cessation success in the general population.

The meta-analyses identified during this review note the high heterogeneity observed across the body of menthol and cessation literature (Sanders et al., 2017; Smith et al., 2020). Variability across study populations and methods likely contributes to differences in findings related to cessation in the general population. Analyses in that were conducted only among Black smokers and those that stratified by race/ethnicity were also evaluated independently. Of these Tier 1 and Tier 2 analyses, a slight majority found an association with Black menthol smokers and decreased cessation success. Although some strong and moderate studies failed to identify an association, the strong longitudinal studies that were generalizable to a population of smokers (including a nationally representative longitudinal study) and the majority of strong nationally representative cross-sectional studies support a role for menthol in reduced cessation success among Black smokers. Given the strength of evidence from studies finding a positive relationship with this outcome, the weight of evidence supports an association between menthol in cigarettes and reduced cessation success among Black smokers. We also note that these conclusions of reduced cessation success among African American menthol smokers are supported by two meta-analyses of the literature (Sanders et al., 2017; Smith et al., 2020).

Menthol's ability to enhance the effects of nicotine in the brain likely contributes to why some menthol smokers have greater difficulty quitting smoking compared to non-menthol smokers. As discussed in the Background and Rationale section of this review, repeated exposure to nicotine through smoking leads to an increase in nicotine levels in the brain, prompting nAChRs to become less responsive to nicotine (desensitization) and increase in number (upregulation) (Benowitz, 2010). When an individual stops smoking, such as overnight or when attempting to quit, nicotine levels fall, returning nAChRs to a responsive state. The combination of high levels of nAChRs and low levels of nicotine in the brain produces the discomfort smokers feel when experiencing signs of nicotine withdrawal (Dani & Heinemann, 1996).

Indeed, smokers with greater brain nicotinic receptor levels have more difficulty quitting than smokers with lower brain nicotinic receptor levels (Brody et al., 2014) Clinical and animal studies show that menthol enhances nAChR upregulation to a greater extent than nicotine alone; these changes occur in brain regions involved in the development of nicotine addiction (Alsharari et al., 2015; Brody et al., 2013; Henderson et al., 2017; Henderson et al., 2016). Although inconsistencies across the body of evidence result in inconclusive conclusions overall regarding the role of menthol in reduced cessation success, these findings suggest a mechanism by which menthol may contribute to greater difficulty quitting among smokers.

XVI.   LIMITATIONS

There are some limitations noted in this review. First, there is the possibility of publication bias, as only articles in English and those that were conducted in the U.S. were included, the cut-off search year was 1980, and unpublished studies were not included. We note that positive results are more likely to be published than negative or null findings and acknowledge that this effect can lead to bias in meta-analyses and drawing erroneous conclusions (Mlinarić, Horvat, & Šupak Smolčić, 2017). We acknowledge the possibility that topics where inconsistent results were reported such that an association could not be determined may have been influenced by

publication bias. Second, we did not consider funding bias, which may influence study outcomes, in the scoring of studies. Although several reviewed studies were sponsored by FDA or industry, outcomes on menthol in cigarettes (i.e., positive, negative, and no effect) were widely dispersed across funding sources. As such, we do not believe funding bias was a major contributing factor to the conclusions. Third, there may be articles that included measures comparing menthol and non-menthol smokers (e.g., CPD) as part of the description of sample characteristics that were not identified in the literature search or during the initial title/abstract screen, because assessing differences in menthol and non-menthol smokers was not a primary study aim. However, it is unlikely such articles would meaningfully contribute to the weight of the evidence. Fourth, because several studies performed analyses using the same sample population (i.e., data set, survey), some publications may present repetitive or duplicative results. We acknowledge that this approach has the potential to conflate findings or yield conflicting findings; however, given different statistical methods, covariates, and definitions of outcomes, we think that each analysis adds value to the evidence base and are transparent about which analyses are duplicative. Although we note data source and sample populations, we considered all analyses to be distinct. Fifth, race and ethnicity were presented as defined in the article reviewed, and racial/ethnic definitions may not be consistent across studies. Lastly, we did not have access to raw data for any study to perform independent statistical analyses and did not obtain additional information about the study beyond what was in the publication.

XVII. CONCLUSIONS

This scientific review evaluated the effects of menthol in cigarettes on addiction, including sensory effects, progression to regular use, dependence, smoking topography, and cessation. The findings from this review are indicated in Table 5 below.

Table 5. Summary of conclusions on menthol in cigarettes

Outcome	Conclusions/Effect of Menthol
Sensory effects	**Associated with positive smoking experiences that contribute to cigarette smoking**
Progression to Regular Use	**Associated with progression to regular cigarette smoking among youth and young adults**
Dependence	Evidence is not sufficient to support conclusions of an association with dependence in adults; **Associated with greater dependence in youth**
Topography	Evidence is not sufficient to support conclusions of an association with altered smoking topography.
Cessation	**Likely associated with reduced cessation success among the general population**; **Associated with reduced cessation success among African American smokers**

The weight of available scientific evidence supports that the sensory effects of menthol contribute to positive smoking experiences that facilitate repeated use. Specifically, the flavor and sensory effects of menthol facilitate repeated experimentation by masking the harsh taste of

tobacco, which introduces nicotine to new users in a less aversive manner than non-menthol cigarettes (Klausner, 2011). Indeed, evidence supports a role for menthol in progression to regular use among youth and young adults, and greater dependence among youth. Youth and young adults are particularly susceptible to the addictive effects of nicotine due to ongoing brain development (U.S. Department of Health and Human Services, 2012; Yuan et al., 2015). Menthol's flavor and sensory effects facilitate repeated experimentation and progression to regular smoking, which repeatedly exposes the brain to nicotine. Menthol also enhances nicotine-induced nAChR upregulation and dopamine release and neuron function to a greater extent than nicotine alone (Alsharari et al., 2015; Brody et al., 2013; Henderson et al., 2017; Henderson et al., 2016; Zhang et al., 2018). Therefore, due to the flavor and sensory effects of menthol, and the combined effects of nicotine and menthol in the developing brain, youth who smoke menthol cigarettes are particularly vulnerable to nicotine addiction.

For studies of cessation, the evidence is sufficient to support a conclusion of a likely association of menthol with reduced cessation success in the general population. Furthermore, among Black smokers, given the strength of evidence from studies finding a positive relationship with the outcome, the weight of evidence supports that menthol is associated with reduced cessation success. Menthol's ability to enhance the effects of nicotine in the brain (e.g., enhanced nAChR upregulation) likely contributes to why some menthol smokers have greater difficulty quitting smoking compared to non-menthol smokers.

Based on the current state of the science, the weight of evidence supports an association between menthol in cigarettes and altered addiction outcomes in menthol smokers compared to non-menthol smokers. The combination of menthol's flavor, sensory effects, and interaction with nicotine in the brain contribute to the effect of menthol on nicotine addiction. Findings from the current review may inform potential future regulatory activities related to menthol in cigarettes.

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XIX. APPENDICES

Appendix A: Full Electronic Search Strategy

Menthol Cigarette Search
9/13/16

PubMed
menthol* AND (cigarette[TW] OR cigarettes[TW]) Filters: Publication date from 1980/01/01

Results = 392

EMBASE
menthol* AND ('cigarette'/exp OR cigarette:ab,ti OR cigarettes:ab,ti) AND [1980-2016]/py

Results = 509

Web of Science
TOPIC: menthol* AND (cigarette OR cigarettes)

Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan = 1980-2016

Results = 454

EbscoHOST (PsycInfo and Academic Search Complete)
Menthol* AND (cigarette OR cigarettes)

Limiters - Scholarly (Peer Reviewed) Journals; Published Date: 19840101-20161231

Results = 494

Menthol Cigarette Search

1/2/18

PubMed

menthol* AND (cigarette[TW] OR cigarettes[TW]) Filters: Publication date from 2016/09/13

Results = 92

EMBASE

menthol* AND ('cigarette'/exp OR cigarette:ab,ti OR cigarettes:ab,ti) AND [2016-2018]/py

Results = 103

Web of Science

TOPIC: menthol* AND (cigarette OR cigarettes)

Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1980-2016

Results = 118

EbscoHOST (PsycInfo and Academic Search Complete)

Menthol* AND (cigarette OR cigarettes)

Limiters - Scholarly (Peer Reviewed) Journals; Published Date: 20160901-20180131

Results = 70

Menthol Cigarette Search

1/2/19

PubMed

menthol* AND (cigarette[TW] OR cigarettes[TW]) Filters: Publication date from 2018/01/03 to 2019/01/02

Results = 97

EMBASE

menthol* AND ('cigarette'/exp OR cigarette:ab,ti OR cigarettes:ab,ti) AND [2018-2019]/py

Results = 84

Web of Science

TOPIC: menthol* AND (cigarette OR cigarettes)

Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan = 2018-2019

Results = 90

EbscoHOST (PsycInfo and Academic Search Complete)

Menthol* AND (cigarette OR cigarettes)

Limiters - Scholarly (Peer Reviewed) Journals; Published Date: 20180101-20190131

Results = 87

Menthol Cigarette Search, 1/6/2020

PubMed

menthol* AND (cigarette[TW] OR cigarettes[TW]) Filters: Publication date from 2019/01/03 to 2020/01/03

Results = 107

EMBASE

menthol* AND ('cigarette'/exp OR cigarette:ab,ti OR cigarettes:ab,ti) AND [2019-2020]/py

Results = 115

Web of Science

TOPIC: menthol* AND (cigarette OR cigarettes)

Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan = 2019-2020

Results = 84

EbscoHOST (PsycInfo and Academic Search Complete)

Menthol* AND (cigarette OR cigarettes)

Limiters - Scholarly (Peer Reviewed) Journals; Published Date: 20190101-20200131

Results = 113

Menthol Cigarette Search, 4/30/2021

PubMed

menthol* AND (cigarette OR cigarettes) Filters: **from 2020/1/1 - 2021/4/30**

Results = 168

EMBASE

menthol* AND ('cigarette'/exp OR cigarette:ab,ti OR cigarettes:ab,ti) AND [2020-2021]/py

Results = 174

Web of Science

TOPIC: menthol* AND (cigarette OR cigarettes)

Timespan = 2020-2021

Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC

Results = 134

EbscoHOST (APA PsycInfo and Academic Search Complete)

Menthol* AND (cigarette OR cigarettes)

Limiters =Full Text; Scholarly (Peer Reviewed) Journals; Published Date: 20200101-20210431; English; Exclude Dissertations

Results = 69

Appendix B: Risk Of Bias Assessment In Quantitative Study Designs

External Validity/Generalizability		
Domain and Type of Bias	**Definition**	**Notes/Example of Risk of Bias**
Sampling Bias	The selection of participants may misrepresent the underlying population.	Example: Sampling fails to capture certain groups from the population (e.g., people with low income) or a specific group of participants is excluded from the sample (e.g., people younger than 18 years).
Selection Bias	Systematic differences between baseline characteristics in the groups that are compared	Notes: Randomized studies have the greatest weight. Stratified and unadjusted analyses will also increase study validity.
Internal Validity		
Sources of Bias in Measurement and Procedures		
Domain and Type of Bias	**Definition**	**Notes**
Using measures that are not valid	Key study variables are measured using items or scales that have not been established as valid.	Example: Author-generated scales of dependence that have not been validated.
Threats to Construct Validity	The measure of a construct is unable to accurately capture all of the characteristics of the construct.	Example: A single item is used to measure a multifaceted construct (e.g., frequency of use as a proxy for dependence).
Inaccurate definition of tobacco user groups	Tobacco user groups are defined using inaccurate or incorrect criteria. Criteria supported by published research should be used.	Example: "Never users" include both former tobacco users and those who have never tried tobacco. Notes: Current users being defined differently between studies will also be considered when evaluating overall conclusions.
Response Biases (including Social Desirability Bias, Mode Change Bias, Demand Characteristics, Coercion or Payment Bias, Confirmation Bias, Extreme responding, Halo effect, Differential and Non-Differential Misclassification Bias, etc.)	Cognitive Biases, such as, a participant may be reluctant to or is unwilling or unable to report an exposure accurately because of attitudes, beliefs, and perceptions due to social or contextual cues that affect his/her judgments and responses.	Example: Research conducted in a setting where strong anti-tobacco norms or other cultural biases are present. Therefore, social desirability bias among respondents may be present when reporting tobacco use. Other examples include changing the mode of measurement, such as from paper to web-based, or the effect of participant payment on responses.
Recall Bias	A considerable length of time has taken place between assessment of an exposure or outcome and the time when the exposure or outcome took place.	Example: The length of time between tobacco use initiation and assessment of prior initiation is greater than five years.
Domain and Type of Bias	**Definition**	**Notes**
Reporting Bias	Systematic differences between reported and unreported findings. Within a published report those analyses with statistically	Example: The findings were not presented clearly or there was not consistency between the data presented and the summary of findings. The claims made are not

	significant differences between intervention groups are more likely to be reported than non-significant differences. This sort of "within-study publication bias" is usually known as outcome reporting bias or selective reporting bias, and may be one of the most substantial biases affecting results from individual studies.	supported by sufficient evidence. Differences in sample sizes across analyses were not accounted for, or the claims made are not supported by sufficient evidence.

Sources of Bias in Analysis		
Domain and Type of Bias	**Definition**	**Notes**
Addressing missing data in analysis (Attrition bias)	Systematic differences between groups in withdrawals from a study. Withdrawals from the study lead to incomplete outcome data.	Notes: Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors. Indicate whether authors mishandled missing data.
Insufficient accounting for potential confounders	There was confounding not controlled for in the study design or analysis. Furthermore, there was no attempt to balance the allocation between groups or to match groups (e.g., through stratification, matching, or propensity scores).	Example: Cessation study in African American and European American smokers found that menthol smokers are less likely to quit than non-menthol smokers. The study did not control for race; differences in cessation success could be driven by race.
Appropriate statistical tests	The statistical tests used to assess the main outcomes were not appropriate for the data.	Example: The authors used an analytic approach that was not appropriate for the structure of the data, such as a logistic regression for a continuous outcome variable.

Appendix C: Quantitative Scoring Sheet

Human studies

Ref:	Authors. (2011). Title. Journal.						Tier 1	Human Longitudinal
							Tier 2	Human Cross-sectional
Tier:	Include tier based on type of analyses within the study (i.e., longitudinal analysis, cross-sectional analysis)							

	Quantitative Criteria	Yes (2)	Partial (1)	No (0)	N/A	Check	Rules
1	Primary question/objective is related to menthol in cigarettes		x			√	**Yes** - address menthol, specific to the topic/question; **Partial** - address menthol, but not the specific topic/question; **No** - primary question/objective not about menthol, but contains baseline info comparing menthol vs. nonmenthol smokers
2	Study design evident and appropriate to examine menthol in cigarettes		x			√	**Yes** - address menthol, specific to the topic/question; **Partial** - address menthol, but not the specific topic/question; **No** - primary question/objective not about menthol, but contains baseline info comparing menthol vs. nonmenthol smokers
3	Method of subject/comparison group selection or source of information/input variables described and appropriate; appropriate comparator group selected in experimental studies			x		√	Criteria for yes/no/partial taken from Kmet et al 2004
4	Subject (and comparison group, if applicable) characteristics sufficiently described			x		√	**Yes** - Includes at least 4 demographic variables on the study population (e.g., sex, age, race, education); **Partial** - contains less than 4 demographic variables on the study population; **No** - does not contain any information on the study population
5	If interventional and random allocation was possible, was it described			x		√	Criteria for yes/no/partial taken from Kmet et al 2004
6	Sample is nationally representative			x		√	**Yes** - sample is nationally representative (of US population); **Partial** - sample is representative of a large subset of US population (e.g., soutwest region, north) **No** - sample is not nationally representative (of US population)
7	Sample is random and representative of the general study population (no selection or sampling bias)	x				√	**Yes** - sample is randomized and representative of the general study population, has stratified and unadjusted analysis; **Partial** - sample is randomly selected, but not representative of the general study population (e.g., study recruits a random sample of smokers from a cessation center in a study not about cessation); **No** - study limited to a subset that is not representative of the general study population, sample not randomly selected, not randomly distributed, or unclear if sample is randomly selected
8	A considerable length of time has not passed between assessment of outcome/exposure and the time when outcome/exposure occurred (no recall bias)		x			√	**Yes** - if self-report is quantitatively confirmed (e.g., biochemical analysis, cigarette butts collected); **Partial** - responses collected less than or equal to one week (7 days) after testing; **No** - responses collected greater than or equal to one week (7 days) after testing or if timing is unknown; N/A if analysis is all biochemical or behavioral (e.g. topography studies, pharmacokinetic studies with no self-report)

#	Criteria					√	Notes
9	Measure of a construct captures all characteristics of the construct (no threat to construct validity or use of measures that have not been validated)			x		√	*For dependence, sensory, and topography:* **No**– if only one measure to assess the outcome was used (e.g., CPD only, puff volume/puff number only, harshness only) or assessment has not been validated; **partial**– if two proxies of dependence, sensory, or topography measures are used, **yes**– if a scale of dependence/sensory measures and/or 3+ proxies for dependence or multiple sensory and topography measures are used; *For initiation/progression* - **Yes** if two or more measures of initiation age are used, **Partial**- for one measure of initiation age or if more than one measure was used, but all measures did not appropriately capture age of initiation, **No** - question is intended to capture age of initiation, but is not phrased appropriately to capture this construct; *For cessation* - **Yes**– at least one question that accurately captures cessation success, **Partial**– Not an option for this measure, **No** - question is intended to capture cessation success, but is not phrased appropriately to capture this construct (e.g., measures longest period of abstinence in relaped smokers)
10	Free from response bias			x		√	Self-report often has response bias. Score is at least **Partial** for most because product use is self-report; Can be **yes** if quantitatively confirmed (e.g., biomarkers of use, cigarette butts collected) or if participants smoke both types of products in w/i subject comparison; **No** - self-report only for several measures in the study, no quantitative confirmation (e.g., bias for first type of cigarette used, CPD, TTFC with no quantitative confirmation of any measure)
11	Missing data has been addressed in analysis (no attrition bias)			x		√	**Yes** - Discussion of attrition rate and/or how missing data points were addressed was included; Partial- No discussion, but not presumed to be an issue; **No** - attrition bias was not discussed and presumed to be an issue
12	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported		x			√	**Yes** - all outcome measure variables are defined; **Partial**- some,but not all outcome measure variables are defined; **No** - no outcome measure variables are defined
13	Sample size appropriate	x				√	Consider overall sample size based on the nature of the study (e.g., fewer subjects may be acceptable in topography studies compared to cessation studies); **Yes** if sample size of menthol and non-menthol smokers is appropriate to support conclusions based on statistical analyses; **Partial**- substantial differences in menthol vs. non-menthol distribution that may influence results, but sample size is sufficent to support conclusions based on statistical analyses; **No** - substantial differences in menthol vs. non-menthol distribution that may influence results, sample size insuffient to support conclusions based on statistical analyses
14	Analytic methods described/justified and appropriate	x				√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
15	Estimate of variance is reported for the main results	x				√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
16	Controlled for confounding		x			√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
17	Results reported in sufficient detail		x			√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
18	Conclusions supported by the results	x				√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
19	Long term (≥ 6 months) follow-up (vs. short term, < 6 months)	x				√	**Yes** or **No**; **Partial** was not an option; cessation studies only
20	Cessation study conducted in current and former smokers (vs. relapsed, current smokers)	x				√	**Yes** or **No**; **Partial** was not an option; cessation studies only
21	Biochemically-verified cessation outcomes (vs. self-report)	x				√	**Yes** or **No**; **Partial** was not an option; cessation studies only
22	Continuous abstinence outcome measure (vs. 7-day point prevalence outcome)	x				√	**Yes** or **No**; **Partial** was not an option; cessation studies only

Nonclinical studies

Ref:	Authors. (2011). Title. Journal.						
Tier 3:	Nonclinical						

	Quantitative Criteria	Yes (2)	Partial (1)	No (0)	N/A	Check	Rules
1	Primary question/objective is related to menthol in cigarettes	X				√	**Yes** – address menthol, specific to the topic/question; **Partial** – address menthol, but not the specific topic/question; **No** – primary question/objective not about menthol, but contains at least one menthol test group (e.g., as a control condition)
2	Study design evident and appropriate to examine menthol in cigarettes	X				√	**Yes** – address menthol, specific to the topic/question; **Partial** – address menthol, but not the specific topic/question; **No** – primary question/objective not about menthol, but contains at least one menthol test group (e.g., as a control condition)
3	Method of subject/comparison group selection or source of information/input variables described and appropriate; appropriate comparator group selected in experimental studies	X				√	**Yes** – Has appropriate testing and control groups to address the main questions for the study; **Partial** – includes some, but not all necessary control groups for the study; however, those not included do not raise questions about the validity of study conclusions; **No** – Control groups are not included or those included are not appropriate for the study
4	Subject (and comparison group, if applicable) characteristics sufficiently described		X			√	**Yes** – Includes at a minimum, age, sex, and animal species and strain indicated for all groups; **Partial** – includes some, but not all information on animal age, sex, and animal species/strain (e.g., references all information except animal age), but enough that study can be replicated; **No** – includes minimal information on animal background, such that variables that may influence study outcome are not included, should the study be replicated (e.g., only mentions animal sex and species, no other information provided, though strain differences could also lead to different outcomes)
5	Doses and dosing scheme are relevant to exposure in humans	X				√	**Yes** – if author has provided some discussion of relevance to actual menthol doses found in cigarettes or draws some connection between menthol and nicotine associated behaviors. If there is no such discussion, but dosing scheme is relevant (e.g., menthol in smoke, menthol given concurrently with nicotine), mark "**partial**". If there is no such discussion AND dosing scheme is not relevant or questionable to human exposure (e.g., one dose of menthol pretreatment prior to nicotine exposure), mark "**no**"

#	Criteria	X					√	Notes
6	Study outcomes are measured within the half life of the drug in the species selected	X					√	**Yes** or **No, Partial**– in the case of multiple assessments in one study, some measures were completed outside the half life window
7	Study uses a validated animal or cell model to appropriately assess the behavior or biochemical measure	X					√	**Yes**– animal model is valid for the behavioral or biochemical measure of question, and has been replicated across several studies; **Partial**– animal model is being validated as part of the current study, but has not yet been replicated in any other studies. **No**– animal model is inappropriate to address the research question (e.g., nicotine reward model being used to assess nicotine reinforcement)
8	Sample size appropriate	X					√	Determined based on the behavioral or biochemical model tested, and statistical power of the study. **Yes**– if sample size for all test groups is appropriate for the model being tested. **Partial**– sample size is appropriate for some, but not all groups (e.g., very few vehicle animals are tested compared to drug groups, given that the investigator does not anticipate any effects under control conditions); however, this does not hinder abilities to draw conclusions from the study. Weaknesses that sample size is skewed, and may affect interpretation are presented. **No**– sample size is not appropriate to draw conclusions from any group, such that accurate between group comparisons cannot be made
9	Analytic methods described/justified and appropriate	X					√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
10	Estimate of variance is reported for the main results	X					√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
11	Controlled for confounding					X	√	**Yes**–In animal studies, if male and female animals are used, or animals of different ages (adolescent and adult), the author justifies how sex and gender differences have not conributed to the results or shows that there are no significant sex/age differences in this model; **No**– Author uses animals of different sex, age, strain, etc. in the same test group, but does not justify lack of interaction such that the groups can be combined. **Partial**–not an option for this criteria
12	Results reported in sufficient detail	X					√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004
13	Conclusions supported by the results	X					√	Criteria for yes/no/partial taken from Appendix A, Kmet et al 2004

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Appendix D: Qualitative Scoring Sheet

Ref:	Authors. (2011). Title. Journal.						Tier 1	Human Longitudinal
							Tier 2	Human Cross-sectional
Tier:	Include tier based on type of analyses within the study (i.e., longitudinal analysis, cross-sectional analysis)							

	Qualitative Criteria	Yes (2)	Partial (1)	No (0)	N/A	Check	Rules*
1	Question/objective sufficiently described		X			√	
2	Study design evident and appropriate	X				√	
3	Context for the study clear		X			√	
4	Connection to theoretical framework/wider body of knowledge			X		√	
5	Sampling strategy described, relevant, justified?			X		√	
6	Data collection methods clearly described and systematic?		X			√	
7	Data analysis clearly described and systematic?	X				√	
8	Use of verification procedure(s) to establish credibility?		X			√	
9	Conclusions supported by the results?			X		√	
10	Reflexivity of the account?			X		√	
							*Criteria for yes/no/partial for all qualitative criteria taken from Appendix B, Kmet et al 2004

Appendix E: Data Extraction 1980-2021

Sensory Effects Studies

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
(Bagdas, Cam, et al., 2020)	Impact of menthol on oral nicotine consumption in female and male Sprague Dawley rats	Male and female Sprague Dawley rats (10-12 weeks old), n = 64 total	Two bottle choice test	Tier 3: Nonclinical, Strong
(Bagdas, Jackson, et al., 2020)	Impact of menthol on nicotine intake and preference in mice: Concentration, sex, and age differences	Male and female adult (PND 77) and adolescent (PND 21) C57Bl 6/J mice	Two bottle choice test	Tier 3: Nonclinical, Strong
Amy M. Cohn and D'Silva (2019)	Menthol smoking and subjective response to the first cigarette smoked	N = 2319 youth (aged 12-17) and young adult (age 18-24 years) ever smokers from Wave 2 (2014-2015) of the PATH study	Respondents were asked to rate the intensity of the pleasant and unpleasant sensations of their first cigarette smoked via 2 questions: "How much did you experience unpleasant [pleasant] sensations the first time you smoked a cigarette?" (1 = not at all, 2 = "a little", 3 = "somewhat" and 4 = "a lot").	Tier 2: Human Cross-sectional, Strong
(A. M. Cohn et al., 2019)	Menthol smoking patterns and smoking perceptions among youth: Findings from the Population Assessment	N = 2797 youth (aged 12-17) ever smokers, past 30 day smokers, and past 30 day smokers who reported a usual brand cigarette from Wave 1 (2013-2014) of the PATH study	All respondents were asked: Are cigarettes flavored like menthol	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
	of Tobacco and Health study		or mint harder to smoke, about the same, or easier to smoke than regular cigarettes?	
(A. M. Cohn et al., 2020)	Menthol cigarette smoking is associated with greater subjective reward, "satisfaction", and "throat hit", but not greater behavioral economic demand	N = 600 current adult smokers (aged 18+) enrolled in an online smoking cessation program	The Modified Cigarette Evaluation Questionnaire (mCEQ) is a 12-item self-report questionnaire that was used to measure subjective responses to cigarette smoking in four domains: *Reward*, *Satisfaction*, *Aversion*, and *Throat Hit*	Tier 2: Human Cross-sectional, Moderate
(Denlinger-Apte, Cassidy, et al., 2019)	Effects of cigarette nicotine content and menthol preference on perceived health risks, subjective ratings, and carbon monoxide exposure among adolescent smokers	N = 28 menthol and N = 22 non-menthol adolescent smokers (aged 15-19 years) recruited in Providence, Rhode Island	Cigarette Evaluation Scale	Tier 2: Human Cross-sectional, Moderate
(D'Silva et al., 2018)	Differences in subjective experiences to first use of menthol and non-menthol cigarettes in a national sample of young adult cigarette smokers	N = 251 young adult current smokers (aged 18-34) from the Truth Initiative Young Adult Cohort	Initial Use Module of the Lifetime Tobacco Use Questionnaire; participants who reported initiating smoking in the last 6 months were asked to "indicate how well these words describe how [they] felt immediately after [they] used tobacco or nicotine or the first time" from a scale of 1 (not at all) to 5 (intense): dizzy, lightheaded like fainting, nauseated, coughing	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
			or choking, difficulty inhaling, rush or buzz, relaxed or calm, liked the taste, and liked the smell	
(D'Silva et al., 2021)	Because there's just something "bout that menthol": exploring Africa' American smokers' perspectives on menthol smoking and local menthol sales restrictions	N = 27 current African American smokers in the Minneapolis-St. Paul area	Focus group interviews. Findings were organized into themes: (1) Reasons for smoking menthol cigarettes; (2) Perceptions of the harm of menthol cigarettes; (3) Perspectives of menthol in the community; (4) Awareness of policy discussions; and (5) Reactions to local menthol restrictions	Tier 2: Human Cross-sectional, Strong
(DiFranza et al., 2004)	Recollections and repercussions of the first inhaled cigarette	N = 237 seventh grade youth (age 12-15 years) in central Massachusetts who had ever inhaled a cigarette	Subjective ratings: irritation, nausea, dizziness, relaxation	Tier 2: Human Cross-sectional, Moderate
(Fan et al., 2016)	Menthol decreases oral nicotine aversion in C57BL/6 mice through a TRPM8-dependent mechanism	N = 3-8 male C57Bl/6 mice per group, aged 11 weeks	Two-bottle choice test	Tier 3: Nonclinical, Strong
(Gunawan & Juliano, 2020)	Differences in smoking topography and subjective responses to smoking among African American and white menthol and non-menthol smokers	N = 100 adult smokers in the Washington, DC area [menthol n = 27 African American smokers and 27 White smokers, non-menthol n = 17 African American smokers and 29 White smokers]	The modified Cigarette Evaluation Scale was used to evaluate the sensory and subjective properties of smoking (i.e., sensory stimulation, smoking satisfaction, psychological stimulation, psychological relaxation, cigarette strength,	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
			aversion, and craving reduction)	
(Ha et al., 2015)	Menthol attenuates respiratory irritation and elevates blood cotinine in cigarette smoke exposed mice	N = 3-7, female C57Bl6/J mice per group, aged 8-14 weeks	Breathing frequency, tidal volume, duration of braking during early expiration, peak inspiratory and peak expiratory flow	Tier 3: Nonclinical, Strong
(Jarvik et al., 1994)	Mentholated cigarettes decrease puff volume of smoke and increase CO absorption	N = 20 Black and White male smokers recruited from the community and the West Los Angeles Veterans Administration Medical Center menthol n = 10, non-menthol n = 10	Subjective ratings: harshness, satisfaction, and post-cigarette urge to smoke	Tier 2: Human Cross-sectional, Moderate
(Perkins et al., 2018)	Evaluation of menthol per se on acute perceptions and behavioral choice of cigarettes differing in nicotine content	N = 73 dependent smokers, mean aged 33.4; menthol n = 44, non-menthol n = 29	Behavioral choice procedure of puffs between the two cigarettes differing in nicotine content	Tier 2: Human Cross-sectional, Moderate
(Pickworth et al., 2002)	Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery	Current smokers: menthol n = 18, non-menthol, n = 18	Duke Sensory Questionnaire, Cigarette Evaluation Scale	Tier 2: Human Cross-sectional, Strong
(Richter et al., 2008)	Small-group discussions on menthol cigarettes: listening to adult African American smokers in Atlanta, Georgia	African American current cigarette smokers who reported as current or past users of menthol cigarettes, aged 45-64: n = 54; 87% smoked menthol cigarettes	Smoking behaviors, preferences, perceptions	Tier 2: Human Cross-sectional, Moderate
(Strasser et al., 2013)	The effect of menthol on cigarette smoking behaviors, biomarkers and subjective responses	Adult menthol smokers (n = 22)	Subjective ratings: strength, harshness, heat, draw, taste, aftertaste, mild taste, too mild, stale, satisfaction, burned, smoke strength, smoke harshness, smoke smell	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
(Wackowski et al., 2018)	In their own words: young adults' menthol cigarette initiation, perceptions, experiences and regulation perspectives	N = 45 young adult current menthol smokers (aged 18-24) across six focus groups in New Jersey	Participants were asked open-ended questions in focus groups about their smoking initiation (e.g., "describe for us the very first time you tried smoking a cigarette"), experiences with and perceptions of menthol cigarettes (e.g., "how would you compare smoking menthols to non-menthol cigarettes?"), menthol cigarette brands and marketing (e.g., "what are some of the reasons why you smoke your particular brand?") and a potential menthol cigarette ban (e.g., "what do you think you would do if menthol cigarettes were no longer sold in the United States?")	Tier 2: Human Cross-sectional, Strong
(T. Wang et al., 2014)	Menthol facilitates the intravenous self-administration of nicotine in rats	Female adolescent (post-natal day 31-55) Sprague Dawley rats, n = 5-8 per group	Self-administration	Tier 3: Nonclinical, Strong
(Watson et al., 2017)	Smoking behavior and exposure: results of a menthol cigarette cross-over study	N = 42 African American or Caucasian current daily smokers (aged 21+) of at least 6 CPD for at least 3 years. menthol, n = 26; non-menthol, n = 16	6-point Likert style survey that rated participant impression of the test cigarette in terms of satisfaction, enjoyment, throat irritation, aftertaste, smoke smell, and package smell	Tier 2: Human Cross-sectional, Moderate
(Wickham et al., 2018)	Evaluating oral flavorant effects on nicotine self-	Male Sprague Dawley rats, n = 4-11 rats/group	Intraoral and i.v. self-administration	Tier 3: Nonclinical, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
	administration behavior and phasic dopamine signaling			
(Willis et al., 2011)	Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants	N = 4-6 female C67Bl/6J mice (aged 8-16 weeks) per group	Respiratory sensory irritation	Tier 3: Nonclinical, Strong
(Wiseman & McMillan, 1998)	Rationale for cigarette smoking and for mentholation preference in cocaine- and nicotine-dependent outpatients	N = 43 outpatients voluntarily receiving treatment at a Veterans Affairs rehabilitation program	Open-ended questions	Tier 2: Human Cross-sectional, Moderate
(Young-Wolff et al., 2015)	Menthol use in smokers with mental illness: examination of sensory preferences and price sensitivity	Adult smokers hospitalized with mental illness in the San Francisco Bay area: menthol only n = 130, dual users n = 149, non-menthol n = 202	Taste preferences, sensory experience, perceptions	Tier 2: Human Cross-sectional, Strong

Progression to Regular Use Studies

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Amy M. Cohn & D'Silva, 2019)	Menthol smoking and subjective response to the first cigarette smoked	N = 2319 youth and young adult ever-smokers from Wave 2 of the PATH study (2014-2015)	Initiation with menthol vs. non-menthol and past 30-day cigarette smoking, non-cigarette smoking, and heavy smoking (>30 CPD)	Tier 2: Human Cross-sectional, Strong
(Delnevo et al., 2016)	The influence of menthol, e-cigarettes and other tobacco products on young adults' self-reported changes in past year smoking	Established smokers, aged 18-34: menthol n = 355, non-menthol n = 554	Self-reported current and former smoking status (every day, some days, not at all)	Tier 2: Human Cross-sectional, Strong
(Nonnemaker et al., 2013)	Initiation with menthol cigarettes and youth smoking uptake	Middle school and high school students who were nonsmokers at baseline, under age 18 at baseline, and initiated smoking at wave 1 or 2 during the study (n = 638)	Change in smoking behavior: smoked ≥ 100 cigarettes and reported smoking cigarettes on the past 20 of 30 days, or quit smoking	Tier 1: Human Longitudinal, Strong
(Nonnemaker et al., 2019)	Examining the role of menthol cigarettes in progression to established smoking among youth	N = 4,210 youth (aged 11-16 at baseline) from the Evaluation of Public Education Campaign on Teen Tobacco (ExPECTT) Cohort Study (2013 to 2016)	Established smoking: progression from <100 cigarettes lifetime to established 100+ cigarettes lifetime. Current smoking: past 30 days. Frequent smoking: smoking on 20 or more days in the past 30 days.	Tier 1: Human Longitudinal, Strong
(Villanti et al., 2019)	Association of flavored tobacco use with tobacco initiation and subsequent use among us youth and adults, 2013-2015	N = 11,996 youth and 26,447 adults from Waves 1 and 2 of the PATH study (2013-2015)	Initiation with flavored cigarette and association with subsequent tobacco use (past 12-months, past 30-days, ≥ 6 days in past month, ≥ 20 days in past month, daily use).	Tier 1: Human Longitudinal, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Villanti et al., 2021)	Menthol and mint cigarettes and cigars: Initiation and progression in youth, young adults and –dults in Waves 1 - 4 of the–PATH Study, 2013 - 2017	N = 10,086 youth and 21,281 adults from Waves 1 – 4 of the PATH study (2013-2017)	Initiation with mint/menthol cigarette/cigar and association with subsequent use (past 12-months, past 30-days, moderate use, frequent use, daily use).	Tier 1: Human Longitudinal, Strong

Dependence Studies

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
Adults				
(Abobo et al., 2012)	Effect of menthol on nicotine pharmacokinetics in rats after cigarette smoke inhalation	8 rats for single and multiple exposures	Nicotine exposure	Tier 3: Nonclinical, Strong
(Ahijevych & Wewers, 1994)	Patterns of cigarette consumption and cotinine levels among African American women smokers	African American smokers recruited at urban health centers and worksites: menthol n = 130, non-menthol n = 12.	Nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Ahijevych et al., 1996)	Menthol and non-menthol cigarettes and smoke exposure in black and white women	Women smokers recruited based on race: menthol n = 15, non-menthol n = 18	Nicotine exposure	Tier 1: Longitudinal, Moderate Tier 2: Human Cross-sectional, Moderate
(Ahijevych et al., 2002)	Factors influencing cotinine half-life during smoking abstinence in African American and Caucasian women	African American and Caucasian female smokers, aged 18-50: menthol n = 20, non-menthol n = 12	TTFC, CPD, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Ahijevych & Ford, 2010)	The relationships between menthol cigarette preference and state tobacco control policies on smoking behaviors of young adult smokers in the 2006-2007 Tobacco	Data from 2006/07 TUS-CPS young adults (aged 18-24) who reported smoking daily (total n = 2241, menthol n = 670) or non-daily (total n = 688, menthol n = 177)	TTFC, CPD	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	Use Supplements to the Current Population Surveys (TUS-CPS)			
(Ahijevych & Parsley, 1999)	Smoke constituent exposure and stage change in black and white women cigarette smokers	Female smokers: menthol n = 49, non-menthol n = 46)	TTFC, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Ahijevych et al., 2018)	Effects of menthol flavor cigarettes or total urinary menthol on biomarkers of nicotine and carcinogenic exposure and behavioral measures	N = 136 White and African American smokers; n = 35 White regular and 35 White menthol smokers; n = 30 African American regular and n = 36 African American menthol smokers	Plasma cotinine, plasma nicotine, TTFC, CPD	Tier 2: Human Cross-sectional, Strong
(Allen & Unger, 2007)	Sociocultural correlates of menthol cigarette smoking among adult African Americans in Los Angeles	African American current, daily smokers in Los Angeles: menthol n = 296, non-menthol n = 136	FTND, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Alsharari et al., 2015)	Effects of menthol on nicotine pharmaco-kinetics, pharmacology, and dependence in mice	Adult male ICR mice, n = 6-8 mice per group	Nicotine exposure, withdrawal symptoms	Tier 3: Nonclinical, Strong
(Bello et al., 2016)	Tobacco withdrawal amongst African American, Hispanic, and White smokers.	African American, White, and Hispanic daily smokers aged 18+: menthol n = 117, non-menthol n = 207	BQSU, MNWS	Tier 2: Human Cross-sectional, Not included

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Benowitz et al., 2004)	Mentholated cigarette smoking inhibits nicotine metabolism	Current smokers with experience with menthol and non-menthol cigarettes (n = 14)	Nicotine exposure, nicotine pharmacokinetics	Tier 1: Human Longitudinal, Strong
(Benowitz et al., 2010)	Urine menthol as a biomarker of mentholated cigarette smoking	Non-Hispanic White or African American current smokers: menthol n = 60, non-menthol n = 67	CPD, TTFC, FTND, nicotine exposure	BOE Score: Tier 2: Human Cross-sectional, Strong Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Benowitz et al., 2011)	Racial differences in the relationship between number of cigarettes smoked and nicotine and carcinogen exposure	Adult smokers: menthol n = 60, non-menthol n = 67	CPD, nicotine exposure, nicotine pharmacokinetics	BOE Score: Tier 2: Human Cross-sectional, Moderate Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Biswas et al., 2016)	Enhancing effect of menthol on nicotine self-administration in rats	Male Sprague-Dawley rats (n = 9-11 per group)	Self-administration	Tier 3: Nonclinical, Strong
(Blot et al., 2011)	Lung cancer risk among smokers of menthol cigarettes	Smokers enrolled in the SCSS: menthol n = 7,886, non-menthol n = 4,487	CPD	Tier 2: Human Cross-sectional, Moderate
(Bover et al., 2008)	Waking at night to smoke as a marker for tobacco dependence: patient characteristics and relationship to treatment outcome	Smokers wanting to quit: menthol n = 1,048, non-menthol n = 1,226	Night waking to smoke	Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Brinkman et al., 2012)	Exposure to and deposition of fine and ultrafine particles in smokers of menthol and non-menthol cigarettes	Caucasian smokers: menthol n = 1, non-menthol n = 8	CPD, nicotine exposure	BOE Score: Tier 1: Human Longitudinal, Moderate Behavioral score: Tier 2: Human Cross-sectional, Moderate
(Brunette et al., 2018)	Menthol cigarette use in young adult smokers with severe mental illnesses	N = 81 daily smoking young adults (aged 18-30) with severe mental illness	FTND, CPD	Tier 2: Human Cross-sectional, Moderate
(Caraballo et al., 2011)	Comparison of serum cotinine concentration within and across smokers of menthol and non-menthol cigarette brands among non-Hispanic Black and non-Hispanic White US adult smokers, 2001-200 6	2001-2006 NHANES: menthol n = 677, non-menthol n = 1,241	Nicotine exposure	Tier 2: Human Cross-sectional, Strong
(Chenoweth et al., 2014)	Known and novel sources of variability in the nicotine metabolite ratio in a large sample of treatment-seeking smokers.	Smokers seeking cessation treatment: menthol n = 550, non-menthol n = 605	Nicotine pharmaco-kinetics	Tier 2: Human Cross-sectional, Moderate
(Clark et al., 1996)	Effect of menthol cigarettes on biochemical markers of	Black and White smokers: menthol n = 76, non-menthol n = 85	Nicotine exposure	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	smoke exposure among black and white smokers			
(Cubbin et al., 2010)	The intersection of gender and race/ethnicity in smoking behaviors among menthol and non-menthol smokers in the United States	2005 NHIS-CCS data from adult Black, Hispanic, and White current daily smokers (total n = 3,902)	CPD	Tier 2: Human Cross-sectional, Moderate
(Curtin et al., 2014b)	Primary measures of dependence among menthol compared to non-menthol cigarette smokers in the United States	Adult smokers in 1999-2010 NHANES, 2000-2009 NSDUH, 2005 and 2010 NHIS and 2003, 2006/07 TUS-CPS. Sample sizes of the analyses were not provided.	CPD, TTFC, HSI	Tier 2: Human Cross-sectional, Moderate
(D'Silva et al., 2012)	Cessation outcomes among treatment seeking-menthol and non-menthol smokers	Smokers: menthol n = 1172, non-menthol n = 5058	CPD, TTFC	Tier 2: Human Cross-sectional, Moderate
(Davis et al., 2019)	Response to reduced nicotine content in vulnerable populations: effect of menthol status	Adult smokers with comorbid mental illness, substance use disorder, or socioeconomic disadvantage (n = 61 menthol, n = 108 non-menthol)	CPD, FTND	Tier 2: Human Cross-sectional, Moderate
(Denlinger-Apte, Kotlyar, et al., 2019)	Effects of very low nicotine content cigarettes on smoking behavior and biomarkers of exposure in menthol and non-menthol smokers	Adult non-treatment seeking menthol (n = 346) and non-menthol (n = 406) recruited from 10 sites across the U.S.	CPD, FTND, TNE	BOE Score, Tier 2: Human Cross-sectional, Strong Behavioral Score, Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Duffy et al., 2019)	Heightened olfactory dysfunction and oral irritation among chronic smokers and heightened propylthiouracil (PROP) bitterness among menthol smokers	N = 51 menthol and N = 84 non-menthol adult smokers recruited from the Hartford, CT area between May 2014 and December 2016	CPD	Tier 2: Human Cross-sectional, Moderate
(DeVito et al., 2016)	Effect of menthol-preferring status on response to intravenous nicotine	Treatment-seeking, current, daily smokers, aged 18-50, in New Haven, CT: menthol n = 110, non-menthol n = 24	FTND, CPD, MNWS, BQSU, nicotine exposure, nicotine pharmaco-kinetics	Tier 2: Human Cross-sectional, Strong
(Emond, Soneji, Brunette, & Sargent, 2018)	Flavour capsule cigarette use among US adult cigarette smokers	N = 10,322 adult current established smokers and adult former established smokers from the PATH 2013-2014 survey; dependence assessments limited to adult current smokers aged 18–24 years who reported a usual brand (n = 2,659)	Some day vs. every day smoker, first cigarette of the day more than one hour after waking, CPD	Tier 2: Human Cross-sectional, Not included
(Fagan et al., 2010)	Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns	2003, 2006/07 TUS-CPS Adult daily smokers: menthol n = 11,671, non-menthol n = 33,644	CPD, TTFC	Tier 2: Human Cross-sectional, Strong
(Fagan et al., 2015)	Comparisons of three nicotine dependence scales in a multiethnic sample of young adult	Adult daily smokers, aged 18-35, in Hawaii: menthol n = 127, non-menthol n = 59	FTND, WISDM, CPD, NDSS, TTFC, single-item assessment	Tier 2: Human Cross-sectional, Strong (FTND, WISDM,NDSS, single-

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	menthol and non-menthol smokers			item assessment); Moderate (CPD, TTFC)
(Fagan et al., 2016)	Nicotine metabolism in young adult daily menthol and non-menthol smokers	Daily smokers: menthol n = 127, non-menthol n = 59	CPD, nicotine exposure, nicotine pharmacokinetics	BOE Score, Tier 2: Human Cross-sectional, Strong Behavioral Score, Tier 2: Human Cross-sectional, Moderate
(Fait et al., 2017)	Menthol disrupts nicotine's psychostimulant properties in an age and sex-dependent manner in C57BL/6J mice	Male and female adult (77-91 days) and adolescent (21-28 days) mice (C57BL/6J); n = 7-12 per group	Locomotor activity; nicotine intake; plasma nicotine and cotinine levels	Tier 3: Nonclinical, Strong
(Faseru et al., 2011)	Factors associated with smoking menthol cigarettes among treatment-seeking African American light smokers	African American light smokers, interested in quitting smoking: menthol n = 452, non-menthol n = 88	FTND, BQSU, MNWS, CPD, TTFC, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Fernander et al., 2010)	Are age of smoking initiation and purchasing patterns associated with menthol smoking?	2003 and 2006/7 TUS-CPS data from current daily or someday smokers (n = 61,447; approximately 26% menthol)	Smoking frequency (every day vs. some days)	Tier 2: Human Cross-sectional, Moderate
(Frost-Pineda et al., 2014)	Predictors, indicators, and validated measures	Adult smokers, aged 21+ in TES: menthol n = 1,044, non-menthol n = 2,297	FTND, HSI, CPD, TTFC	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	of dependence in menthol smokers			
(Fu et al., 2008)	Menthol cigarettes and smoking cessation during an aided quit attempt	Male African American smokers (veterans) who had previously received nicotine replacement therapy or bupropion for smoking cessation: menthol n = 342, non-menthol n = 1,001	CPD, TTFC	Tier 2: Human Cross-sectional, Not included
(Gan et al., 2016)	Association between overall and mentholated cigarette smoking with headache in a nationally representative sample	N = 8,399 participants aged 20+ years (n = 2548 smokers and n = 5491 nonsmokers) from the NHANES 1999-2004; n = 739 menthol smokers; n = 1,719 non-menthol smokers	CPD	Tier 2: Human Cross-sectional, Moderate
(Gandhi et al., 2009)	Lower quit rates among African American and Latino menthol cigarette smokers at a tobacco treatment clinic	Smokers attending a specialist smoking cessation service: menthol n = 778, non-menthol n = 910	CPD, TTFC, waking at night to smoke	Tier 2: Human Cross-sectional, Moderate
(Gubner et al., 2018)	Menthol cigarette smoking among individuals in treatment for substance use disorders	Survey data from the NIDA Clinical Trials Network; n = 863 current cigarette smokers across 24 substance use disorder treatment centers	CPD, smoking days/week, TTFC	Tier 2: Human cross-sectional, Strong
(Gunawan & Juliano, 2020)	Differences in smoking topography and subjective responses to smoking among African American and white menthol and non-menthol smokers	N = 100 adult smokers in the Washington, DC area [menthol n = 27 African American smokers and 27 White smokers, non-menthol n = 17 African American smokers and 29 White smokers]	FTND, CPD, TTFC	Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Ha et al., 2015)	Menthol attenuates respiratory irritation and elevates blood cotinine in cigarette smoke exposed mice	Female C57Bl/6J mice	Nicotine exposure	Tier 3: Nonclinical, Strong
(Harrison et al., 2017)	Effects of menthol and its interaction with nicotine-conditioned cue on nicotine-seeking behavior in rats	Male Sprague-Dawley rats, n = 10 per group	Self-administration cue conditioning- acquisition, extinction, reinstatement	Tier 3: Nonclinical, Strong
(Heck, 2009)	Smokers of menthol and non-menthol cigarettes exhibit similar levels of biomarkers of smoke exposure	Current smokers: menthol n = 54, non-menthol n = 58	CPD, nicotine exposure	BOE Score: Tier 2: Human Cross-sectional, Strong Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Henderson et al., 2016)	Menthol alone upregulates midbrain nAChRs, alters nAChR subtype stoichiometry, alters dopamine neuron firing frequency, and prevents nicotine reward	Male (n = 14) and female (n = 17) C57Bl/6 mice, aged 3-6 months	Nicotine reward	Tier 3: Nonclinical, Strong
(Henderson et al., 2017)	Menthol enhances nicotine reward-related behavior by potentiating nicotine-induced changes in nAChR function,	Male and female mice aged 3-6 months; n = 5-21 mice per group depending on the assessment	Conditioned place preference; midbrain DA (dopamine) neuronal activity; nAChR upregulation	Tier 3: Nonclinical, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	nAChR upregulation, and da neuron excitability			
(Hickman et al., 2014)	Menthol use among smokers with psychological distress: findings from the 2008 and 2009 National Survey on Drug Use and Health	Current adult smokers in the 2008 and 2009 NSDUH: menthol n = 9,198, non-menthol n = 14,959	CPD, TTFC	Tier 2: Human Cross-sectional, Strong
(Ho et al., 2009)	Utility and relationships of biomarkers of smoking in African American light smokers.	African American light smokers enrolled in a smoking cessation study: menthol n = 131, non-menthol n = 569	CPD, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Hooper et al., 2011)	Menthol cigarette smoking and health, Florida 2007 BRFSS	Current smokers in Florida who completed the follow-up survey: menthol n = 876, non-menthol n = 2,520	NDSS	Tier 2: Human Cross-sectional, Moderate
(Hsu et al., 2017a)	Menthol smokers: metabolomic profiling and smoking behavior	N = 105 participants, at least 18 years of age and who smoked > 10 CPD for at least 5 years with a stable smoking pattern (menthol n = 71, non-menthol n = 34)	FTND; nicotine, cotinine, trans-3-hydrosycotinine in blood; NMR	BOE Score: Tier 2: Human Cross-sectional, Strong Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Hsu et al., 2017b)	Metabolomic profiles of current cigarette smokers	N = 105 participants	Baseline cotinine levels, nicotine boost	Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Hyland et al., 2002)	Mentholated cigarettes and smoking cessation: findings from COMMIT	COMMIT telephone-based smoking intervention program: menthol n = 3,188, non-menthol n = 10,080	TTFC, CPD	Tier 2: Human Cross-sectional, Strong
(Jain, 2014)	Trends in serum cotinine concentrations among daily cigarette smokers: data from NHANES 1999-2010.	1999-2010 NHANES data from current daily smokers: menthol n = 1,181, non-menthol n = 2,604	CPD, Nicotine exposure	BOE Score: Tier 2: Human Cross-sectional, Strong Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Jao et al., 2017)	Does menthol cigarette use moderate the effect of nicotine metabolism on short-term smoking cessation?	N = 474 cigarette smokers, aged 18+	HSI, CPD, NMR	BOE Score: Tier 2: Human Cross-sectional, Strong Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Jarvik et al., 1994)	Mentholated cigarettes decrease puff volume of smoke and increase CO absorption	Black and White smokers: menthol n = 10, non-menthol n = 10	FTND, Stanford dependence score, CPD	Tier 2: Human Cross-sectional, Moderate
(Jones et al., 2013)	Menthol cigarettes, race/ethnicity, and biomarkers of tobacco use in US adults: the 1999-2010 National Health and Nutrition Examination Survey (NHANES)	1999-2010 NHANES data from current smokers: menthol n = 1,393, non-menthol n = 3,210	TTFC, CPD, nicotine exposure	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Kosiba et al., 2019)	Menthol cigarette use and pain reporting among african american adults seeking treatment for smoking cessation	Adult menthol (n = 90) and non-menthol (n = 25) smokers recruited from Houston, TX.	CPD, HSI, Smoking frequency	Tier 2: Human Cross-sectional, Moderate
(Lawrence et al., 2010)	National patterns and correlates of mentholated cigarette use in the United States	2003 and 2006/07 TUS-CPS data from current daily or someday adult smokers: menthol n = 16,294, non-menthol n = 46,899	CPD, TTFC, smoking frequency (every day vs. some days)	Tier 2: Human Cross-sectional, Strong
(MacDougall et al., 2003)	Inhibition of human liver microsomal (s)-nicotine oxidation by (-)-menthol and analogues	Human liver microsomes	Nicotine pharmacokinetics	Tier 3: Nonclinical, Moderate
(Mendiondo et al., 2010)	Health profile differences for menthol and non-menthol smokers: findings from the national health interview survey	2005 NHIS current (40.8% menthol n = 6,055) and former (51.9% menthol n = 5,949) smokers	CPD	Tier 2: Human Cross-sectional, Moderate
(Miller et al., 1994)	Cigarette menthaolation increases smokers' exhaled CO levels	African American male smokers undergoing treatment for alcohol or drug dependence: menthol n = 6, non-menthol n = 6	FTND, CPD	Tier 2: Human Cross-sectional, Moderate
(Murray et al., 2007)	Menthol cigarettes and health risks in Lung Health Study data	Smokers with early evidence of obstructive lung impairment: menthol n = 1,216, non-menthol n = 1,671	Partial FTND, CPD, nicotine exposure	Tier 2: Human Cross-Sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Muscat et al., 2002)	Mentholated cigarettes and smoking habits in whites and blacks	Current and former smokers from hospitals in New York; Washington, DC; and Pennsylvania: menthol n = 3,005, non-menthol n = 16,540	CPD	Tier 2: Human Cross-sectional, Moderate
(Muscat et al., 2009)	Effects of menthol on tobacco smoke exposure, nicotine dependence, and NNAL glucuronidation	Current smokers: menthol n = 255-270, non-menthol n = 226-230	FTND, TTFC, nicotine exposure	Tier 2: Human Cross-sectional, Strong
(Muscat et al., 2012)	Menthol smoking in relation to time to first cigarette and cotinine: Results from a community-based study	Current daily male and female cigarette smokers of ≥ 5 CPD for one or more years, aged 18-55: menthol n = 221, non-menthol n = 274	TTFC, nicotine exposure	BOE Score: Tier 2: Human Cross-sectional, Strong Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Mustonen et al., 2005)	The influence of gender, race, and menthol content on tobacco exposure measures	Current adult smokers enrolled in smoking cessation trial: menthol n = 88, non-menthol n = 219	CPD, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Nelson et al., 2011)	A survey of mouth level exposure to cigarette smoker in the United States	Smokers of a particular brand: menthol n = 280, non-menthol n = 1050	Nicotine exposure	Tier 2: Human Cross-Sectional, Strong
(Odani et al., 2020)	Flavored tobacco product use and its association with indicators of tobacco	Adult smokers (n = 163,920) from the 2014-2015 TUS-CPS	Daily smoking, smoking within 30 min of waking	Tier 2: Human Cross-Sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	dependence among US adults, 2014–2015			
(Okuyemi et al., 2003)	Does menthol attenuate the effect of bupropion among African American smokers?	African American smokers enrolled in a clinical cessation: menthol n = 471, non-menthol n = 129	FTND, CPD, TTFC, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Okuyemi, Ebersole-Robinson, Nazir, & Ahluwalia, 2004)	African American menthol and non-menthol smokers: differences in smoking and cessation experiences	African American current smokers at an inner-city health center: menthol n = 407, non-menthol n = 73	FTND, CPD	Tier 2: Human Cross-sectional, Not included
(Okuyemi et al., 2007)	Relationship between menthol cigarettes and smoking cessation among African American light smokers	African American light smokers seeking treatment: menthol n = 615, non-menthol n = 138	NDSS, MNWS, CPD, nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Oviedo et al., 2016)	Evaluation of the Tobacco Heating System 2.2. Part 6: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of a mentholated version compared with mentholated and non-	Outbred adult male and female Sprague-Dawley rats	Urinary nicotine metabolites	Tier 3: Nonclinical, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	mentholated cigarette smoke			
(Palmatier et al., 2020)	Nicotine self-administration with tobacco flavor additives in male rats	Male CD rats (n = 140)	Nicotine i.v. self-administration	Tier 3: Nonclinical, Strong
(Perkins et al., 2017)	Threshold dose for behavioral discrimination of cigarette nicotine content in menthol vs. non-menthol smokers	Menthol (n = 40) and non-menthol (n = 21) dependent smokers (based on DSM-V criteria)	CPD, FTND	Tier 2: Human Cross-sectional, Moderate
(Perkins et al., 2018)	Evaluation of menthol per se on acute perceptions and behavioral choice of cigarettes differing in nicotine content	N = 73 dependent smokers, mean age 33.4 years; menthol n = 44, non-menthol = 29	Behavioral choice procedure of puffs between the two cigarettes differing in nicotine content	Tier 2: Human Cross-sectional, Moderate
(Pletcher et al., 2006)	Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function: the Coronary Artery Risk Development in Young Adults (CARDIA) Study	Current smokers, aged 18-30, enrolled in CARDIA study: menthol n = 563, non-menthol n = 972	CPD	Tier 2: Human Cross-sectional, Moderate
(Reitzel, Etzel, et al., 2013)	Associations of menthol use with motivation and confidence to quit smoking	Current adult smokers in Houston, Texas in lung cancer case-control study: menthol n = 313, non-menthol n = 754	HSI	Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Reitzel, Li, et al., 2013)	Race moderates the effect of menthol cigarette use on short-term smoking abstinence	Current smokers attempting to quit: menthol n = 83, non-menthol n = 100	HSI	Tier 2: Human Cross-sectional, Moderate
(Rojewski et al., 2014)	Menthol cigarette use predicts treatment outcomes of weight-concerned smokers	Weight-concerned smokers: menthol n = 61, non-menthol n = 105	FTND, CPD, TTFC	Tier 2: Human Cross-sectional, Moderate
(Rosenbloom et al., 2012)	A cross-sectional study on tobacco use and dependence among women: Does menthol matter?	Female current smokers seeking cessation treatment: menthol n = 335, non-menthol n = 593	TTFC, CPD	Tier 2: Human Cross-sectional, Moderate
(Ross, Dempsey, et al., 2016)	The influence of puff characteristics, nicotine dependence, and rate of nicotine metabolism on daily nicotine exposure in African American smokers.	African American smokers: menthol n = 50, non-menthol n = 10	Nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Ross, Gubner, et al., 2016)	Racial differences in the relationship between rate of nicotine metabolism and nicotine intake from cigarette smoking	Smokers participating in a free smoking cessation trial (n = 1178)	NMR	Tier 2: Human Cross-sectional, Moderate
(Rostron, 2013)	NNAL exposure by race and menthol cigarette use among US smokers	NHANES 2007-2010; everyday smokers: menthol n = 1,098, non-menthol n = 465	CPD, nicotine exposure	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Sanders et al., 2017)	Menthol Cigarettes, Time to First Cigarette, and Smoking Cessation	Meta-analysis	TTFC	Not scored.
(Sarkar et al., 2012)	Metabolism of nicotine and NNK in menthol and non-menthol cigarette smokers	TES: menthol n = 1,044, non-menthol n = 2,297	CPD, nicotine pharmacokinetics, nicotine exposure	BOE Score: Tier 2: Human Cross-sectional, Strong Behavioral Score: Tier 2: Human Cross-sectional, Moderate
(Schauer et al., 2018)	Trends in and characteristics of marijuana and menthol cigarette use among current cigarette smokers, 2005–2014	Past month smokers aged 12 and older from the NSDUH between 2013 and 2014 (n = 5942 menthol, n = 8509 non-menthol)	CPD, daily and non-daily smoking frequency, Nicotine dependence (based on NDSS and FTND scores)	Tier 2: Human Cross-sectional, Moderate
(L. M. Schneller et al., 2020a)	Menthol cigarettes and smoking cessation among adult smokers in the US	N = 8,292 current adult cigarette smokers who completed W1 and W2 of the PATH surveys	HSI	Tier 1: Human Longitudinal, Strong
(Signorello et al., 2009)	Racial difference in serum cotinine levels of smokers	SCSS: menthol n = 139, non-menthol n = 116	Nicotine exposure	Tier 2: Human Cross-sectional, Moderate
(Soulakova & Danczak, 2017)	Impact of menthol smoking on nicotine dependence for diverse racial/ethnic groups of daily smokers	N = 19,961 daily smokers (White, Black, Hispanic, Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, Multiracial) 2010–2011 TUS-CPS	The study considered three (binary) nicotine dependence measures, i.e., heavy smoking status (smoking 1–15 CPD, smoking 16+ CPD), Sw30 (yes, no), and night-smoking (yes, no). The heavy	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
			smoking status and night-smoking were defined using responses to the survey questions "On average, about how many cigarettes do you now smoke each day?" and "Do you sometimes awaken during the night to have a cigarette?" respectively. The Sw30 measure was defined as follows. First, all daily smokers were asked "How soon after you wake up do you typically smoke your first cigarette?" If the respondent could not specify the exact time, then the respondent was asked the follow-up question "Would you say you smoke your first cigarette of the day within the first 30 min?" Responses to these two questions were pooled to define (approximately) the Sw30 measure.	
(S. S. Smith et al., 2014)	Smoking cessation in smokers who smoke menthol and non-menthol cigarettes	African American and White smokers seeking treatment in Wisconsin Smokers Health Study: menthol n = 648, non-menthol n = 847	CPD, FTND	Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(St Helen et al., 2021)	Differences in exposure to toxic and/or carcinogenic volatile organic compounds between Black and White cigarette smokers	Adult Black and White smokers (n = 161 Black and 68 White menthol smokers; n = 21 Black and 116 White non-menthol smokers)	TNE	Tier 2: Human Cross-sectional, Strong
(Squier et al., 2010)	Effect of menthol on the penetration of tobacco carcinogens and nicotine across porcine oral mucosa ex vivo	Porcine tissue	Nicotine pharmacokinetics	Tier 3: Nonclinical, Moderate
(Stahre et al., 2010)	Racial/ethnic differences in menthol cigarette smoking, population quit ratios and utilization of evidence-based tobacco cessation treatments	Adult current (menthol n = 1,700, non-menthol n = 4,355) and former (menthol n = 1,515, non-menthol n = 4,344) smokers	CPD	Tier 2: Human Cross-sectional, Moderate
(Strasser et al., 2013)	The effect of menthol on cigarette smoking behaviors, biomarkers and subjective responses	Adult menthol smokers (n = 22)	Nicotine exposure	Tier 1: Human Longitudinal, Strong
(Veldheer et al., 2018)	Acceptability of SPECTRUM Research Cigarettes among Participants in Trials of Reduced Nicotine Content Cigarettes	N = 341 smokers of at least 5 CPD (menthol n = 200; non-menthol n = 141) who were not interested in quitting; aged 18-65	CPD, FTND, PSCDI, HONC, cotinine	Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Vogel et al., 2021)	Correlates of the nicotine metabolite ratio in Alaska Native people who Smoke Cigarettes	N= 244 Alaska Native adult smokers (N=160 non-menthol smokers)	NMR	Tier 2: Human Cross-sectional, Moderate
(J. Wang et al., 2010)	The effect of menthol containing cigarettes on adult smokers exposure to nicotine and CO	TES: menthol n = 1,044, non-menthol n = 2,297	CPD, Nicotine exposure, nicotine pharmacokinetics	Tier 2: Human Cross-sectional, Strong
(Watson et al., 2017)	Smoking behavior and exposure: Results of a menthol cigarette cross-over study	N = 42 African American and Caucasian cigarette smokers, aged 21+, who have smoked at least 6 CPD for 3 years	CPD, TTFC, HSI, salivary cotinine, mouth level nicotine	Tier 1: Human Longitudinal, Strong Tier 2: Human Cross-sectional, Moderate
(Wickham et al., 2018)	Evaluating oral flavorant effects on nicotine self-administration behavior and phasic dopamine signaling	Male Sprague Dawley rats, n = 4-11 rats/group	i.o. and i.v. self-administration, fast scan cyclic voltammetry	Tier 3: Nonclinical, Strong
(Williams et al., 2007)	Higher nicotine and CO levels in menthol cigarette smokers with and without schizophrenia	Patients with schizophrenia and control participants enrolled in a study for effectiveness of high dose nicotine patch or a study to measure serum nicotine levels: menthol n = 68, non-menthol n = 63	Nicotine exposure, nicotine pharmacokinetics	Tier 2: Human Cross-sectional, Strong
(Winhusen et al., 2013)	A tale of two stimulants: Mentholated cigarettes	Cocaine- (menthol n = 201, non-menthol n = 100) and methamphetamine- (menthol n = 33, non-menthol n = 176)	FTND, CPD	Tier 2: Human Cross-sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	may play a role in cocaine, but not meth-amphetamine, dependence	dependent smokers seeking smoking cessation treatment		
(Zhang et al., 2018)	Menthol facilitates dopamine-releasing effect of nicotine in rat nucleus accumbens	N = 18-24 male Sprague Dawley rats trained in 20 daily 1 hr nicotine self-administration sessions (15 μg/kg/infusion) followed by injection of menthol (0, 1, 2.5, and 5 mg/kg, i.p.), nicotine (0.2 mg/kg, s.c.), or both, 5 min before microdialysis	Dopamine release in the nucleus accumbens (NAc) core via microdialysis	Tier 3: Nonclinical, Strong
(Zuo et al., 2015)	Sex-specific effects of cigarette mentholation on brain nicotine accumulation and smoking behavior	Smokers: menthol n = 10, non-menthol n = 9	FTND, CPD, nicotine pharmacokinetics	Tier 2: Human Cross-sectional, Moderate
Adolescents				
(Azagba et al., 2020)	Cigarette smoking behavior among menthol and nonmenthol adolescent smokers	N = 1707 youth current cigarette smokers (aged 12-17) in the 2017-2018 NYTS survey	Smoking frequency, measured as currently smoking cigarettes ≥10 days versus 1- 9 days to capture smoking at a higher level; For sensitivity analysis, measured as currently smoke cigarettes ≥ 20 days versus 1-19 days and currently smoke cigarettes every day (all 30 days) versus 1-29 days	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(A. M. Cohn et al., 2019)	Menthol smoking patterns and smoking perceptions among youth: findings from the Population Assessment of Tobacco and Health study	N = 383 menthol and n = 250 non-menthol youth current cigarette smokers (aged 12-17) from Wave 1 PATH data	CPD	Tier 2: Human Cross-sectional, Moderate
(Collins & Moolchan, 2006)	Shorter time to first cigarette of the day in menthol adolescent smokers	European American and African American adolescent smokers: menthol n = 531, non-menthol n = 41	FTND, CPD, TTFC	Tier 2: Human Cross-sectional, Moderate
(Curtin et al., 2014a)	Measures of initiation and progression to increased smoking among current menthol compared to non-menthol cigarette smokers based on data from four US government surveys	Youth past-month, regular, or daily smokers in NHANES and TUS-CPS. Sample sizes of the analyses were not provided.	Smoking frequency (daily vs. nondaily use)[8]	Tier 2: Human Cross-sectional, Moderate
(Curtin et al., 2014b)	Primary measures of dependence among menthol compared to non-menthol cigarette smokers in the United States	Adult smokers in NHANES, NSDUH, NHIS and TUS-CPS. Youth smokers in NHANES, TUS-CPS. Sample sizes of the analyses were not provided.	CPD, TTFC, HSI	Tier 2: Human Cross-sectional, Moderate

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[8] This measure was evaluated as a measure of progression in the Curtin et al. (2014a) paper. However, given the cross-sectional nature of the study, it is unclear how the assessment of odds of being a daily vs. nondaily smoker could be classified as progression without a baseline reference point of initial use. As such, this measure was evaluated as "smoking frequency" under a dependence measure in the context of this review.

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Cwalina et al., 2020)	Adolescent menthol cigarette use and risk of nicotine dependence: Findings from the national Population Assessment on Tobacco and Health (PATH) study	N = 434 youth current cigarette smokers (aged 12-17) from Wave 2 of the PATH survey	Eight items from the WISDM that each reflected a separate dependence construct	Tier 2: Human Cross-sectional, Strong
(DiFranza et al., 2004)	Recollections and repercussions of the first inhaled cigarette	N = 237 youth (aged 12-15 years) who had ever inhaled a cigarette and had a favorite brand	HONC	Tier 2: Human Cross-sectional, Moderate
(Denlinger-Apte, Cassidy, et al., 2019)	Effects of cigarette nicotine content and menthol preference on perceived health risks, subjective ratings, and carbon monoxide exposure among adolescent smokers	N = 28 menthol and N = 22 non-menthol adolescent smokers (aged 15-19 years) recruited in Providence, Rhode Island	CPD, mFTQ	Tier 2: Human Cross-sectional, Moderate
(Fait et al., 2017)	Menthol disrupts nicotine's psychostimulant properties in an age and sex-dependent manner in C57BL/6J mice	Male and female adult (77-91 days) and adolescent (21-28 days) mice (C57BL/6J); n = 7-12 per group	Locomotor activity; nicotine intake; plasma nicotine and cotinine levels	Tier 3: Nonclinical, Strong
(Hersey et al., 2006)	Are menthol cigarettes a starter product for youth?	Youth reporting current smoking in 2000 and 2002 NYTS: menthol n = 1552, non-menthol n = 1650	Nicotine Dependence Scale for Adolescents	Tier 2: Human Cross-sectional, Strong
(Hersey et al., 2010)	Menthol cigarettes contribute to the appeal	Youth reporting past 30-day smoking in 2006 NYTS: menthol n = 1458, non-menthol n = 1710	Craving	Tier 2: Human Cross-sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	and addiction potential of smoking for youth			
(Muilenburg & Legge, 2008)	African American adolescents and menthol cigarettes: smoking behavior among secondary school students	Ever-smokers, aged 12-19: total n = 2,068, menthol n = 383, "other brand" n = 1,685	CPD, Past-month smoking frequency (ever daily use)	Tier 2: Human Cross-sectional, Moderate
(Nesil et al., 2018)	Effect of menthol on nicotine intake and relapse vulnerability in a rat model of concurrent intravenous menthol/nicotine self-administration	Adolescent male Sprague-Dawley rats (n = 95), trained to self-administer nicotine (0.01 mg/kg/infusion) beginning PND 30 through PND 36; PR schedule of reinforcement beginning PND 35 or 36 through PND 41-46; 10 day abstinence period followed by nicotine seeking assessed PND 55 or 56	Concurrent i.v. menthol (0.16, 0.32, or 0.64 mg/kg/infusion) and nicotine (0.01 mg/kg/infusion) self-administration procedure	Tier 3: Nonclinical, Strong
(Nonnemaker et al., 2013)	Initiation with menthol cigarettes and youth smoking uptake	Middle school and high school students who were nonsmokers at baseline, under age 18 at baseline, and initiated smoking at wave 1 or 2 during the study (n = 638)	Nicotine dependence scale generated from 5 individual items based on ALLTURS survey questions	Tier 1: Human Longitudinal, Strong
(Sawdey et al., 2020)	Trends and associations of menthol cigarette smoking among US middle and high school students—National Youth Tobacco Survey, 2011–2018	N = 427- 683 youth current cigarette users (aged 12-17) in the 2016-2018 NYTS survey	Number of days smoked in past 30 days, CPD, lifetime cigarettes	Tier 2: Human Cross-sectional, Strong
(Thompson et al., 2018)	Menthol enhances nicotine-induced locomotor sensitization and in vivo functional	Male Sprague Dawley rats, adolescent (arrived PND 21±1, MRI PND 28-36; drug administration PND 41-49 [late adolescence], scanning PND 50) and	Locomotor activity, brain functional connectivity	Tier 3: Nonclinical, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	connectivity in adolescence	adult (arrived PND ≥ 90, followed similar schedule as adolescents); n = 5-18 per group, depending on the assessment		
(Villanti et al., 2021)	Menthol and mint cigarettes and cigars: Initiation and progression in youth, young adults and adults in waves 1–4 of the PATH Study, 2013–2017	N = 10,086 youth (aged 12-17) and n = 21,281 adults (aged 18+) in PATH Waves 1-4	Average score on a 16-item nicotine dependence scale created by PATH investigators	Tier 1: Human Longitudinal, Moderate
(Wackowski & Delnevo, 2007)	Menthol cigarettes and indicators of tobacco dependence among adolescents	Current established high school students in 2004 NYTS: Total n = 1,345, menthol n = 323	Craving	Tier 2: Human Cross-sectional, Moderate
(T. Wang et al., 2014)	Menthol facilitates the intravenous self-administration of nicotine in rats	Female adolescent (PND 31-55) Sprague Dawley rats, n = 5-8 per group	Self-administration	Tier 3: Nonclinical, Strong

Topography Studies

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
(Ahijevych et al., 1996)	Menthol and non-menthol cigarettes and smoke exposure in black and white women	Adult, female daily smokers: 18 Black (n = 8 menthol) and 19 White (n = 10 menthol)	Flow-meter holder attached to differential pressure transducer and Respigraph inductive plethysmography: puff duration, puff volume, interpuff interval, number of puffs, inhalation duration/ volume, exhalation duration/ volume	Tier 2: Human Cross-sectional, Moderate
(Ahijevych & Parsley, 1999)	Smoke constituent exposure and stage of change in black and white women cigarette smokers	Adult, female daily smokers: menthol n = 49, non-menthol n = 46	Flow-meter holder attached to differential pressure transducer and Respigraph inductive plethysmography: puff duration, puff volume, interpuff interval, number of puffs, inhalation duration/ volume, exhalation duration/ volume	Tier 2: Human Cross-sectional, Not included
(Ahijevych et al., 2018)	Effects of menthol flavor cigarettes or total urinary menthol on biomarkers of nicotine and carcinogenic exposure and behavioral measures	Adult, daily smokers (N = 136); n = 35 White non-menthol and 35 White menthol smokers; n = 30 Black non-menthol and 36 Black menthol smokers	CReSS device: puff volume	Tier 2: Human cross-sectional, (Moderate)
(Brinkman et al., 2012)	Exposure to and deposition of fine and ultrafine particles in	9 Caucasian, adult, daily smokers (one participant preferred menthol cigarettes,	SPA-D, Sodim device: puff volume, puff duration, average and peak flow,	Tier 1: Human Longitudinal, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
	smokers of menthol and non-menthol cigarettes	one stated he sometimes smoked menthol cigarettes)	interpuff interval, number of puffs, post-puff inhalation (peak inspiratory flow, peak expiratory flow, inspiration time, expiration time, inspiration volume, expiration volume)	
(Caskey et al., 1993)	Rapid smoking of menthol and non-menthol cigarettes by black and white smokers	Adult, male daily smokers, inpatients for drug and alcohol treatment: menthol n = 12, non-menthol n = 16	Number of puffs-to-stopping	Tier 1: Human Longitudinal, Not included
(Gunawan & Juliano, 2020)	Differences in smoking topography and subjective responses to smoking among African American and white menthol and non-menthol smokers	Adult, daily smokers (n = 100): menthol n = 27 African American + 27 White, non-menthol n = 17 African American + 29 White	CReSS device: puff count, puff volume, puff duration, and mean peak puff flow, interpuff interval	Tier 2: Human Cross-sectional, Strong
(Hsu et al., 2017a)	Menthol smokers: metabolomic profiling and smoking behavior	Adult, daily smokers: menthol n = 71, non-menthol n = 34	CReSS device: puff volume, puff duration, interpuff interval, number of puffs, puff velocity, and smoke exposure (puff number x puff volume)	Tier 2: Human Cross-sectional, Strong
(Jarvik et al., 1994)	Mentholated cigarettes decrease puff volume of smoke and increase CO absorption	Adult, male daily smokers recruited from the community and the West Los Angeles Veterans Administration Medical Center: menthol n = 10, non-menthol n = 10	Fleisch pneumotachygraph attached to differential pressure transducer and inductive plethysmography: number of puffs, puff volume, puff duration,	Tier 1: Human Longitudinal, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
			mean/peak puff flow rate, interpuff interval, lung retention time, cigarette butt length, inhaled volume	
(McCarthy et al., 1995)	Menthol vs non-menthol cigarettes: effects on smoking behavior	Adult, male daily smokers, inpatients for drug and/or alcohol abuse or dependence: menthol n = 11, non-menthol n = 18	Number of puffs-to-stopping, puff volume	Tier 1: Human Longitudinal, Moderate
(Miller et al., 1994)	Cigarette mentholation increases smokers' exhaled CO levels	Adult, African American male daily smokers, inpatients for substance use treatment in the West Lost Angeles VA medical center: menthol n = 6, non-menthol n = 6	Number of puffs, puff volume	Tier 1: Human Longitudinal, Moderate
(Pickworth et al., 2002)	Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery	Adult, daily smokers: menthol n = 18, non-menthol n = 18	Time to smoke to a defined length (50 mm of tobacco rod) and number of puffs	Tier 2: Human Cross-sectional, Moderate
(Strasser et al., 2007)	An association of CYP2A6 genotype and smoking topography	Cessation clinical trial adult participants (menthol n = 73, non-menthol n = 43 smokers) at initial study. 80% of menthol cigarette smokers were non-White	CReSS device: number of puffs, puff volume	Tier 2: Human Cross-sectional, Strong
(Strasser et al., 2013)	Smoking behavior and exposure: Results of a menthol cigarette cross-over study	African American or White, adult daily smokers: menthol n = 26, non-menthol n = 16	CReSS device: number of puffs, duration of puffs, puff volume, peak puff flow and inter-puff interval	Tier 1: Human Longitudinal, Strong
(Watson et al., 2017)	The effect of menthol on cigarette smoking behaviors, biomarkers	Adult, daily menthol smokers (total n = 22)	CReSS device: puff volume, number of puffs, puff duration, interpuff interval	Tier 1: Human Longitudinal, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Score
	and subjective responses			

Cessation Studies

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Alexander, Crawford, & Mendiondo, 2010)	Occupational status, work-site cessation programs and policies and menthol smoking on quitting behaviors of US smokers	Current smokers in 2006 TUS-CPS: n = 30,176	Longest length of time with no smoking in current smokers	Tier 2: Human Cross-Sectional, Not included
(Blot et al., 2011)	Lung cancer risk among smokers of menthol cigarettes	Smokers enrolled in the SCSS: menthol n = 7,886, non-menthol n = 4,487	Self-report: Prospectively and retrospectively-defined cessation	Tier 1: Human Longitudinal, Moderate Tier 2: Human Cross-Sectional, Moderate
(Bover et al., 2008)	Waking at night to smoke as a marker for tobacco dependence: patient characteristics and relationship to treatment outcome	Smokers wanting to quit: menthol n = 1,048, non-menthol n = 1,226	Self-reported cessation assessed 26 weeks after quit date	Tier 1: Human Longitudinal, Moderate
(Brunette et al., 2018)	Menthol cigarette use in young adult smokers with severe mental illnesses	N = 81 daily smoking young adults (aged 18-30) with severe mental illness	Self-report 7-day abstinence, confirmed abstinence at 3-month follow-up	Tier 2: Human cross-sectional, Moderate
(Cropsey et al., 2009)	Differential success rates in racial groups: Results of a clinical trial of smoking cessation among female prisoners	Female prisoners in smoking cessation trial: menthol n = 143, non-menthol n = 36	Biochemically confirmed 7-day point prevalence abstinence at 12 months	Tier 1: Human Longitudinal, Moderate
(Cubbin et al., 2010)	The intersection of gender and	Adult Black, Hispanic, and White current daily smokers (total n = 3,902)	Proportion of menthol versus non-menthol daily smokers	Tier 2: Human Cross-Sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	race/ethnicity in smoking behaviors among menthol and non-menthol smokers in the United States		reporting a quitting attempt in the past year; and time since quitting menthol among current versus former menthol smokers	
(Delnevo et al., 2011)	Smoking-cessation prevalence among US smokers of menthol versus non-menthol cigarettes	Current and former smokers in 2003 and 2006/07 TUS-CPS: Total n = 24,465-71,193	Self-report; Odds of being a former smoker	Tier 2: Human Cross-Sectional, Strong
(Delnevo et al., 2016)	The influence of menthol, e-cigarettes and other tobacco products on young adults' self-reported changes in past year smoking	2011 NYAHS: Established smokers, aged 18-34: menthol n = 355, non-menthol n = 554	Self-report of current and former smoking status	Tier 2: Human Cross-Sectional, Moderate
(D'Silva et al., 2012)	Cessation outcomes among treatment-seeking menthol and non-menthol smokers	Smokers who called a quitline and registered in intervention: menthol n = 1,172, non-menthol n = 5,085	Self-report 30-day point prevalence abstinence assessed at 7 months after program registration	Tier 1 Human Longitudinal, Strong
(Fagan et al., 2010)	Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns	2003 & 2006/7 TUS-CPS: menthol n = 11,671, non-menthol n = 33,644	Self-reported length of smoking abstinence in the past year	Tier 2: Human Cross-Sectional, Moderate
(Faseru et al., 2013)	Predictors of cessation in African American light smokers enrolled	African American light smokers enrolled in pharmacotherapy cessation trial: menthol n = 452; non-menthol n = 88	Biochemically confirmed 7-day point prevalence abstinence assessed at week	Tier 1: Human Longitudinal, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	in a bupropion clinical trial		7 (end of treatment) and week 26	
(Fu et al., 2008)	Menthol cigarettes and smoking cessation during an aided quit attempt	Participants seeking treatment: menthol n = 342, non-menthol n = 1,001	Self-reported 7-day point prevalence cessation assessed at 6 months after randomization	Tier 1: Human Longitudinal, Moderate
(Gandhi et al., 2009)	Lower quit rates among African American and Latino menthol cigarette smokers at a tobacco treatment clinic	Current smokers seeing cessation treatment: menthol n = 778, non-menthol n = 910	Biochemically confirmed 7-day point prevalence cessation assessed 4 weeks and 6 months after quit date	Tier 1: Human Longitudinal, Strong
(Gundersen et al., 2009)	Exploring the relationship between race/ethnicity, menthol smoking, and cessation, in a nationally representative sample of adults	2005 NHIS participants who have made a quit attempt: n = 7,815	Self-report; likelihood of being a former smoker	Tier 2: Human Cross-Sectional, Strong
(K. J. Harris et al., 2004)	Predictors of smoking cessation among African Americans enrolled in a randomized controlled trial of bupropion	African American smokers seeking treatment: menthol n = 417, non-menthol n = 118	Biochemically confirmed 7-day point prevalence assessed at end of treatment phase (7 weeks)	Tier 1: Human Longitudinal, Strong
(Hyland et al., 2002)	Mentholated cigarettes and smoking cessation: findings from COMMIT	COMMIT telephone-based smoking intervention program: menthol n = 3,188, non-menthol n = 10,080	Self-report 6-month point prevalence smoking abstinence assessed at 5-year follow-up	Tier 1 Human Longitudinal, Strong
(Jao et al., 2017)	Does menthol cigarette use moderate the effect of nicotine metabolism	Secondary analysis of clinical trial: n = 474	Biochemically confirmed 7-day point prevalence	Tier 1 Human Longitudinal, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	on short-term smoking cessation?		abstinence assessed at 8 weeks post quit date	
(Keeler et al., 2016)	The association of menthol cigarette use with quit attempts, successful cessation, and intention to quit across racial/ethnic groups in the United States.	2006/07 & 2010/11 TUS/CPS: menthol n = 16,871, non-menthol n = 41,333	Self-report quit at least 3 months, less than 12 months	Tier 2: Human Cross-Sectional, Strong
(Keeler et al., 2018)	Effects of cigarette prices on intention to quit, quit attempts, and successful cessation among African American smokers.	2006/07 and 2010/11 TUS/CPS: African American menthol n = 3,096, non-menthol n = 997; White menthol n = 3,324, non-menthol n = 31,079 smokers	Self-reported cessation for at least 3 months	Tier: 2: Human Cross-Sectional, Strong
(Kumar et al., 2021)	The impact of menthol cigarette use on quit attempts and abstinence among smokers with opioid use disorder	N = 268 participants across three randomized controlled trials examining varenicline for smoking cessation among individuals with opioid use disorder	Whether participants achieved a 24-hour quit attempt during the intervention, total number of quit attempts, and whether participants achieved 7-day point prevalence abstinence	Tier 1: Human Longitudinal, Strong
(Levy et al., 2011)	Quit attempts and quit rates among menthol and non-menthol smokers in the United States	2003 (n = 34,206), 2006-7 (n = 31,250) TUS-CPS	Self-report; Short-term quitters: >3 months, < 1 year; Long-term quitters: >3 months, < 5 years	Tier 2: Human Cross-Sectional, Strong
(McCarthy et al., 1995)	Menthol vs non-menthol cigarettes:	Laboratory study in smokers: menthol n = 11, non-menthol n = 18	Self-report longest period of abstinence	Tier 2: Human Cross-Sectional, Score: Not included

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	effects on smoking behavior			
(Miller et al., 1994)	Cigarette mentholation increases smokers' exhaled CO levels	Laboratory study in African American male smokers: menthol n = 6, non-menthol = 6	Self-report longest number of days without smoking	Tier 2: Human Cross-Sectional, Not included
(Mills et al., 2020)	The relationship between menthol cigarette use, smoking cessation and relapse: Findings from waves 1 to 4 of the Population Assessment of Tobacco and Health Study	Adult (aged 18+) cigarette smokers who completed W1-W4 of the PATH survey (N = 17,318)	Cessation (self-reported no smoking in past 30 days), Relapse (self-reported smoking in the past 30 days following cessation)	Tier 1: Human Longitudinal, Strong
(Muench & Juliano, 2017)	Predictors of smoking lapse during a 48-hour laboratory analogue smoking cessation attempt	Current cigarette smokers: menthol n = 60, non-menthol n = 21	Smoking relapse after 48 hrs of smoking cessation	Tier 1: Human Longitudinal, Strong
(Murray et al., 2007)	Menthol cigarettes and health risks in Lung Health Study data	Smokers with COPD seeking smoking cessation treatment in Lung Health Study: menthol n = 1,216, non-menthol n = 4,667	Sustained quitters (5 years of biochemically confirmed abstinence); Intermittent quitters (at least one visit of biochemically confirmed abstinence and smoking at other visits); continued smokers.	Tier 1: Human Longitudinal, Moderate
(Muscat et al., 2002)	Mentholated cigarettes and smoking habits in whites and blacks	Participants in a case-control study of tobacco-related cancers: menthol n = 3,005, non-menthol n = 16,540	Self-report; Likelihood of being a former vs. current smoker.	Tier 2: Human Cross-Sectional, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Okuyemi et al., 2003)	Does menthol attenuate the effect of bupropion among African American smokers?	African American smokers seeking treatment: menthol n = 417, non-menthol n = 118	Biochemically confirmed 7-day point prevalence at 6 weeks and 6 months after quit date	Tier 1: Human Longitudinal, Strong
(Okuyemi et al., 2004)	African American menthol and non-menthol smokers: differences in smoking and cessation experiences	African American current smokers at an inner-city health center: menthol n = 407, non-menthol n = 73	Self-reported quit duration	Tier 2: Human Cross-Sectional, Not Included
(Okuyemi et al., 2007)	Relationship between menthol cigarettes and smoking cessation among African American light smokers	African American light smokers seeking treatment: menthol n = 615, non-menthol n = 138	8 and 26 weeks after randomization	Tier 1: Human Longitudinal, Strong
(Pletcher et al., 2006)	Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function	Current smokers, aged 18-30, enrolled in the CARDIA study: menthol n = 563, non-menthol n = 972	Self-reported cessation	Tier 1: Human Longitudinal, Strong
(Reitzel et al., 2011)	Race/ethnicity moderates the effects of prepartum menthol cigarette use on postpartum smoking abstinence	Female smokers who quit within 2 months prior to becoming pregnant or during pregnancy: menthol n = 123, non-menthol n = 121	Biochemically confirmed continuous abstinence at 8- and 26-weeks post-partum	Tier 1 Human Longitudinal, Strong
(Reitzel, Etzel, et al., 2013)	Race moderates the effect of menthol cigarette use on short-term smoking abstinence	Smokers motivated to quit: menthol n = 83, non-menthol n = 100	Biochemically confirmed continuous cessation (no smoking since the quit date, verified at each follow-up visit) assessed three weeks after the quit date.	Tier 1: Human Longitudinal, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
(Rojewski et al., 2014)	Menthol cigarette use predicts treatment outcomes of weight-concerned smokers	Weight-concerned smokers seeking treatment: menthol n = 61, non-menthol n = 105	Biochemically confirmed 7-day point prevalence abstinence assessed at 14- and 26-weeks after the quit date.	Tier 1: Human Longitudinal, Strong
(Rosenbloom et al., 2012)	A cross-sectional study on tobacco use and dependence among women: does menthol matter?	Female current smokers seeking cessation treatment: menthol n = 335, non-menthol n = 593	Longest previous quit attempt	Tier 2: Human Cross-Sectional, Not included
(Sanders et al., 2017)	Menthol cigarettes, time to first cigarette, and smoking cessation	Meta-analysis, including 29 studies	Cessation success	Not scored.
(L. M. Schneller et al., 2020a)	Menthol cigarettes and smoking cessation among adult smokers in the US.	N = 8,292 current adult cigarette smokers who completed W1 and W2 of the PATH surveys	Cessation (self-reported smoking in W1 but not W2),	Tier 1: Human Longitudinal, Moderate
(S. S. Smith et al., 2014)	Smoking cessation in smokers who smoke menthol and non-menthol cigarettes	African American and White smokers seeking treatment in Wisconsin Smokers Health Study: menthol n = 648, non-menthol n = 847	Biochemically confirmed abstinence assessed at 26 weeks post quit date.	Tier 1: Human Longitudinal, Strong
P. H. Smith et al. (2020)	Use of mentholated cigarettes and likelihood of smoking cessation in the United States: a meta-analysis.	Meta-analysis (N = 22 studies)	Proportion of studies in which there was a significant association between menthol use and cigarette smoking cessation	Not scored.
(Stahre et al., 2010)	Racial/ethnic difference in menthol cigarette smoking, population quit ratios and	2005 NHIS Cancer Control Supplement: menthol n = 3,215, non-menthol n = 8,789	Self-report; Population quit ratio	Tier 2: Human Cross-Sectional, Strong

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	utilization of evidence-based tobacco cessation treatments			
(Steinberg et al., 2011)	Abstinence and psychological distress in co-morbid smokers using various pharmacotherapies	Smokers with co-morbid with psychological distress evaluated at dependence clinic from 2006-2008: menthol n = 331, non-menthol n = 361	Self-reported or biochemically confirmed 7-day point prevalence quit rates assessed 6 months after the quit date.	Tier 1: Human Longitudinal, Strong
(Sulsky et al., 2014) and corrigendum (Sulsky et al., 2015)	Evaluating the association between menthol cigarette use and the likelihood of being a former versus current smoker	Daily, regular, and former smokers menthol and non-menthol smokers in the 2005, 2010 NHIS and 2010/11 TUS-CPS	NHIS: long-term former smoker (self-report quit duration ≥ 1 year); NHIS, TUS-CPS: short-term former smoker (self-report quit duration 1-3 years)	Tier 2: Human Cross-Sectional, Strong
(Tanner et al., 2020)	Association of cigarette type and nicotine dependence in patients presenting for lung cancer screening	N = 14, 123 current and former smokers enrolled in the National Lung Screening Trial	Smoking abstinence; Participants were defined as abstinent from smoking when they answered "no" to the smoking status question, "In the past 6 months, have you smoked any cigarettes?" in their final questionnaire response	Tier 1: Human Longitudinal, Moderate
(Trinidad et al., 2010)	Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States	Former smokers in the 2003 and 2006/7 TUS-CPS who reported quitting 6+ months; menthol n = 950; non-menthol n = 3015	Successful smoking cessation/long-term quitting was defined as being quit for at least 6 months at the time of the survey	Tier 2: Human Cross-Sectional, Moderate
(Winhusen et al., 2013)	A tale of two stimulants: mentholated cigarettes may play a	Cocaine- (menthol n = 201, non-menthol n = 100) and methamphetamine- (menthol n = 33,	Biochemically confirmed abstinence assessed 10 weeks after quit date.	Tier 1: Human Longitudinal, Moderate

Author Name(s), Publication Year	Title	Sample Size and Characteristics	Outcome Measures	Analysis Tier and Article Score
	role in cocaine, but not methamphetamine, dependence	non-menthol n = 176) dependent smokers seeking smoking cessation treatment		

Appendix F: Weak Analyses Not Included in the Weight of Evidence

Studies presented in this section were eligible for inclusion in the review based on study criteria. However, analyses were scored as weak and determined to not meaningfully contribute to the totality of evidence. Summaries of these studies are presented below.

Sensory Effects

None.

Progression to Regular Use

None.

Dependence

Adult analyses

Scales of dependence

Bello et al. (2016) examined differences in tobacco withdrawal across African American, White, and Hispanic smokers. A variant of the 11-item MNWS was used to evaluate withdrawal symptoms among participants on 6-point Likert scales. One sentence in the article suggests comparisons between menthol and non-menthol smokers in the study: "Two-way factorial analysis of covariance involving race/ethnicity and cigarette type (menthol vs. non-menthol) found that significant differences in withdrawal between racial/ethnic groups were not dependent on cigarette type." The study was scored as weak for inclusion in this review because the primary goal of the study was not to examine effects of menthol and cigarettes on dependence and the study was not designed to address this question. The statement presented suggests no difference in MNWS between menthol and non-menthol smokers across race/ethnicity; however, there is no additional information presented in the document by which to evaluate these conclusions (e.g., no information in a table, no discussion in conclusion).

Okuyemi et al. (2004) examined differences in smoking cessation experiences in a sample of African American menthol and non-menthol smokers at an inner-city health center. Demographic and smoking characteristics of participants indicate no significant difference in FTND score between menthol and non-menthol smokers. The primary objective of the study was not to evaluate menthol and dependence. This data was reported as baseline characteristics in the study, did not control for confounding, and it is not clear what type of statistical analysis was conducted.

TTFC

Fu et al. (2008) compared characteristics of African American male smokers who were veterans in a study examining the effect of menthol cigarette smoking on smoking cessation. The study asked baseline demographic questions about TTFC two years ago. There was no significant difference in TTFC between menthol and non-menthol smokers. The primary objective of the study was not to evaluate menthol and dependence. The study did not control for confounding of these variables because bivariate analyses were conducted to determine variables to include in logistic regression analyses for the study's primary outcome (cessation). The sample consists of

only male African American veterans, limiting generalizability. The study also suffers from recall bias in that the TTFC from two years ago was used for evaluation.

CPD

Fu et al. (2008) compared baseline characteristics of male African American menthol and non-menthol smokers who were veterans in a study examining the effect of menthol cigarette smoking on smoking cessation. The study asked about CPD two years ago. Bivariate analyses indicated that menthol smokers smoked fewer CPD than non-menthol smokers ($p < 0.001$). The primary objective of the study was not to evaluate menthol and dependence. The study did not control for confounding of these variables because bivariate analyses were conducted to determine variables to include in logistic regression analyses for the study's primary outcome (cessation). The sample consists of only male African American veterans, limiting generalizability. The study also suffers from recall bias in that the CPD from two years ago was used for evaluation.

Okuyemi et al. (2004) examined differences in smoking cessation experiences in a sample of African American menthol and non-menthol smokers at an inner-city health center. Analysis of baseline smoking characteristics indicated no significant difference in CPD between menthol and non-menthol smokers. The primary objective of the study was not to evaluate menthol and dependence. This data was reported as baseline characteristics in the study, did not control for confounding, and it is not clear what type of statistical analysis was conducted.

Topography

Ahijevych and Parsley (1999) used a between-subject design to measure topography in Black and White women who preferred menthol (n = 49) or non-menthol (n = 46) cigarettes. On average, participants smoked 17 CPD. Participants were not overnight abstinent (time since last cigarette average = 95 min). Own brand cigarettes were used during topography (puff duration, puff volume, interpuff interval, number of puffs) and respiratory (inhalation duration/volume, exhalation duration/volume) measurement. Significantly larger puff volumes were identified in menthol compared to non-menthol smokers (45.8 vs. 37.8 mL, $p = 0.03$). These findings have limited generalizability because the study was conducted in women only; used cigarettes that vary in nicotine, tar, and CO delivery; and did not include a cross-over component for cigarette type. The authors did not report whether data analysis controlled for race and did not address why puff volume differences were present in this study but not in their previous study. This study was not included due to having limited generalizability and providing limited description of design, analysis methods, and results on topography, potentially because it was in a brief report format. Moreover, smoking topography was not a primary outcome of the study.

Caskey et al. (1993) used a repeated measures cross-over design in male Black and White smokers of menthol (n = 12) and non-menthol (n = 16) cigarettes who were inpatients for drug and alcohol treatment at the West Los Angeles VA Medical Center. Participants were daily smokers of ≥ 15 CPD and had smoked for at least one year. Participants completed two sessions, one week apart, where they smoked each cigarette type. In each session, they were asked to inhale two-second 40 cc puffs of cigarette smoke with 15-second inter puff intervals. They were asked to inhale as many puffs as they could until they could no longer continue. Menthol and non-menthol cigarettes were commercially available and selected for near equivalence in 1991

FTC ratings of tar, nicotine, and CO delivery. The number of puffs each participant took had a high correlation between the two cigarette types. No difference was observed between cigarette type for the average number of puffs taken "until they could no longer continue" (puffs-to-stopping). In a subsample analysis of Black menthol (n = 9) and non-menthol smokers (n = 8), there was no difference in number of puffs-to-stopping. Limitations of this study include the prescribed method of rapid smoke inhalation, racial differences, and inclusion of only male veterans in addiction treatment. Although smokers of regular cigarettes balanced on race (8 Black, 8 White), only three of the menthol smokers were White; the three White menthol smokers were excluded from analyses related to race due to sample size. Moreover, White smokers were found to have taken significantly more puffs to reach the stopping point, suggesting that race plays a role in this topography metric. This study was not included due to having limited generalizability due to topography methodology and sample characteristics, having the primary objective of the study and study design not targeting menthol smoking, using a non-random/representative sample, using a metric (number of puffs) that does not adequately capture smoking topography, having a limited sample size, and did not report results in sufficient detail.

Cessation

Current (Relapsed) Smokers

Alexander et al. (2010) analyzed the longest length of time of no smoking among current smokers in the nationally representative 2006 TUS-CPS (n = 30,176). In unadjusted analyses, menthol smokers were more likely stop smoking for at least one day in the past year than non-menthol smokers. However, the longest length of time before relapse was not statistically significant between menthol (2.0 days) and non-menthol (2.2 days) smokers. This study was not included because the study's outcomes focus primarily on quit attempts and duration of prior smoking abstinence, the outcomes are subject to recall bias and the relevant results were not presented with sufficient detail.

McCarthy et al. (1995) collected data on longest period of abstinence in a small study designed to evaluate the effects of menthol cigarettes on smoking behavior. Longest period of abstinence was 42.54 days for menthol smokers (n = 11) and 181.59 days for non-menthol ("regular") smokers (n = 18); however, the difference was not significant. This study was not included because the study's outcomes assessed longest period of abstinence among current smokers (and not an accurate indication of cessation success), the analyses were subject to recall bias, and limited results were reported for the longest period of abstinence outcome.

Miller et al. (1994) collected data on the longest number of days without smoking for menthol (n = 6) and non-menthol ("regular"; n = 6) smokers in a small laboratory study in male African American smokers designed to evaluate how menthol cigarettes affect exhaled CO levels. Although menthol smokers (60.33 ± 94.12 days) tended to have shorter lengths of longest quit attempt than non-menthol smokers (98.00 ± 177.77 days), these findings were not statistically significant. The study was not designed to evaluate these characteristics, and therefore the sample size may have been too small to detect differences. This study was not included because the study was not developed to look at cessation outcomes, the analyses were subject to recall bias, and limited results were reported for the longest period of abstinence outcome.

Okuyemi et al. (2004) reported longest-ever quit attempt in African American current smokers who visited an inner-city health center. Quit durations were non-significantly shorter for menthol (n = 407; 90 days) compared to non-menthol (n = 73; 157.5 days) smokers. This study was not included because the study assessed longest period of abstinence (and not a true indication of cessation success), the analyses were subject to recall bias, and the sample was predominately menthol smokers.

Rosenbloom et al. (2012) analyzed data from women interested in quitting smoking, and assessed differences in the longest previous quit attempt between menthol and non-menthol smokers. Among all women, menthol smokers (n = 335; 44.0%) were significantly less likely than non-menthol smokers (n = 593; 68.3%) to report a previous quit attempt that lasted more than 90 days (p < 0.01). When stratified by race, no significant differences were observed. This study was not included in the weight of evidence because it assessed longest period of abstinence in current smokers and this outcome was used to estimate dependence. Furthermore, the population is not nationally representative and the cessation outcome is subject to recall bias.