

Menthol Cigarettes, Time to First Cigarette, and Smoking Cessation *

by

Edward Sanders¹, Rolf Weitkunat², and Ruth Dempsey²

¹ Edward Sanders Scientific Consulting, Peseux, Switzerland

² Philip Morris Products SA, Philip Morris International, Research & Development, Neuchâtel, Switzerland

SUMMARY

The goal of the present work is to determine if menthol and non-menthol cigarette smokers differ with respect to time to first cigarette (TTFC) and successful smoking cessation via a meta-analysis of published results. For 13 independent estimates, menthol smokers were slightly but statistically significantly more likely to exhibit TTFC < 5 min (random-effects odds ratio (OR) = 1.12; 95% confidence interval (CI), 1.04-1.21), while 17 independent estimates provided a non-significant difference for TTFC \leq 30 min (random-effects OR = 1.06; 95% CI, 0.96-1.16). For cessation studies, meta-analysis of 30 published estimates indicated a decreased likelihood for menthol cigarette smokers to quit (random-effects OR = 0.87; 95% CI, 0.80-0.96). There was no difference between cessation rates for Caucasian menthol and non-menthol cigarette smokers, but the results support that African American menthol cigarette smokers find it more difficult to quit. Adjustment of cessation for socioeconomic status eliminated any statistically significant advantage for smoking cessation in non-menthol smokers. In conclusion, these results suggest that the observed differences in cessation rates between menthol and non-menthol cigarette smokers are likely explained by differences in socioeconomic status and also suggest that TTFC may not be a robust predictor of successful smoking cessation. [Beitr. Tabakforsch. Int. 27 (2017) 4-32]

AllyZiel der vorliegenden Meta-Analyse veröffentlichterninErgebnisse ist es, zu bestimmen, ob sich Raucher von

menthol; socioeconomic status

ZUSAMMENFASSUNG

mentholhaltigen bzw. -freien Zigaretten hinsichtlich der morgendlichen Zeit bis zur ersten Zigarette (TTFC) sowie hinsichtlich der erfolgreichen Beendigung des Rauchens unterscheiden. Bei Rauchern von mentholhaltigen Zigaretten fand sich eine statistisch signifikante, leicht erhöhte Wahrscheinlichkeit für TTFC < 5 min (Zufallseffekt Odds Ratio (ZE-OR) = 1.12; 95% Konfidenzintervall (KI), 1.04–1.21) auf der Basis von 13 unabhängigen Schätzungen, wohingegen sich auf der Basis von 17 unabhängigen Schätzungen ein nicht-signifikanter Unterschied für TTFC \leq 30 min ergab (ZE-OR = 1.06; 95% KI, 0.96–1.16). Dreißig veröffentlichte Schätzungen aus Rauchentwöhnungsstudien deuten auf einen reduzierten Erfolg bei Rauchern von mentholhaltigen Zigaretten hin (ZE-OR = 0.87; 95% KI, 0.80-0.96). Während sich bei Kaukasiern kein Unterschied in der erfolgreichen Rauchentwöhnung zwischen Rauchern von Zigaretten mit bzw. ohne Menthol zeigte, schienen afroamerikanische Raucher größere Schwierigkeiten mit erfolgreicher Rauchentwöhnung zu haben, wenn sie mentholhaltige Zigaretten rauchten. Die Bereinigung der Entwöhnungsraten um den Einfluss des sozioökonomischen

KEYWORDS: Smoking cessation; time to first cigarette;

^{*}Received: 09th August 2016 – accepted: 25th October 2016

Status eliminierte alle statistisch signifikanten Vorteile von Rauchern mentholfreier Zigaretten. Insgesamt deuten die Ergebnisse darauf hin, dass die beobachteten Unterschiede in den Entwöhnungsraten zwischen Rauchern von Zigaretten mit bzw. ohne Menthol auf Unterschiede im sozioökonomischen Status zurückzuführen sind. Dies weist darauf hin, dass TTFC möglicherweise kein robuster Prädiktor für erfolgreiche Rauchentwöhnung ist. [Beitr. Tabakforsch. Int. 27 (2017) 4-32]

RESUME

Le but du présent travail est de déterminer, grâce à une méta-analyse de résultats publiés, si le temps de latence avant la première cigarette ("time to first cigarette", TTFC) ainsi que la capacité à arrêter de fumer diffèrent entre fumeurs de cigarettes mentholées et non-mentholées. Treize des estimations indépendantes montrent que les fumeurs de ciagrettes mentholées sont légèrement, mais de manière statistiquement significative, plus susceptibles de présenter TTFC \leq 5 minutes (effets aléatoires odds ratio (OR) = 1.12; intervalle de confiance (IC) 95%, 1.04 à 1.21), alors que 17 estimations indépendantes rapportent une différence non significative pour TTFC < 30 minutes (effets aléatoires OR = 1.06; IC 95%, 0.96 à 1.16). En ce qui concerne les études de sevrage tabagique, la méta-analyse des 30 estimations publiées indique que les fumeurs de cigarettes mentholées ont une probabilité plus faible d'arrêter de fumer (effets aléatoires OR = 0.87; IC 95%, 0.87 à 0.96). Il n'y a pas de différence entre les taux de sevrage des caucasiens fumeurs de cigarettes mentholées et ceux des fumeurs de cigarettes non-mentholées, mais les résultats soutiennent que les afro américains fumeurs de cigarettes mentholées trouvent qu'il est plus difficile de cesser. L'ajustement du taux de sevrage en fonction du statut socio-économique élimine tout avantage statistiquement significatif du sevrage tabagique chez les fumeurs de cigarettes non-mentholées. En conclusion, ces résultats suggèrent que les différences observées entre les taux de sevrage de fumeurs de cigarettes mentholées et nonmentholées peuvent s'expliquer par des différences de statut socio-économique. Ces résultats suggèrent également que TTFC peut ne pas être un prédicateur robuste de la capacité de cesser de fumer. [Beitr. Tabakforsch. Int. 27 (2017) 4 - 32]

ABBREVIATIONS

CI	Confidence interval
CPD	Cigarettes per day
CPS	Current population survey
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
GED	General education development
HSI	Heaviness of smoking index
I^2	Index of heterogeneity-attributable
	variance percent
NHANES	National health and nutrition examination
	survey
NHIS-CCS	National health interview survey - cancer

control supplement
National survey on drug use and health
Odds ratio
Probability value
Randomized controlled trial
Socioeconomic status
Time to first cigarette
Tobacco use supplement
Tobacco use supplement - current
population survey

INTRODUCTION

The considerable negative impact of cigarette smoking on individual and public health (1) and the benefits of smoking cessation (2) have been conclusively established for many years. As a consequence, identification of a particular type of cigarette for which either dependence is increased or for which cessation would be more difficult would be of particular public health interest. One type of cigarette product that is currently receiving some attention in many parts of the world including the US with respect to these two issues is the mentholated cigarette. It has been suggested that menthol in cigarette smoke may reduce the irritation and harshness of smoking thus altering smoking topography and leading to inhalation of greater amounts of nicotine. Increased nicotine exposure could in turn lead to increased dependence and possibly a greater difficulty of menthol cigarette smokers to quit (3).

This publication reports the results of a meta-analysis that addresses two key questions dealing with dependence and cessation: (1) are menthol smokers more likely to smoke their first cigarette of the day sooner than non-menthol smokers (TTFC), and (2) is there an association between menthol smoking and cessation rates?

METHODS

Identification of relevant studies

For TTFC the initial basis for the literature selection was all references cited in a recent FDA report (3). A literature search was also conducted in PubMed and the Cochrane database using the terms "time to first cigarette [and] menthol", "dependence [and] menthol", and "time to first cigarette". References were checked from all retained papers, and a search was performed in PubMed for "similar articles" to check for completeness.

Similarly, for cessation studies, articles were identified from the FDA report and from the results of a PubMed and Cochrane database search using the terms "smoking cessation [and] menthol". References were checked from all retained papers and from two review articles (4, 5), and a search was performed in PubMed for "similar articles" to check for any missed studies.

All papers published until February 2015 were included, provided that the data were available in a format that allowed calculation of an odds ratio (OR) and confidence interval (CI) for use in the meta-analysis. This was the only inclusion criterion.

Selection of estimates

Where multiple papers were based on the same source data for either TTFC or cessation, the paper that utilized the largest percentage of the data was generally selected. In some cases additional criteria were required to determine which paper should be selected (see Appendices A and C). This process was conducted prior to inspection of the results or to any calculations being made.

Where papers presented multiple estimates, the following criteria were applied to select the estimates for inclusion in the meta-analyses.

- 1. Preference was given to adjusted estimates as opposed to unadjusted estimates, with a specific exception noted in the next point.
- Cessation estimates for which an adjustment had been made for TTFC or a dependence index that includes TTFC, such as the Heaviness of Smoking Index (HSI)
 (6) or the Fagerström Test for Nicotine Dependence (FTND) (7), were not included in any of the metaanalyses. These estimates were excluded to avoid overadjustment (8, 9).
- 3. For RCT studies, all estimates are based on intention-totreat effects, and the estimate relating to the longest period of cessation up to and including one year was selected. This selection rule was maintained even if it was necessary to utilize an unadjusted OR as opposed to an adjusted OR.

Statistics

The DerSimonian-Laird method was used to meta-analyze the data and was implemented in an Excel spreadsheet based on the description provided by NORMAND (10). This methodology uses weighting by inverse standard error and provides both fixed-effect and random-effects pooled results. Given that ORs are lognormally distributed, the meta-analyses were conducted on the natural log of the ORs (ln(OR)). Standard errors of ln(OR) were calculated

Table 1.	Results	(US) f	or time	to first	cigarette	(TTFC).
----------	---------	--------	---------	----------	-----------	---------

when not provided in the relevant publication either directly from the 95% CI or by calculating the variance of the ln(OR) from the raw data. Reference categories for ORs were non-mentholated cigarettes in the TTFC analysis and menthol cigarettes in the cessation analysis. This was done in order to be consistent with the vast majority of the published literature.

Sensitivity analysis was conducted according to VANDERWEELE and ARAH (11) based on adjusting estimates and confidence interval limits according to a bias factor. This factor is calculated on the basis of specified exposure prevalence levels of an unmeasured binary confounder U (see the Results section for a detailed discussion of U) in the two exposure groups as well as on an assumed effect size of the unmeasured confounder on the outcome. A general assumption of the method is that the effect of U on the outcome is constant across the considered exposure levels/groups.

Pairwise comparison of ORs to assess if differences were statistically significant was conducted using the z test at a 5% level of significance as for all other inferential comparisons. Funnel plots were created using the metafor package in R.

RESULTS

Time to first cigarette (TTFC)

Of the 57 publications identified as potentially relevant in the literature search conducted for menthol smokers and TTFC, 18 were identified with results meeting the inclusion criterion. These papers are listed in Appendix B, which provides demographic data as well as information on each study. All studies were cross-sectional and all were conducted in the US except for HYLAND *et al.* (12) for which about 10% of the subjects were Canadian. The 30 nonoverlapping estimates taken from 15 out of these 18 publications that were used for the meta-analyses are listed in Table 1. Explanation of the choice of estimates to be

Est.	Publ.	First author	Year	Sample	Menth. smokers	TTFC range	Number of in TTFC in	of smokers range (%)	Covariates	OR, 95% CI [b]
NO.	NO.			size	(%)	(min)	Menthol	Non-menthol	adjusted for [a]	
1	1	Hyland (12)	2002	13,268 [c]	24.0	< 10	947 (29.7%)	3,338 (33.1%)	s, a, r, edu, cpd, other [d]	0.90, 0.81–0.99
2	1	Hyland (12)	2002	13,268 [c]	24.0	≤ 30	1,699 (56.0%)	6,520 (63.9%)	None	0.72, 0.66–0.78 [e]
3	2	Окиуемі (31)	2003	600	78.5	≤ 30	385 (81.7%)	90 (69.8%)	None	1.94, 1.25–3.02 [e]
4	3	COLLINS (32)	2006	572	92.8	≤ 5	239 (45%)	12 (29%)	None	1.98, 0.99–3.96 [e]
5	3	COLLINS (32)	2006	572	92.8	≤ 30	398 (75%)	27 (66%)	None	1.55, 0.79–3.05 [e]
6	4	Fu (33)	2008	1,343	25.5	≤ 30	256 (75%)	791 (79%)	None	0.79, 0.59–1.05 [e]
7	5	Gandhi (34)	2009	1,664	46.1	≤ 5	187 (24.3%)	178 (19.9%)	None	1.30, 1.03–1.64 [e]
8	5	Gandhi (34)	2009	1,664	46.1	≤ 30	622 (81.0%)	744 (83.0%)	None	0.87, 0.68–1.12 [e]
9	6	MUSCAT (35)	2009	525	54.1	≤ 30	n.a. (34%)	n.a. (21%)	s, a, r, edu	2.1, 0.96–3.8
10	7	Fagan, ≤ 5 cpd (36)	2010	3,541	33.0	≤ 5			a, r, edu, inc, occ, aoo, dur, ss-12	0.94, 0.60–1.47
11	7	Fagan, 6–10 cpd (36)	2010	11,873	31.1	≤ 5			s, a, r, edu, mar, inc, occ, reg, met, aoo, dur, ss-12	1.22, 1.05–1.43

Table 1. Continued

Est.	Publ.	First author	Year	Sample	Menth.	TTFC	Number of in TTFC	of smokers range (%)	Covariates adjusted for	OR 95% CL[b]
No.	No.			size	(%)	(min)	Menthol	Non-menthol	[a]	, [-]
12	7	Fagan, 11–19 cpd (36)	2010	6,405	25.7	≤ 5			s, a, r, edu, mar, inc, occ, reg, met, aoo, dur, ss-12, itq(10)	1.18, 0.97–1.45
13	7	FAGAN, > 20 cpd (36)	2010	23,496	22.0	≤ 5			s, a, r, edu, mar, inc, occ, reg, met, aoo, dur, ss-12, itq(30)	1.03, 0.95–1.13
14	7	Fagan, ≤ 5 cpd (36)	2010	3,541	33.0	≤ 30			a, r, edu, inc, occ, aoo, dur, ss-12	1.20, 0.96–1.50
15	7	Fagan, 6–10 cpd (36)	2010	11,873	31.1	≤ 30			s, a, r, edu, mar, inc, occ, reg, met, aoo, dur, ss-12, yr	1.09, 0.97–1.22
16	7	FAGAN, 11–19 cpd (36)	2010	6,405	25.7	≤ 30			s, a, r, edu, mar, inc, occ, reg, met, aoo, dur, ss-12, itq(30)	0.98, 0.84–1.14
17	7	FAGAN, > 20 cpd (36)	2010	23,496	22.0	<u>≤</u> 30			a, r, edu, mar, inc, occ, reg, met, yr, aoo, dur, ss-12, itq(30)	1.05, 0.95–1.16
18	8	Аныеvycн (37), daily smokers	2010	2,241	29.9	≤ 30			s, r, edu, occ, hsr [f]	1.16, 0.98–1.38 [g]
19	8	Аніјеvүсн (37), non-daily smokers	2010	688	25.7	≤ 30			s, r, scal [f]	2.03, 1.09–3.78 [g]
20	10	Faseru (38)	2011	540	83.7	≤ 30	330 (73.0%)	60 (68.2%)	None	1.26, 0.77–2.07 [e]
21	11	Reitzel (39)	2011	244	50.5	≤ 5	90 (73.2%)	101 (83.5%)	None	0.54, 0.29–1.01 [e]
22	12	D'SILVA (40)	2012	6,257	18.7	≤ 5	543 (46.3%)	2,192 (43.1%)	None	1.14, 1.00–1.29 [e]
23	13	ROSENBLOOM (41)	2012	928	36.1	≤ 5	164 (49.0%)	213 (36.0%)	None	1.71, 1.30–2.25 [e]
24	16	Rojewski (42)	2014	166	36.7	≤ 30	47 (82.4%)	83 (79.8%)	None	1.19, 0.52–2.74 [e]
25	17	FROST-PINEDA (43)	2014	3,341	31.2	≤ 5	337 (33.8%)	661 (30.1%)	None	1.19, 1.01–1.39 [e]
26	17	FROST-PINEDA (43)	2014	3,341	31.2	≤ 30	782 (74.9%)	1,636 (71.2%)	s, a, r, edu, "tar"	1.17, 0.96–1.42
27	18	CURTIN (44) [h]	2014	77,183	32.0	≤ 5	5,383 (21.8%)	10,457 (19.9%)	None	1.12, 1.08–1.16 [e]
28	18	CURTIN (44) [h]	2014	77,183	32.0	≤ 30	13,231 (53.5%)	27,643 (52.7%)	None	1.03, 1.00–1.06 [e]
29	18	Curtin (44) [i]	2014	4,759	31.6	≤ 5	492 (32.7%)	1,007 (30.9%)	None	1.08, 0.95–1.24 [e]
30	18	Curtin (44) [i]	2014	4,759	31.6	≤ 30	910 (60.5%)	1,970 (60.5%)	None	1.00, 0.88–1.13 [e]

[a] Abbreviations: a - age; aoo - age of onset; cpd - cigarettes/day; dur - daily smoking duration; edu - education; hsr = home smoking rules; inc - annual family income; itq() - intention to quit (days); mar - marital status; met - metropolitan status; occ employment/occupational status; r - race; reg - region; s - sex; scal - state clean air laws; ss-12 - smoking status 12 months ago; "tar" - "tar" yield; yr - survey year.

[b] OR >1 indicates a greater likelihood of menthol smokers smoking their first cigarette earlier than non-menthol smokers.

[c] Includes 1,382 Canadian smokers.

[d] Other covariates: history of past serious quit attempts, age started smoking, desire to stop smoking, frequency of alcohol consumption, use of a non-cigarette tobacco product, pricing tier of cigarette smoked, presence of another smoker in household.
 [e] Calculated from data provided using 2 x 2 table.

[f] Covariates that were significant in the multivariate model.

[g] OR and 95% CI calculated from the binary logit model coefficient and standard error.

[h] Data were obtained from the 2001–2009 National Survey on Drug Use and Health (NSDUH).

[i] Data were obtained from NHANES, 2001–2010.

included is provided in Appendix A, which also includes an analysis demonstrating that the choices made do not bias the results in the direction of a longer TTFC for menthol smokers.

Overall, 5 meta-analyses were performed on the appropriate data from the selected 30 TTFC estimates. These included an overall meta-analysis utilizing the shortest time period for each study (N = 20 estimates), two subgroup analyses for studies that reported data on TTFC \leq 5 minutes (N = 13) or TTFC \leq 30 minutes (N = 17); and finally for large studies (> 1,000 subjects, N = 12) or small studies (< 1,000 subjects, N = 8), again using the shortest time period available. The results of these meta-analyses are reported in Table 2.

For the overall meta-analysis both fixed-effect and randomeffects models indicate a small but significant difference between menthol and non-menthol cigarette smokers, with menthol cigarette smokers being more likely to smoke their first cigarette in the morning before non-menthol cigarette smokers. When comparing studies that determined TTFC of ≤ 5 min alone, the estimates also indicate that menthol cigarette smokers were more likely to smoke their first cigarette within 5 minutes of waking as compared to nonmenthol cigarette smokers. For the studies that report TTFC of ≤ 30 min, although menthol cigarette smokers were more likely to smoke their first cigarettes within 30 min of waking, neither the fixed-effect nor the random-effects pooled estimate was statistically significant. The difference between the two fixed-effect estimates ($\leq 5 \text{ min or } \leq 30$ min) was statistically significant (p < 0.0001), however there was no statistically significant difference between the 2 random-effects estimates (p = 0.37). It can be observed from Table 2 that there was a considerable amount of heterogeneity in the result obtained when the 20 estimates representing the shortest time period from each study were combined ($I^2 = 69\%$). Stratification of the results based on time period (\leq 5 or \leq 30 min) led to an increase in heterogeneity for both sets of pooled results, indicating that this factor does not contribute to the heterogeneity of the pooled result for all studies.

The second comparison that was made concerns study size. Some of the studies were very large population-based studies, whereas others were small, usually based on base-line data from subjects who participated in clinical studies. Setting N = 1,000 subjects as the arbitrary dividing point resulted in two groups of estimates, with 8 estimates for small studies (N = 166-928) and 12 estimates for large studies (N = 1,343-77,183). The results show that the tendency for menthol cigarette smokers to be more likely

than non-menthol cigarette smokers to smoke their first cigarette of the morning early is much more clearly seen in small than in large studies, a difference that is statistically significant. Once again, considerable heterogeneity remained for these pooled estimates. It should be noted that no stratification by race could be performed, since none of the studies provided usable TTFC data stratified for both menthol and race.

In order to check for publication bias, we created a funnel plot for those studies that were used to calculate the pooled meta-analytic result for TTFC ≤ 5 min (Figure E1, Appendix E). As can be seen, there are quite a few studies missing to the left of the point estimate of 1.12, the pooled random-effects meta-analytic result for these estimates. This indicates that the estimate being > 1 is at least partially due to publication bias; that is, there appears to be a preference to publish studies with OR > 1. Therefore, the differences between menthol and non-menthol with respect to TTFC ≤ 5 min, which is already quite modest, may well be to some extent a result of publication bias.

To summarize, the estimates for TTFC indicate that menthol cigarette smokers have a tendency to smoke their first cigarette in the morning earlier than do non-menthol smokers. The increase in the ORs for TTFC associated with menthol smokers is modest, with small studies showing a 40-50% increase, while all other categories indicated only about a 10% increase, except for TTFC of 30 min which showed no increase. In addition, as shown by an analysis of publication bias, this small difference may be even further reduced. It has been suggested that a decrease in TTFC associated with menthol smokers would indicate a concomitant increase in difficulty in smoking cessation for menthol smokers. In order to investigate this possibility, a second set of meta-analyses on studies comparing cessation rates between menthol and non-menthol smokers has been performed and is described below.

Smoking cessation - description of studies

Of the 69 publications identified as potentially relevant in the literature search conducted for menthol cigarette smokers and smoking cessation, 27 were identified that reported results meeting the inclusion criteria; 2 of those presented data on two different studies. These papers are listed in Appendix D, which provides demographic data as well as information on the studies. All studies were conducted in the US except as previously noted for HYLAND *et al.* (12). Of the 29 studies listed in Appendix D, 13 were randomized controlled trials (RCT), 10 were cross-

Description of group (N)	Fixed-effect OR (95% CI) ^a	Random-effects OR (95% CI) ^a	l ^{2 b}
Shortest time period (20)	1.10 (1.07–1.13)	1.14 (1.06–1.23)	69.17
TTFC ≤ 5 min (13)	1.10 (1.07–1.13)	1.12 (1.04–1.21)	71.76
TTFC ≤ 30 min (17)	1.01 (0.99–1.04)	1.06 (0.96–1.16)	84.20
Small studies (< 1000) (8)	1.57 (1.32–1.86)	1.51 (1.13–2.00)	54.73
Large studies (>1000) (12)	1.08 (1.05–1.11)	1.08 (1.00–1.16)	76.13

Table 2. Meta-analytic results for TTFC.

^a OR >1 indicates a greater likelihood of menthol smokers smoking their first cigarette earlier than non-menthol smokers

^b Index of heterogeneity-attributable variance percent

sectional, 5 were prospective studies, and 1 was a retrospective cohort study. There were 3 studies that analyzed data from the National Health Interview Survey Cancer Control Supplement (NHIS-CCS), and 4 studies that analyzed data from the Tobacco Use Supplement to the US Current Population Survey (TUS-CPS). To avoid overlap, only one study from each group was chosen for inclusion in the meta-analysis. The rationale for the choice of study used is provided in Appendix C.

Table 3 contains the 43 estimates derived from nonoverlapping studies used for the meta-analysis of cessation rates for menthol and non-menthol smokers. These estimates have been selected using the criteria specified in the Methods section. Estimates 42 and 43 derived from SULSKY et al. (2014) (publication #27) (13) require a special comment. The published 95% confidence limits appeared to be too narrow, leading to a very large weight for these estimates. Given that the actual number of subjects was not specified, this point could not be checked. Discussions between Mr. Peter N. Lee, of PN Lee Statistics & Computing, and Dr. Sulsky led to an acknowledgment that the confidence limits were indeed too narrow and revised estimates that will be published as a correction (P.N. Lee, personal communication). The estimates shown in Table 3 are these corrected estimates.

Smoking cessation - meta-analyses

The results of various meta-analyses on the cessation data are shown in Table 4. The first result considers all subjects, with no stratification based on race (N = 30). Both the fixed-effect and the random-effects results indicate a very small but statistically significant difference with respect to cessation rates between menthol and non-menthol smokers, suggesting that menthol smokers find it more difficult to quit. Stratification of these studies by race provides an interesting contrast. The pooled fixed-effect and random-effects results for the 10 estimates for Caucasian smokers indicate that there is no difference in cessation rates between menthol and nonmenthol smokers. The situation for African American subjects (14 estimates) is rather different. Both the fixed-effect and the random-effects pooled ORs (OR = 0.93, 95% CI, 0.87-0.98 and OR = 0.76, 95% CI, 0.62-0.92, respectively) show a statistically significant difference indicating that African American menthol cigarette smokers find it more difficult to guit smoking than African American non-menthol cigarette smokers, although the difference for the fixed-effect estimate is small. The pooled results for the small number of estimates (4) for Hispanic smokers do not show a statistically significant difference for cessation rates between menthol and non-menthol cigarette smokers.

Lastly, as with TTFC, we compared large studies to small studies. In this case, rather than simply using size as the differentiating factor, longitudinal and cross-sectional (population) studies, which are invariably large (N = 1,343–65,316), were compared to RCTs, which tend to be small (N = 109–1439). As can be seen there is no difference between cessation rates in menthol cigarette smokers and non-menthol cigarette smokers in the large studies (N = 13). For the 17 RCT estimates, however, there was a clear difference between menthol and non-menthol cigarette smokers. The pooled fixed-effect OR was 0.73

(95% CI, 0.65–0.81) and the pooled random-effects OR was 0.70 (95% CI, 0.60–0.82). Both of these results show a statistically significant disadvantage with respect to cessation rates in menthol cigarette smokers. Simple inspection indicates that the differences between the pooled ORs for population and RCT estimates are statistically significant. As was the case for the TTFC results, there was considerable heterogeneity when results were obtained for population and RCT studies grouped together, and the level of heterogeneity remained high when the results were stratified by race. Stratification by study size resulted in a considerable reduction of heterogeneity for RCT estimates ($I^2 = 42\%$) but not for population estimates ($I^2 = 91\%$). However, there was close agreement between the fixed-effect and random-effects pooled estimates for both types of studies.

To summarize, these results are somewhat inconsistent. They indicate that African American menthol cigarette smokers have more difficulty quitting than African American non-menthol cigarette smokers. Secondly, the results from RCT studies also clearly support a greater difficulty for menthol smokers to quit compared to nonmenthol smokers. On the other hand, the reverse was true for Caucasians, where Caucasian menthol cigarette smokers appear to be directionally slightly more likely to successfully quit smoking than are Caucasian non-menthol cigarette smokers. Lastly, there was no difference in cessation results for population studies comparing menthol to non-menthol cigarette smokers.

We also investigated possible publication bias for cessation results, and the relevant funnel plot is shown in Figure E2, Appendix E. In this case it can be seen that there are quite a few studies missing to the right of 0.87, the pooled random-effects meta-analytic results for all included cessation studies not stratified by race. This indicates that the fact that the estimate is < 1 is perhaps partially due to publication bias; that is, there appears to be a preference to publish studies with OR < 1.

Effect of residual confounding - description of approach

A possible explanation for the difference in comparative cessation rates for African American menthol cigarette smokers compared to Caucasian menthol cigarette smokers might be residual confounding. To attempt to quantitatively determine if such a residual confounder could significantly affect the results, we conducted a conceptual sensitivity analysis. This was done by assuming that some unmeasured confounder, designated as U, might be related both to the exposure, i.e., type of cigarette smoked (menthol vs. nonmenthol), as well as to the outcome under consideration, i.e., TTFC or cessation. This sensitivity analysis indicated that if such a confounder U would be two to three times as prevalent in menthol than in non-menthol cigarette smokers (70 vs. 25 percent), an association of U and TTFC of the same magnitude as the random-effects OR estimate of cigarette type on TTFC of 1.14 (95% CI,1.06-1.23) would reduce that estimate to 1.07 (95% CI, 1.00-1.16) upon adjustment for U. The overall random-effects estimate of cigarette type on cessation would be upwardly adjusted by U from 0.87 (95% CI, 0.80–0.96) to 0.91 (95% CI, 0.83–1.00), by assuming a prevalence of U in menthol smokers of 55 percent (rather than 70 percent as in the above TTFC case)

										Mathed			
Firs	t	Year	Race	Group size	Menthol	Non-	Cessation	rate (No.)	Relevant	Method used for	Covariates	OR 95% CI [d]	Comments
(Re	2	5	stratification [a]			menthol	Menthol	Non-menthol	time period	calculation [b]	adjusted for [c]		
Ω Μ	SCAT 45)	2002	U	17,639	2,350	15,289	43.7% (1,027)	52.9% (8,088)	19 years	ulr	s, a, edu, ccs, dur, cpd	1.1, 1.0–1.3	
Σ	SCAT 45)	2002	AA	1,906	655	1,251	29.4% (194)	35.7% (447)	19 years	ulr	s, a, edu, ccs, dur, cpd	1.1, 0.8–1.4	
ð	UYEMI 31)	2003	AA	600	471	129	18.5% (87)	23.2% (30)	6 months	2x2	None	0.75, 0.47–1.20	[e] [t] [6] [µ]
Ч÷	ETCHER 46)	2006	none	1,535	972	563	31% (301)	46% (259)	15 years	느	s, a, eth, edu, mar, occ, ins	0.71, 0.49–1.02	[] []
Щ	ourbs (24)	2006	none	1,021	418	595	24.9% (104)	35.8% (213)	26 weeks	2x2	None	0.59, 0.44–0.77	[k] [l]
ō	<uyemi (47)</uyemi 	2007	AA < 50 yrs of age	Not specified			n.a.	n.a.	26 weeks	slr	s, a, edu, mar, occ, inc, trt, cqs	0.48, 0.22–1.06	[e]
0	КՍҮЕМІ (47)	2007	AA <u>≥</u> 50 yrs of age	Not specified			n.a.	n.a.	26 weeks	slr	s, a, edu, mar, occ, inc, trt, cqs	0.60, 0.27–1.32	[e]
Σ	URRAY (48)	2007	none	5,734	1,191	4,543	15.4% (183)	16.6% (752)	5 years	2x2	None	0.92, 0.77–1.10	8
щ	ן (33)	2008	none	1,343	342	1,001	n.a.	n.a.	About 6 months	γq	None	1.14, 0.85–1.53	[e] [l]
Q	andhi (34)	2009	O	1,086	348	738	29% (101)	31% (229)	6 months	hm	None	0.88, 0.66–1.10	[e] [l] [m] [u]
G	ANDHI (34)	2009	AA	374	302	72	19% (57)	36% (26)	6 months	hm	None	0.40, 0.23–0.70	[e] [l] [m] [u]
G	ANDHI (34)	2009	т	149	66	50	6) %6	27% (14)	6 months	hm	None	0.32, 0.13–0.77	[e] [l] [m]
ō	ROPSEY (49)	2009	U	109	53	56	13.5% (7)	8% (4)	12 months	2x2	None	1.98, 0.54–7.19	[e] [m]
C	ROPSEY (49)	2009	AA	124	117	7	14% (16)	8% (1)	12 months	2x2	None	0.95, 0.11–8.42	[e] [m]
Ś	ТАНRЕ (50)	2010	none	12,004	3,215	8,789	47.1% (1,515)	50.4% (4,434)	≥12 months	2x2	None	0.87, 0.81–0.95	

Table 3. Results (US) for cessation.

Comments		[0]	[d]		[e] [d]	[J] [J]	[j] [m] [s]	[j] [m] [s]	[j] [m] [s]	[m] [t]	[ɯ]	[ɯ]	[ɯ]		
טא מלא רו ואו		1.07, 0.97–1.18	0.55, 0.43–0.69	0.82, 0.65–1.05	0.74, 0.51–1.05	0.79, 0.50–1.24	0.17, 0.02–1.38	0.36, 0.09–1.43	1.59, 0.54–4.72	0.92, 0.88–0.97	0.95, 0.90–1.00	0.78, 0.64–0.95	0.97, 0.82–1.14	1.55, 1.41–1.70	1.03, 0.96–1.11
Covariates	adjusted for [c]	None	None	None	None	None	None	None	None	s, a, r, occ, inc, y, m	s, a, edu, inc, rec, BMI	s, a, edu, inc, rec, BMI			
Method used for	calculation [b]	2x2	2x2	2x2	2x2	crl	2x2	2X2	2x2	mlr	mlr	mlr	mlr	ulr	ulr
Relevant time	period	≥12 months	≥12 months	≥12 months	6 months	26 weeks post partum	26 weeks post partum	26 weeks post partum	26 weeks post partum	5 years	5 years	5 years	5 years	6.5 years	6.5 years
rate (No.)	Non-menthol	50.7% (4,051)	50.4% (210)	44.6% (510)	25.0% (135)	n.a.	24% (16)	35% (4)	18% (8)	n.a.	n.a.	n.a.	n.a.	40.3% (4,905)	41.4% (2,347)
Cessation	Menthol	52.4% (1,096)	35.7% (363)	39.9% (139)	19.7% (53)	n.a.	6% (1)	17% (12)	27% (9)	n.a.	n.a.	n.a.	n.a.	49.6% (2,162)	29.7% (8,521)
Non-	menthol	7,987	417	1,143	540	121	68	5	42	47,613	n.a.	n.a.	n.a.	12,164	5,666
Menthol		2,092	1,017	348	269	123	20	20	33	17,703	n.a.	n.a.	n.a.	4,358	28,676
Group size		10,079	1,434	1,491	809	244	88	81	75	65,316	55,347	5,448	4,521	16,522	34,342
Race	stratification [a]	U	AA	т	none	none	U	АА	т	none	U	АА	т	C (retrospective)	AA (retrospective)
Vear	2	2010	2010	2010	2010	2011	2011	2011	2011	2011	2011	2011	2011	2011	2011
First	(Ref.)	STAHRE (50)	STAHRE (50)	STAHRE (50)	Rose (51)	Reitzel (39)	Reitzel (39)	REITZEL (39)	Reitzel (39)	DELNEVO (52)	DELNEVO (52)	DELNEVO (52)	DELNEVO (52)	ВLОТ (53)	ВLОТ (53)
Publ.	No.	13	13	13	15	17	17	17	17	18	18	18	18	19.1	19.1
Esti- mate	No.	16	17	18	19	20	21	52	23	24	25	26	27	28	29

Table 3. Continued

Continued
ы.
Table

Esti- moto	Publ.	Eiret outbor	Voor	Race	Croup cito	Monthol	Non-	Cessation	rate (No.)	Relevant	Method used for	Covariates		Commonte
No.	No.	riist autiol	נמ	stratification [a]	aloup alze		menthol	Menthol	Non-menthol	time period	calculation [b]	adjusted for [c]		0011110110
30	19.2	ВLОТ (53)	2011	none (prospective)	12,373	7,886	4,487	n.a.	n.a.	4.3 years	ulr	s, a, r, edu, inc, rec, BMI, pyb, tel	1.02, 0.89–1.16	[ʌ] [ŋ]
31	20	STEINBERG (25)	2011	none	692	331	361	19.9% (66)	26.0% (94)	6 months	2x2	None	0.71, 0.49–1.01	[e] [s] [m]
32	21	D'SILVA (40)	2012	none	715	120	595	17.3% (21)	13.8% (82)	7 months	2x2	None	1.33, 0.78–2.24	[x] [s]
33	22	Faseru (26)	2013	AA	540	452	88	10.0% (45)	20.4% (18)	26 weeks	2x2	None	0.43, 0.24–0.78	[y]
34	23	Reitzel (54)	2013	none	183	83	100	12.1% (10)	19.0% (19)	3 weeks	crl	s, a, r, edu, inc, occ, par, stg	0.73, 0.33–1.61	5
35	23	Reitzel (54)	2013	U	95	18	77	n.a.	n.a.	3 weeks	crl	s, a, r, edu, inc, occ, par, stg	0.21, 0.05–0.98	5
36	23	Reitzel (54)	2013	AA	88	65	23	n.a.	n.a.	3 weeks	crl	s, a, r, edu, inc, occ, par, stg	1.72, 0.58–5.00	5
37	24	RoJEWSKI (42)	2014	none	166	61	105	13% (8)	30% (32)	26 weeks	느	σ	0.40, 0.17–0.96	[e]
38	25	LEWIS (55)	2014	none	1,582	454	1,128	20.3% (92)	26.2% (296)	≥1 year	cph	None	0.79, 0.64–0.99	[z]
39	25	LEWIS (55)	2014	AA	189	103	86	17.0% (18)	18.5% (16)	≥1 year	2x2	None	0.93, 0.44–1.95	[z]
40	26	SMITH (56)	2014	none	1,439	625	814	29.9% (187)	35.9% (292)	26 weeks	gee	t, trt	0.71, 0.59–0.86	[e] [aa]
41	26	SMITH (56)	2014	ပ	1,253	439	814	32.6% (143)	35.9% (292)	26 weeks	2x2	None	0.86, 0.68–1.10	[e]
42	27	SULSKY (13)	2014	U	n.a.	n.a.	n.a.	n.a.	n.a.	1–3 years	느	men, cpd, dur	0.90, 0.84–0.96	[ab]
43	27	SULSKY (13)	2014	AA	n.a.	n.a.	n.a.	n.a.	n.a.	1–3 years	Ir	men, sia, dur	0.84, 0.67–1.05	[ab]

Table 3. Continued

- AA = African American; C = Caucasian; H = Hispanic; none = subjects not stratified by race. D 🛛
- 2x2 = calculated from 2x2 table; bv = bivariate test; cph = Cox proporortional hazards; crl = CR logit modelling; gee = generalized estimating equations; lr = logistic regression; mh = Mantel-Haenszel estimate; mlr = multiple logistic regression; slr stepwise logistic regression; ulr = unconditional logistic regression
- = income; ins = health insurance status; m = month; mar = marital status; men = menthol cigarette use; occ = employment/occupation; par = partner status; pyb = pack-years at baseline; a = age; BMI = body mass index; ccs = case-control status; cpd = cigarettes/day; cqs = confidence in quitting smoking; dur = duration of smoking; edu = education; eth = ethnicity; inc = race; rec = recruitment source; s = sex; sia = smoking initiation age; stg = stage; t = time; tel = time elapsed between baseline and follow-up questionnaire; trt = treatment arm; y= vear. $\overline{\mathbf{O}}$
- DR < 1 indicates a lesser likelihood of menthol smokers to quit compared to non-menthol smokers.
 - Based on 7-day point prevalence.
- Based on the statement that attrition rates were equal for menthol and non-menthol smokers, since only rates were provided.
- Cessation rates, but not numbers of quitters, were also reported for the treatment arm (buproprion) and the placebo arm but only for 6-week cessation.
 - Reported ORs were reported separately for < 50 and > 50 years of age, for 6-week cessation, and were adjusted for TTFC.
 - Apparently based on N = 1,260 with no obvious explanation for the difference between this number and the total sample of 1,535.
- Based on sustained quitters.
- Apparently there were 8 smokers who could not be classified as menthol or non-menthol.
 - Reported ORs using multiple logistic regression were adjusted for TTFC.
 - Results obtained graphically.
- Cessation rates as a function of employment were presented.
- The reported OR for Caucasian smokers was the reference.
- The reported OR for African American smokers was based on a reference OR of 1.00 for Caucasian smokers.
- Results were obtained from a meeting abstract.
- The reported unadjusted OR was used since TTFC was a covariate used in the adjusted OR.
- Reported ORs were adjusted for TTFC.
- Numbers of menthol and non-menthol smokers are based on the percentages for the total sample.
- Overall cessation rate was 21%; cessation rates were not specified for menthol and non-menthol smokers.
 - Cessation was defined as a current smoker at baseline reporting non-smoking at a follow-up interview.
- Although not apparently stated in the publication, 61 subjects did not specify menthol or non-menthol.
 - Based on 30-day point prevalence.
- The reported adjusted OR was for 7 weeks of cessation.
- Cessation defined by no cigarette purchase for a period of 1 year.
- Data were analyzed using a "marginal or 'population average' model that permit inferences about the effects of covariates on population and sub-population means via generalized estimating equations (GEE)..." A detailed explanation of this method applied to a relevant data set has been pubished by LEE *et al.* (57) [aa]
 - Data obtained from the 2010/2011 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) for regular and former smokers. [ab]

Table 4. Meta-analytic results for smoking cessation.

Description of group (N)	Fixed-effect OR (95% CI) ^a	Random-effects OR (95% CI) ^a	l ^{2 b}
Not stratified by race (30)	0.96 (0.94–0.99)	0.87 (0.80–0.96)	84.24
Caucasian (10)	1.02 (0.98–1.05)	1.02 (0.87–1.19)	91.82
African American (14)	0.93 (0.87–0.98)	0.76 (0.62–0.92)	77.71
Hispanic (4)	0.91 (0.79–1.04)	0.85 (0.63–1.14)	60.07
RCT study estimates (17)	0.73 (0.65–0.81)	0.70 (0.60–0.82)	42.12
Longitudinal and cross-sectional study estimates (13)	0.98 (0.95–1.01)	0.98 (0.89–1.09)	90.64

^a OR > 1 indicates that menthol smokers are more likely to quit smoking than are non-menthol smokers

^b Index of heterogeneity-attributable variance percent

and an association of U and cessation of the same magnitude as the random-effects estimate of cigarette type on cessation. Similarly, the random-effects cessation estimate of 0.76 (95% CI, 0.62-0.92) in African Americans would adjust away under the same assumptions, except that a 56% instead of a 55% prevalence of U in menthol smokers would be required. In these scenarios, neither the prevalence of an unmeasured confounder U in menthol and non-menthol cigarette smokers nor the magnitude of the association of U and the respective outcome (TTFC or cessation) appear to be unrealistic.

Mechanistically, such a confounder would be associated with a simultaneous increased likelihood of smoking menthol rather than non-menthol cigarettes and smoking shortly after waking or finding it difficult to quit smoking. Race is a variable that would fit this description, based on the high prevalence of menthol cigarette use in African American smokers (3) and on a higher prevalence of smoking in this sociocultural subpopulation, although this difference is not large (14). However, even after conditioning the analyses on race (by stratification), cessation rates remain lower in African American menthol cigarette smokers compared to African American nonmenthol cigarette smokers. There appear to be only two explanations for this finding. The first is that there is an interaction between African American smokers and menthol cigarettes, perhaps genetic, which would make it more difficult for African American menthol cigarette smokers to quit. The second is that in addition to race, and possibly associated with it, residual confounding is operative in this subgroup. Such a residual confounder could be related to some socioeconomic, lifestyle, and/or cultural factor that could selectively affect certain subgroups of African American smokers. This is quite reasonable given the well-known inverse correlation of socioeconomic status (SES) and smoking cessation (15) as well as the fact that African Americans are more likely to be socially, economically, and educationally disadvantaged than are Caucasians (16). Such differences may also play a role with respect to smoking cessation of African American menthol cigarette smokers.

Effect of residual confounding - results

In order to evaluate empirically if SES may be playing a role as a confounder in the analyzed studies, stratification of cessation results based on presence or absence of adjustment for SES was conducted separately for all subjects, Caucasian subjects, African American subjects, RCT studies, and longitudinal and cross-sectional studies. Both adjusted and unadjusted results were available for certain estimates. However, in many cases only one type of estimate could be utilized. It is important to note that in no case was any estimate included where the results were adjusted for TTFC. The results of this analysis are presented in Table 5. As can be seen, not only does adjustment for SES provide results that are much closer to the null hypothesis than those that were not adjusted for SES (with the exception of the results for Caucasian smokers), but none of the adjusted estimates exhibited a statistically significant tendency for menthol cigarette smokers to find it more difficult to quit. The fixed-effect pooled estimates adjusted for SES for all subjects and Caucasian smokers, as well as results from longitudinal and cross-sectional studies indicate a statistically significantly greater ease of menthol cigarette smokers to quit as opposed to non-menthol cigarette smokers. Lastly, it should be noted that the adjusted pooled RCT ORs were no longer statistically significant; however, this result was based on only three estimates. Although not shown in Table 5, I² values were calculated for all pooled ORs resulting from stratification based on SES factors. There was no material change in heterogeneity as a result of this stratification, meaning that SES factors are not the cause of the observed heterogeneity.

To further investigate the possible role that SES may be playing as a key residual confounder, baseline data were evaluated for each study used in the cessation metaanalyses in order to determine if there was indeed a tendency for menthol cigarette smokers to reflect lower SES "scores". These results are summarized in Table 6 for three SES factors; namely, education, employment, and income. With respect to education, 6 studies indicated that menthol cigarette smokers had less education than nonmenthol cigarette smokers (noted in bold), 2 studies indicated the opposite (noted in italics), whereas 4 studies showed no difference between the 2 types of smokers. Only 7 studies provided information relating to employment, with 4 showing that a greater number of non-menthol cigarette smokers were employed compared to menthol cigarette smokers, one showing the opposite, and 2 studies showing no difference. Lastly, 5 studies reported results on income, 2 of which indicated lesser earnings for menthol cigarette smokers and 3 of which indicated no difference.

Table 5. Meta-analytic results for smoking cessation effect of adjustment for SES.

Description of group (N)	Fixed-effect OR (95% CI) ^a	Random-effects OR (95% CI) ^a
All (Table 4) (30)	0.96 (0.94–0.99)	0.87 (0.80–0.96)
All, adjusted for SES (10)	1.03 (1.00–1.07)	1.06 (0.90–1.24)
All, unadjusted for SES (25)	0.80 (0.78–0.82)	0.76 (0.67–0.87)
Caucasian (Table 4) (10)	1.02 (0.98–1.05)	1.02 (0.87–1.19)
Caucasian, adjusted for SES (5)	1.07 (1.03–1.12)	1.14 (0.83–1.55)
Caucasian, unadjusted for SES (8)	0.95 (0.93–0.98)	0.93 (0.76–1.13)
African American (Table 4) (14)	0.93 (0.87–0.98)	0.76 (0.62–0.92)
African American, adjusted for SES (7)	1.00 (0.94–1.07)	1.02 (0.95–1.09)
African American, unadjusted for SES (11)	0.62 (0.59–0.65)	0.65 (0.58–0.73)
RCT estimates (Table 4) (17)	0.73 (0.65–0.81)	0.70 (0.60–0.82)
RCT estimates, adjusted for SES (3)	0.96 (0.50-1.82)	0.89 (0.54–1.48)
RCT estimates, unadjusted for SES (15)	0.71 (0.64–0.78)	0.69 (0.59–0.81)
Long and CS estimates (Table 4) (13)	0.98 (0.95–1.01)	0.98 (0.89–1.09)
Long and CS estimates, adjusted for SES (7)	1.03 (1.00–1.07)	1.06 (0.90–1.25)
Long and CS estimates, unadjusted for SES (12)	0.84 (0.82–0.87)	0.85 (0.72–1.00)

^a OR > 1 indicates that menthol smokers are more likely to quit smoking than are non-menthol smokers

Table 6. Comparison of SES factors menthol (M) and non-menthol (NM) smokers.

Study	Mea	sure of educ	ation	Meas	sure of emplo	oyment	Me	easure of inco	ome
Sludy	%M	%NM	р	%M	%NM	р	%M	%NM	р
Окиуемі, 2003 (31)	≥ Hig	h school gra	duate		Employed		Montl	nly income >	\$1,800
	50.7%	47.3%	p = 0.487	78.3%	65.9%	p = 0.004	45.4%	45.3%	p = 0.977
PLETCHER, 2006 (46)	:	Some colleg	е	E	mployed full t	ime		NS ^a	
	35.3%	53.5%	p < 0.001	45.5%	62.2%	p < 0.001			
Окиуемі, 2007 (47)	≥ Hig	h school edu	ucation		Employed		Montl	nly income >	\$1,800
	83.2%	84.8%	p = 0.705	47.5%	49.3%	p = 0.707	40.4%	43.9%	p = 0.494
Murray, 2007 (48)	Ec	lucation (yea	ars)		NS			NS	
Ett. 2000 (22)	13.0 %	13.070			NO			NC	
FU, 2008 (33)	50m 61%	e college or 39%	more p < 0.001		N5			NS	
Gandhi, 2009 (34)	Bad	chelors or high	gher	E	mployed full t	ime		NS	
	14.9%	30.8%	p < 0.001	41.2%	48.8%	p < 0.001			
Stahre, 2010 (50)	Som 38 7% ^b	ne college/de 44.3% ^b	egree p = 0 025		NS			NS	
	~ L				NS			\$20,000/vo	or
REIIZEL, 2011 (39)	23.6%	13.2%	p = 0.037		NO		56.0%	75.9%	p = 0.002
Delnevo, 2011 (52)	E	BA/BS or mo	re		NS		:	≥ \$75,000/ye	ar
	15.4%	11.1%					15.2%	18.6%	
D'SILVA, 2012 (40)	Less	s than high s	chool		NS			NS	
	14.4%	8.9%							
Reitzel, 2013 (54)	> Hię	gh school dip	oloma		Employed			≥ \$20,000/ye	ar
	60.2%	73.0%	p = 0.067	43.4%	58.0%	p = 0.049	47.5%	58.6%	p = 0.14
Rojewski, 2014 (42)		NS		70 70/	Employed			NS	
0			. 1	10.1%	80.0%			NO	
SMITH, 2014 (56)	> Hiç 63.9%	gn school dip 76.9%	pioma p < 0.0001 ^c	75.8%	Employed 80.2%	p = 0.0056 ^c		NS	

^a Not specified
 ^b For current smokers
 ^c p value for group difference

These results, although not unidirectional, show that menthol cigarette smokers are more likely to have lower SES "scores" than non-menthol cigarette smokers.

Stratification based on adjustment for SES was also carried out for large studies that investigated the relationship of menthol cigarette smoking with respect to TTFC. Only large studies were investigated, since no small study had results that were adjusted for SES. The effect of adjustment of TTFC for SES moved the results in the opposite direction than those obtained for cessation. The pooled fixed-effect OR for the six adjusted estimates was 1.10 (95% CI, 1.03–1.17) and the random-effects TTFC OR was 1.11 (95% CI, 1.04-1.19). The seven unadjusted estimates gave results of 1.04 (95% CI, 1.01-1.07) and 1.02 (95% CI, 0.92-1.13), respectively. Although adjustment for SES resulted in a directional increase in menthol cigarette smokers smoking their first cigarette within the first 5 min of waking, the difference was not statistically significant with p = 0.12 for the two fixed-effect estimates and p = 0.21 for the random-effects estimates.

DISCUSSION

The major strengths of this analysis are: 1) a comprehensive literature search was conducted that appears to have identified all relevant published studies, and 2) a quantitative analysis was undertaken.

The results of these meta-analyses without inclusion of confounding by SES are quite consistent with the qualitative analysis conducted by the FDA (3); namely, that menthol cigarette smokers are more likely to smoke their first cigarette of the day earlier than non-menthol cigarette smokers, while African American menthol cigarette smokers are more likely to find it difficult to quit smoking as compared to African American non-menthol cigarette smokers. However, comparison of cessation studies that adjusted for SES compared to those that did not make this adjustment showed no statistically significant difference for African American menthol and non-menthol smokers. On the other hand adjustment of TTFC for SES factors slightly increased the difference between menthol and non-menthol cigarette smokers. As a consequence, it is of interest to examine more closely the claim that TTFC is a valid marker of ease of smoking cessation.

The FDA (3) suggested that TTFC is the best measure of nicotine dependence primarily based on a study by BAKER *et al.* (17). These authors indicated that the specific question regarding TTFC in the FTND (question 1) was the best predictor of smoking cessation success at both 1 week and 6 months in 5 US studies. In addition they reported that smokers whose TTFC was < 5 min were more likely to experience difficulty in quitting than those whose TTFC was between 5 and 30 min. It should be noted that none of these studies compared cessation results separately for menthol and non-menthol cigarette smokers.

There are other studies that have confirmed the positive relationship between TTFC and successful smoking cessation. HADDOCK *et al.* (18) reported that the TTFC question in the FTND was strongly related to 1 year of smoking cessation. TOLL *et al.* (19) suggested that TTFC was strongly related to cigarette craving, and that craving,

in turn, was a strong predictor of the tendency of smokers to relapse following cessation. SWEITZER *et al.* (20) reported that TTFC was significantly associated with success rate in a smoking cessation trial (hazard ratio [HR] = 6.97, 95% CI, 1.67–29.12), although the length of this trial was only 8 days.

Other published results, however, call into question the value of TTFC as a predictor of smoking cessation, particularly with respect to longer-term smoking cessation. Based on the HSI, which is composed of TTFC and cigarettes per day (CPD), FIDLER et al. (21) found only a weak association with 6-month smoking cessation rates (OR = 1.21, 95% CI, 1.07–1.38). Moreover, after adjusting for urge to smoke, the relationship was no longer statistically significant (OR = 1.11, 95% CI, 0.97-1.28). COURVOISIER and ETTER (22) reported that although the HSI was a significant predictor of success of smoking cessation at 8 days, this index could explain only 1-3% of the variance in smoking cessation at 31 days. A recent paper similarly suggested a lack of correlation between TTFC and smoking cessation for longer cessation periods (23). This study indicated a significant association between TTFC and short-term smoking abstinence (7- or 14-days), which was considerably reduced and no longer significant for 30-day smoking abstinence. It should be noted that all subjects suffered from substance use disorder, although this seems unlikely to have affected the association between TTFC and smoking cessation.

The above discussion suggests that any direct correlation between TTFC and smoking cessation results may be attenuated as the time of cessation increases.

The evidence that TTFC may not be effective in predicting long-term smoking cessation coupled with the generally very small difference obtained herein with respect to the association of TTFC and menthol cigarette smoking may at least partially explain some of the inconsistencies in the analyses on cessation (see Table 4). For example, the differences in findings between the large longitudinal or cross-sectional studies and smaller RCT studies may be explained in part by the difference in smoking cessation periods, with RCT studies tending to look at cessation at 6 months, whereas longitudinal and cross-sectional studies tend to look at longer-term cessation.

It should be noted that while small studies usually randomly allocated smokers to different types of interventions for cessation, this randomization does not extend to menthol and non-menthol cigarette smokers. This implies that the analysis conducted here, which looks at differences between menthol and non-menthol cigarette smokers, is not protected for imbalance of baseline covariates by randomization. Thus, small studies, even though originally set up as RCTs, should be considered as simply observational studies in the context of the present analysis, albeit they are usually smaller than studies that have been classified as observational studies by design.

It should also be noted that the majority of the studies on African American populations in the meta-analysis for smoking cessation were based on RCT studies. This may provide some explanation for the observed difference in smoking cessation rates between menthol and non-menthol cigarette smokers for this group. A meta-analysis restricted to only African American subjects in longitudinal and cross-sectional studies (estimates 2, 17, 26, 29, and 43) gave a fixed-effect result (OR = 0.95, 95% CI, 0.89-1.01). Although this result was only slightly higher than the fixed-effect result for all African American subjects (OR = 0.93, 95% CI, 0.87-0.98), the result was no longer statistically significant.

The result of the investigation of the possible impact of socioeconomic effects with respect to smoking cessation merits further discussion. Three RCT studies provide further support for the importance of adjustment for SES factors. FOULDS et al. (24) indicated that the OR for successful cessation at 26 weeks for smokers with some college/technical school education was 1.38 (p = 0.092), while for smokers with a bachelor's degree or higher the OR was 1.65 (p = 0.02) compared to less than high school, high school, or General Educational Development (GED) test as the reference value. STEINBERG et al. (25) reported that the OR for successful cessation at 6 months for unemployed smokers was 0.45 (95% CI, 0.25-0.80) compared to employed smokers. They also provide information on the association of successful cessation with educational attainment, but the results were mixed, and none of the ORs were statistically significant. FASERU et al. (26) reported that 14.1% of smokers earning \geq \$1,800/month successfully quit compared to 10.1% of smokers earning less than that amount, but this result was not statistically significant (p = 0.15). These results add further support to the importance of SES factors playing a key role with respect to smoking cessation.

One major weakness of this analysis is that the results are based on the pooling of numerous different types of studies, and there are insufficient data to stratify the data optimally. In addition, there are wide differences in the extent to which the included studies have been adjusted for covariates, ranging from completely unadjusted estimates to estimates adjusted for numerous covariates. This point is particularly important when considering the findings comparing studies adjusted for SES factors and those that were not. This difference could reflect adjustment for other confounders. An indication that many different types of studies have been pooled is clearly illustrated by the high levels of heterogeneity present in all of the meta-analyses. Given the high level of heterogeneity present in virtually all of the pooled estimates, it would not have been unreasonable to have presented only the results from the random-effects analyses. However, in presenting both types of pooled ORs in Tables 2, 4, and 5, it can be seen that the fixed-effect and random-effects estimates are invariably in very good agreement, with the exception of the African American cessation results (Table 4). This suggests that the high level of heterogeneity was not a major factor with respect to the pooled estimates. It should also be noted that stratifying both the TTFC (time period, study size) and cessation (race, study type, SES) results on all reasonable factors, given the available data, did not materially reduce the heterogeneity, meaning that we were unable to identify the source of the heterogeneity. It would be ideal if the pooled raw data could have been analyzed using multiple logistic regression, thereby allowing the contribution of covariates to the pooled estimates to be determined; however, the required data were not available.

With respect to adjustment for smoking cessation studies,

the decision was made to not include estimates that were adjusted for TTFC or a surrogate for TTFC (FTND or HSI) in order to avoid an over-adjusted model. Meta-analyses conducted with these studies included indicated that the differences between the two sets of results were negligible (data not shown). Arguably other factors related to nicotine dependence could also lead to over-adjustment. For example some studies also adjusted for CPD (estimates 1, 2, and 42), duration of smoking (estimates 1, 2, 42, and 43), pack years at baseline (estimate 30) and confidence in quitting smoking (estimates 6 and 7). In the case of CPD, the FDA report (3) took the position that smoking restrictions have led to this marker being less reliable as a measure of dependence, although BAKER et al. (17) reported mixed results for the association of CPD with smoking cessation. Given that only 3 estimates in the data set were corrected for CPD, and that there is some question as to the importance of CPD as a marker of dependence, it was decided to retain these three estimates. With respect to duration of smoking, SWEITZER et al. (20) examined the association between years of smoking and time to first relapse and reported an OR of 1.07 (95% CI, 1.00-1.14). Given the weakness of this association it was felt appropriate to retain the estimates that adjusted for this covariate. There is little information in the literature regarding "confidence in quitting smoking" and successful quitting. Two studies have been published reporting that individuals who have a high level of confidence with respect to quitting smoking are more likely to be successful (27, 28). On the other hand, confidence in quitting was closely related to "self-efficacy" (29), which has been extensively investigated. In a meta-analysis by GWALTNEY et al. (30), all published results through 2006, consisting of 189 analyses drawn from 54 publications, were pooled and it was concluded that "the relationship between SE [selfefficacy] and subsequent smoking was reliable and statistically significant, but small, accounting for only 2% of the variance in outcome ... ". Furthermore, the outcome was substantially lower among studies examining a pre-quit self-efficacy measure, which was the case for the two estimates included in this meta-analysis. As a consequence, these two estimates were retained.

CONCLUSIONS

In conclusion, meta-analysis of the available data on TTFC and menthol cigarette smokers indicates a weak association between menthol cigarette smoking and shorter TTFC. There is clearly a significant difference in small studies indicating that menthol smokers are more likely to have a shorter TTFC than are non-menthol cigarette smokers, but this is not the case in large studies. Inconsistencies exist with respect to the cessation results. There was no difference between Caucasian menthol and non-menthol smokers. On the other hand African American menthol cigarette smokers were less likely to quit smoking than were African American non-menthol cigarette smokers. In this case both the fixed-effect and random-effects estimates were statistically significant. The results of these metaanaylses for cessation tend to support the results of other research cited above suggesting that TTFC is not a meaningful indicator for the ability to quit smoking. It appears possible, however, that the difference for cessation between the two races is attributable to residual confounding. Not only are the SES-adjusted pooled ORs for African American menthol cigarette smokers essentially equal to 1, but there is no longer a statistically significant difference between the pooled adjusted ORs for African Americans and Caucasians. On the other hand, the very high heterogeneity observed in virtually all of the metaanalyses conducted in this study strongly suggests that key potential confounding factors have not yet been identified and adjusted for. As a consequence, further detailed research is still necessary to fully determine if there is indeed any difference between menthol and non-menthol cigarette smokers with respect to smoking cessation.

CONFLICT OF INTEREST

R.D. and R.W. are employees of Philip Morris International. E.S. is a scientific consultant and former employee of Philip Morris International.

ACKNOWLEDGMENTS

The authors would like to thank Mr. Peter N. Lee for helpful assistance with respect to the statistical analysis as well as helpful discussions. The authors would also like to thank Mme. Simone Pfändler for assistance with respect to the correct transfer of the results to the tables.

REFERENCES

- 1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health: How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease. A Report of the Surgeon General; Atlanta, GA, USA, 2010.
- Fagerström, K.: The Epidemiology of Smoking: Health Consequences and Benefits of Cessation; Drugs 62 (Suppl. 2) (2002) 1–9.
- 3. Food and Drug Administration (FDA): Reference Addendum: Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes; 2013. Available at: http://www.fda.gov/downloads/ScienceResearch/Spe cialTopics/PeerReviewofScientificInformationandAs sessments/UCM362600.pdf (accessed November 2016).
- Foulds, J., M.W. Hooper, M.J. Pletcher, and K.S. Okuyemi: Do Smokers of Menthol Cigarettes Find it Harder to Quit Smoking?; Nicotine Tob. Res. 12 (S2) (2010) S102–S109. DOI: 10.1093/ntr/ntq166
- Hoffman, A.C. and D. Miceli: Menthol Cigarettes and Smoking Cessation Behavior; Tob. Induc. Dis. 9 (S1) (2011) S6. DOI: 10.1186/1617-9625-9-S1-S6
- 6. Heatherton, T.F., L.T. Kozlowski, R.C. Frecker, W.

Rickert, and J. Robinson: Measuring the Heaviness of Smoking: Using Self-Reported Time to the First Cigarette of the Day and Number of Cigarettes Smoked per Day; Br. J. Addict. 84 (1989) 791–799.

- Heatherton, T.F., L.T. Kozlowski, R.C. Frecker, and K.O. Fagerström: The Fagerström Test for Nicotine Dependence: A Revision of the Fagerström Tolerance Questionnaire; Br. J. Addict. 86 (1991) 1119–1127.
- 8. Weitkunat, R. and M. Wildner: Exploratory Causal Modeling in Epidemiology: Are All Factors Created Equal?; J. Clin. Epidemiol. 55 (2002) 436–444.
- Schisterman, E.F., S.R. Cole, and R.W. Platt: Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies; Epidemiology 20 (2009) 488–495. DOI: 10.1097/EDE.0b013e3181a819a1
- Normand, S.L.: Meta-Analysis: Formulating, Evaluating, Combining, and Reporting; Stat. Med. 18 (1999) 321–359.
- VanderWeele, T.J. and O.A. Arah: Bias Formulas for Sensitivity Analysis of Unmeasured Confounding for General Outcomes, Treatments, and Confounders; Epidemiology 22 (2011) 42–52. DOI: 10.1097/EDE.0b013e3181f74493
- Hyland, A., S. Garten, G.A. Giovino, and K.M. Cummings: Mentholated Cigarettes and Smoking Cessation: Findings from COMMIT. Community Intervention Trial for Smoking Cessation; Tob. Control 11 (2002) 135–139.
- Sulsky, S.I., W.G. Fuller, C. Van Landingham, M.W. Ogden, J.E. Swauger, and G.M. Curtin: Evaluating the Association between Menthol Cigarette Use and the Likelihood of Being a Former versus Current Smoker; Regul. Toxicol. Pharmacol. 70 (2014) 231–241. DOI: 10.1016/j.yrtph.2014.07.009
- Cokkinides, V., P. Bandi, C. McMahon, A. Jemal, T. Glynn, and E. Ward: Tobacco Control in the United States - Recent Progress and Opportunities; CA Cancer J. Clin. 59 (2009) 352–365. DOI: 10.3322/caac.20037
- 15. Reid, J.L., D. Hammond, C. Boudreau, G.T. Fong, M. Siahpush, and ITC Collaboration: Socioeconomic Disparities in Quit Intentions, Quit Attempts, and Smoking Abstinence among Smokers in Four Western Countries: Findings from the International Tobacco Control Four Country Survey; Nicotine Tob. Res. 12 (Suppl.) (2010) S20–S33. DOI: 10.1093/ntr/ntq051
- Dimou, A., K.N. Syrigos, and M.W. Saif: Disparities in Colorectal Cancer in African-Americans vs Whites: Before and after Diagnosis; World J. Gastroenterol. 15 (2009) 3734–3743. DOI: 10.3748/wjg.15.3734
- Baker, T.B., M.E. Piper, D.E. McCarthy, D.M. Bolt, S.S. Smith, S.-Y. Kim, S. Colby, D. Conti, G.A. Giovino, D. Hatsukami, A. Hyland, S. Krishnan-Sarin, R. Niaura, K.A. Perkins, and B.A. Toll: Time to First Cigarette in the Morning as an Index of Ability to Quit Smoking: Implications for Nicotine Dependence; Nicotine Tob. Res. 9 (Suppl. 4) (2007) S555–S570. DOI: 10.1080/14622200701673480
- Haddock, C.K., H. Lando, R.C. Klesges, G.W. Talcott, and E.A. Renaud: A Study of the Psychometric and Predictive Properties of the Fagerström Test for Nicotine Dependence in a Population of Young Smokers; Nicotine Tob. Res. 1 (1999) 59–66.

- Toll, B.A., T.S. Schepis, S.S. O'Malley, S.A. McKee, and S. Krishnan-Sarin: Subjective Reactivity to the First Cigarette of the Day as a Predictor of Smoking Relapse: A Preliminary Study; Drug Alcohol Depend. 89 (2007) 302–305.
- Sweitzer, M.M., R.L. Denlinger, and E.C. Donny: Dependence and Withdrawal-Induced Craving Predict Abstinence in an Incentive-Based Model of Smoking Relapse; Nicotine Tob. Res. 15 (2013) 36–43. DOI: 10.1093/ntr/nts080
- Fidler, J.A., L. Shahab, and R. West: Strength of Urges to Smoke as a Measure of Severity of Cigarette Dependence: Comparison with the Fagerström Test for Nicotine Dependence and its Components; Addiction 106 (2011) 631–638.

DOI: 10.1111/j.1360-0443.2010.03226.x

- 22. Courvoisier, D.S. and J.F. Etter: Comparing the Predictive Validity of Five Cigarette Dependence Questionnaires; Drug Alcohol Depend. 107 (2010) 128–133. DOI: 10.1016/j.drugalcdep.2009.09.011
- 23. Rohsenow, D.J., R.A. Martin, J.W. Tidey, P.M. Monti, and S.M. Colby: Comparison of the Cigarette Dependence Scale with Four Other Measures of Nicotine Involvement: Correlations with Smoking History and Smoking Treatment Outcome in Smokers with substance Use Disorders; Addict. Behav. 38 (2013) 2409–2413.

DOI: 10.1016/j.addbeh.2013.03.019

- 24. Foulds, J., K.K. Gandhi, M.B. Steinberg, D.L. Richardson, J.M. Williams, M.V. Burke, and G.G. Rhoads: Factors Associated with Quitting Smoking at a Tobacco Dependence Treatment Clinic; Am. J. Health Behav. 30 (2006) 400–412.
- Steinberg, M.B., M.T. Bover, D.L. Richardson, A.C. Schmelzer, J.M. Williams, and J. Foulds: Abstinence and Psychological Distress in Co-Morbid Smokers Using Various Pharmacotherapies; Drug Alcohol Depend. 114 (2011) 77–81.

DOI: 10.1016/j.drugalcdep.2010.06.022

 Faseru, B., N.L. Nollen, M.S. Mayo, R. Krebill, W.S. Choi, N.L. Benowitz, R.F. Tyndale, K.S. Okuyemi, J.S. Ahluwalia, and L. Sanderson Cox: Predictors of Cessation in African American Light Smokers Enrolled in a Bupropion Clinical Trial: Addict. Behav. 38 (2013) 1796–1803.

DOI: 10.1016/j.addbeh.2012.11.010

- 27. Marino, M.G., E. Fusconi, R. Magnatta, A. Panà, and M. Maurici: Epidemiologic Determinants Affecting Cigarette Smoking Cessation: A Retrospective Study in a National Health System (SSN) Treatment Service in Rome (Italy); J. Environ. Public Health 2010 (2010) 183206. DOI: 10.1155/2010/183206
- Khan, N., J.R. Anderson, J. Du, D. Tinker, A.M. Bachyrycz, and R. Namdar: Smoking Cessation and its Predictors: Results from a Community-Based Pharmacy Tobacco Cessation Program in New Mexico; Ann. Pharmacother. 46 (2012) 1198–1204. DOI: 10.1345/aph.1P146
- Etter, J.F., M.M. Bergman, J.P. Humair, and T.V. Perneger: Development and Validation of a Scale Measuring Self-Efficacy of Current and Former Smokers; Addiction 95 (2000) 901–913.

- Gwaltney, C.J., J. Metrik, C.W. Kahler, and S. Shiffman: Self-Efficacy and Smoking Cessation: A Meta-Analysis; Psychol. Addict. Behav. 23 (2009) 56–66. DOI: 10.1037/a0013529
- Okuyemi, K.S., J.S. Ahluwalia, M. Ebersole-Robinson, D. Catley, M.S. Mayo, and K. Resnicow: Does Menthol Attenuate the Effect of Bupropion Among African American Smokers?; Addiction 98 (2003) 1387–1393.
- 32. Collins, C.C. and E.T. Moolchan: Shorter Time to First Cigarette of the Day in Menthol Adolescent Cigarette Smokers; Addict. Behav. 31 (2006) 1460–1464.
- 33. Fu, S.S., K.S. Okuyemi, M.R. Partin, J.S. Ahluwalia, D.B. Nelson, B.A. Clothier, and A.M. Joseph: Menthol Cigarettes and Smoking Cessation During an Aided Quit Attempt; Nicotine Tob. Res. 10 (2008) 457–462. DOI: 10.1080/14622200801901914
- 34. Gandhi, K.K., J. Foulds, M.B. Steinberg, S.E. Lu, and J.M. Williams: Lower Quit Rates Among African American and Latino Menthol Cigarette Smokers at a Tobacco Treatment Clinic; Int. J. Clin. Pract. 63 (2009) 360–367. DOI: 10.1111/j.1742-1241.2008.01969.x
- 35. Muscat, J.E., G. Chen, A. Knipe, S.D. Stellman, P. Lazarus, and J.P. Richie Jr: Effects of Menthol on Tobacco Smoke Exposure, Nicotine Dependence, and NNAL Glucuronidation; Cancer Epidemiol. Biomarkers Prev. 18 (2009) 35–41. DOI: 10.1158/1055-9965.EPI-08-0744
- 36. Fagan, P., E.T. Moolchan, A. Hart Jr, A. Rose, D. Lawrence, V.L. Shavers, and J.T. Gibson: Nicotine Dependence and Quitting Behaviors Among Menthol and Non-Menthol Smokers with Similar Consumptive Patterns; Addiction 105 (S1) (2010) 55–74. DOI: 1111/j.1360-0443.2010.03190.x
- 37. Ahijevych, K. and J. Ford: The Relationships between Menthol Cigarette Preference and State Tobacco Control Policies on Smoking Behaviors of Young Adult Smokers in the 2006-07 Tobacco Use Supplements to the Current Population Surveys (TUS CPS); Addiction 105 (S1) (2010) 46–54. DOI: 10.1111/j.1360-0443.2010.03201.x
- 38. Faseru, B., W.S. Choi, R. Krebill, M.S. Mayo, N.L. Nollen, K.S. Okuyemi, J.S. Ahluwalia, and L.S. Cox: Factors Associated with Smoking Menthol Cigarettes Among Treatment-Seeking African American Light Smokers; Addict. Behav. 36 (2011) 1321–1324. DOI: 10.1016/j.addbeh.2011.07.015
- Reitzel, L.R., N. Nguyen, Y. Cao, J.I. Vidrine, P. Daza, P.D. Mullen, M.M. Velasquez, Y. Li, P.M. Cinciripini, L. Cofta-Woerpel, and D.W. Wetter: Race/Ethnicity Moderates the Effect of Prepartum Menthol Cigarette Use on Postpartum Smoking Abstinence; Nicotine Tob. Res. 13 (2011) 1305–1310. DOI: 10.1093/ntr/ntr095
- D'Silva, J., R.G. Boyle, R. Lien, P. Rode, and K.S. Okuyemi: Cessation Outcomes Among Treatment-Seeking Menthol and Nonmenthol Smokers; Am. J. Prev. Med. 43 (S3) (2012) S242–S248. DOI: 10.1016/j.amepre.2012.07.033
- Rosenbloom, J., V.W. Rees, K. Reid, J. Wong, and T. Kinnunen: A Cross-Sectional Study on Tobacco Use and Dependence Among Women: Does Menthol Matter?; Tob. Induc. Dis. 10 (2012) 19.

DOI: 10.1186/1617-9625-10-19

- 42. Rojewski, A.M., B.A. Toll, and S.S. O'Malley: Menthol Cigarette Use Predicts Treatment Outcomes of Weight-Concerned Smokers; Nicotine Tob. Res. 16 (2014) 115–119. DOI: 10.1093/ntr/ntt137
- Frost-Pineda, K., R. Muhammad-Kah, L. Rimmer, and Q. Liang: Predictors, Indicators, and Validated Measures of Dependence in Menthol Smokers; J. Addict. Dis. 33 (2014) 94–113. DOI: 10.1080/10550887.2014.909696
- 44. Curtin, G.M., S.I. Sulsky, C. Van Landingham, K.M. Marano, M.J. Graves, M.W. Ogden, and J.E. Swauger: Primary Measures of Dependence Among Menthol Compared to Non-Menthol Cigarette Smokers in the United States; Regul. Toxicol. Pharmacol. 69 (2014) 451–466. DOI: 10.1016/j.yrtph.2014.05.011
- 45. Muscat, J.E., J.P. Richie Jr, and S.D. Stellman: Mentholated Cigarettes and Smoking Habits in Whites and Blacks; Tob. Control 11 (2002) 368–371.
- Pletcher, M.J., B.J. Hulley, T. Houston, C.I. Kiefe, N. Benowitz, and S. Sidney: Menthol Cigarettes, Smoking Cessation, Atherosclerosis, and Pulmonary Function: The Coronary Artery Risk Development in Young Adults (CARDIA) Study; Arch. Intern. Med. 166 (2006) 1915–1922. DOI: 10.1001/archinte.166.17.1915
- 47. Okuyemi, K.S., B. Faseru, L. Sanderson Cox, C.A. Bronars, and J.S. Ahluwalia: Relationship Between Menthol Cigarettes and Smoking Cessation Among African American Light Smokers; Addiction 102
- (2007) 1979–1986.
 48. Murray, R.P., J.E. Connett, M.A. Skeans, and D.P. Tashkin: Menthol Cigarettes and Health Risks in Lung Health Study Data; Nicotine Tob. Res. 9 (2007) 101–107.
- Cropsey, K.L., M.F. Weaver, G.D. Eldridge, G.C. Villalobos, A.M. Best, and M.L. Stitzer: Differential Success Rates in Racial Groups: Results of a Clinical Trial of Smoking Cessation Among Female Prisoners; Nicotine Tob. Res. 11 (2009) 690–697. DOI: 10.1093/ntr/ntp051
- Stahre, M., K.S. Okuyemi, A.M. Joseph, and S.S. Fu: Racial/Ethnic Differences in Menthol Cigarette Smoking, Population Quit Ratios and Utilization of Evidence-Based Tobacco Cessation Treatments; Addiction 105 (S1) (2010) 75–83. DOI: 10.1111/j.1360-0443.2010.03200.x
- 51. Rose, J.E. and F. Behm: Menthol Smokers, SES and Quit-Smoking Outcome; Society for Research on Nicotine and Tobacco Conference, Baltimore, MD, USA, February 24-27, 2010; Abstract POS5–58. Available at: https://c.ymcdn.com/sites/ srnt.site-ym.com/resource/resmgr/Conferences/Past_ Annual_Meetings/2010_Annual_Meeting_Abstract.pdf (Accessed November 2016).
- 52. Delnevo, C.D., D.A. Gundersen, M. Hrywna, S.E. Echeverria, and M.B. Steinberg: Smoking-Cessation Prevalence Among U.S. Smokers of Menthol versus Non-Menthol Cigarettes; Am. J. Prev. Med. 41 (2011) 357–365. DOI: 10.1016/j.amepre.2011.06.039
- 53. Blot, W.J., S.S. Cohen, M. Aldrich, J.K. McLaughlin, M.K. Hargreaves, and L.B. Signorello: Lung Cancer

Risk Among Smokers of Menthol Cigarettes; J. Natl. Cancer Inst. 103 (2011) 810–816. DOI: 10.1093/jnci/djr102

- 54. Reitzel, L.R., Y. Li, D.W. Stewart, Y. Cao, D.W. Wetter, A.J. Waters, and J.I. Vidrine: Race Moderates the Effect of Menthol Cigarette Use on Short-Term Smoking Abstinence; Nicotine Tob. Res. 15 (2013) 883–889. DOI: 10.1093/ntr/nts335
- 55. Lewis, M., Y. Wang, and C.J. Berg: Tobacco Control Environment in the United Sates and Individual Consumer Characteristics in Relation to Continued Smoking: Differential Responses Among Menthol Smokers?; Prev. Med. 65 (2014) 47–51. DOI: 10.1016/j.ypmed.2014.04.019
- 56. Smith, S.S., M.C. Fiore, and T.B. Baker: Smoking Cessation in Smokers who Smoke Menthol and Non-Menthol Cigarettes; Addiction 109 (2014) 2107–2117. DOI: 10.1111/add.12661
- 57. Lee, J.H., T.A. Herzog, C.D. Meade, M.S. Webb, and T.H. Brandon: The Use of GEE for Analyzing Longitudinal Binomial Data: A Primer Using Data from a Tobacco Intervention; Addict. Behav. 32 (2007) 187–193.
- 58. Lawrence, D., A. Rose, P. Fagan, E.T. Moolchan, J.T. Gibson, and C.L. Backinger: National Patterns and Correlates of Mentholated Cigarette Use in the United States; Addiction 105 (S1) (2010) 13–31. DOI: 10.1111/j.1360-0443.2010.03203.x
- 59. Jones, M.R., B.J. Apelberg, M. Tellez-Plaza, J.M. Samet, and A. Navas-Acien: Menthol Cigarettes, Race/Ethnicity, and Biomarkers of Tobacco Use in U.S. Adults: The 1999-2010 National Health and Nutrition Examination Survey (NHANES); Cancer Epidemiol. Biomarkers Prev. 22 (2013) 224–232. DOI: 10.1158/1055-9965.EPI-12-0912
- Hickman, N.J. III, K.L. Delucchi, and J.J. Prochaska: Menthol Use Among Smokers with Psychological Distress: Findings from the 2008 and 2009 National Survey on Drug Use and Health; Tob. Control 23 (2014) 7–13.

DOI: 10.1136/tobaccocontrol-2012-050479

- Gundersen, D.A., C.D. Delnevo, and O. Wackowski: Exploring the Relationship between Race/Ethnicity, Menthol Smoking, and Cessation, in a Nationally Representative Sample of Adults; Prev. Med. 49 (2009) 553–557. DOI: 10.1016/j.ypmed.2009.10.003
- 62. Trinidad, D.R., E.J. Pérez-Stable, K. Messer, M.M. White, and J.P. Pierce: Menthol Cigarettes and Smoking Cessation Among Racial/Ethnic Groups in the United States; Addiction 105 (S1) (2010) 84–94. DOI: 10.1111/j.1360-0443.2010.03187.x
- Levy, D.T., K. Blackman, J. Tauras, F.J. Chaloupka, A.C. Vilanti, R.S. Niaura, D.M. Vallone, and D.B. Abrams: Quit Attempts and Quit Rates Among Menthol and Nonmenthol Smokers in the United States; Am. J. Public Health 101 (2011) 1241–1247. DOI: 10.2105/AJPH.2011.300178
- Ahluwalia, J.S., K.J. Harris, D. Catley, K.S. Okuyemi, and M.S. Mayo: Sustained-Release Bupropion for Smoking Cessation in African Americans: A Randomized Controlled Trial; JAMA 288 (2002) 468–474.

- 65. Ahluwalia, J.S., K. Okuyemi, N. Nollen, W.S. Choi, H. Kaur, K. Pulvers, and M.S. Mayo: The Effects of Nicotine Gum and Counselling Among African American Light Smokers: A 2 x 2 Factorial Design; Addiction 101 (2006) 883–891.
- 66. Partin, M.R., L.C. An, D.B. Nelson, S. Nugent, A. Snyder, S.S. Fu, M.L. Willenbring, and A.M. Joseph: Randomized Trial of an Intervention to Facilitate Recycling for Relapsed Smokers; Am. J. Prev. Med. 31 (2006) 293–299.
- Cropsey, K., G. Eldridge, M. Weaver, G. Villalobos, M. Stitzer, and A. Best: Smoking Cessation Intervention for Female Prisoners: Addressing an Urgent Public Health Need; Am. J. Public Health 98 (2008) 1894–1901. DOI: 10.2105/AJPH.2007.128207
- Cox, L.S., N.L. Nollen, M.S. Mayo, W.S. Choi, B. Faseru, N.L. Benowitz, R.F. Tyndale, K.S. Okuyemi, and J.S. Ahluwalia: Bupropion for Smoking Cessation in African American Light Smokers: A Randomized Controlled Trial; J. Natl. Cancer Inst. 104 (2012)

290-298. DOI: 10.1093/jnci/djr513

 Piper, M.E., S.S. Smith, T.R. Schlam, M.C. Fiore, D.E. Jorenby, D. Fraser, and T.B. Baker: A Randomized Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies; Arch. Gen. Psychiatry 66 (2009) 1253–1262. DOI: 10.1001/archgenpsychiatry.2009.142

Corresponding author:

Rolf Weitkunat Philip Morris International, Research & Development, 2000 Neuchâtel, Switzerland Phone: +41 58 242 2563. Fax: +41 58 242 2811 Email: rolf.weitkunat@pmi.com

APPENDIX A

Explanation of choice of TTFC study where more than one study was based on the same data set.

All publications providing data that met the inclusion criterion for the meta-analysis of TTFC for menthol smokers compared to non-menthol smokers are listed in Appendix B. Three publications reported results for the 2003 and 2006/2007 Tobacco Use Supplement to the US Current Population Survey (TUS-CPS). FAGAN et al. (publication 7, Appendix B) (36) reported results for both TTFC \leq 5 min and \leq 30 min, and their results were adjusted for a large number of covariates. LAWRENCE et al. (publication 9) (58) provided a result for \leq 30 min. Although their result was adjusted, the adjustment factors were not specified. Lastly, CURTIN et al. (publication 18) (44) reported results for both \leq 5 and \leq 30 min, but their results were unadjusted. As a consequence, the FAGAN et al. results were used in the meta-analysis for both \leq 5 and \leq 30 min. Lastly, AHIJEVYCH and FORD (publication 8) (37) also reported data from the 2006/7 TUS-CPS, however not from the 2003 survey. Given that data in this publication were analyzed only for subjects between 18 and 24, it was decided to retain this study despite there being some overlap with the FAGAN et al. 2010 study. If there were indeed a difference in TTFC for young smokers between menthol and non-menthol cigarettes, it would not be detectable in the FAGAN et al. results (N = 45,315 subjects) but would be detectable in AHIJEVYCH and FORD (N = 3,129 subjects).

Two studies reported results for data obtained from the National Health and Nutrition Examination Survey (NHANES). JONES *et al.* (publication 15) (59) reported on TTFC results for ≤ 5 min from NHANES 2001–2010, while CURTIN *et al.* (publication 18) (44) reported on results for TTFC (≤ 5 and ≤ 30 min) from the same data base. The sample size analyzed by JONES *et al.* was smaller than that analyzed by CURTIN *et al.* (2,096 *vs.* 4,759 subjects). This was probably a result of the fact that the subject of the JONES *et al.* publication was biomarkers of tobacco use in US adults, and thus it is likely that a

sub-sample was used. As a consequence the CURTIN *et al.* result was used for both the 5 and 30 min time periods.

Lastly, two publications were based on data from the National Survey on Drug Use and Health (NSDUH). HICKMAN *et al.* (publication 14) (60) reported on NSDUH 2008–2009, whereas CURTIN *et al.* (publication 18) (44) covered the period 2001–2009. The sample sizes reflect this point, 24,157 and 77,183 subjects, respectively. The CURTIN *et al.* results were not adjusted. Although it is possible that the OR presented by HICKMAN *et al.* may have been adjusted, this is not certain given that TTFC was only a minor component of the research presented. Therefore, it was decided to use the CURTIN *et al.* results due to the larger number of subjects.

Having made these selections it was necessary to ensure that these choices did not materially bias the results in the direction of a shorter TTFC for menthol smokers. With respect to the TUS-CPS there are four ORs for FAGAN et al. (36) with TTFC \leq 5 min as a function of cigarettes per day (CPD). These range from 0.94-1.22. The OR obtained by CURTIN *et al.* (44) for TTFC $\leq 5 \text{ min was } 0.93$. Therefore, exclusion of CURTIN et al. did not bias the results favorably for menthol smokers. The same is true with respect to the results of the analysis for TTFC \leq 30 min reported in FAGAN et al. In this case the ORs, once again reported as a function of cpd, ranged from 0.98 to 1.20. The OR reported by LAWRENCE et al. (58) was 0.89, clearly indicating a greater tendency of non-menthol smokers to smoke their first cigarette within 30 minutes after waking, while the OR for CURTIN et al. (44) was 1.12, within the range of ORs reported by FAGAN et al.

With respect to the two overlapping studies for NHANES 2001–2010, CURTIN *et al.* (44), the selected study, reported an OR = 1.08 (95% CI, 0.95–1.24) for TTFC \leq 5 min, whereas JONES *et al.* (59), the excluded study, reported on OR = 1.13 (95% CI, 0.93–1.37). These two results are not significantly different. Lastly, CURTIN *et al.* (44) reported an OR = 1.03 (95% CI, 1.00–1.06) for TTFC \leq 30 min based on NSDUH data, while the OR reported by HICKMAN *et al.* (60) was 1.05 (95% CI, 1.00–1.10). Once again, these two results are not significantly different.

	Comments	[b] [c] [q]		[e] [l]	[6]	[J] [J]	6	[k] [l] [m] [n] [o]	[b] [d]	[1] [s] [t]	
	Number (%) for given time to first cigarette by smoker type [a]	< 10 min: 947 M (29.7%); 3,338 NM (33.1%) ≥10 min: 2,231 M (70.3%), 6,704 NM (66.9%)	≤ 30 min: 385 M (81.7%), 90 NM (69.8%) > 30 min: 86 M (18.3%), 30 NM (30.2%)	≤ 5 min: 239 M (45%), 12 NM (29%) > 5 min: 292 M (55%), 29 NM (71%)	≤ 30 min: 256 M (75%), 791 NM (79%) > 30 min: 86 M (25%), 210 NM (21%)	≤ 5min: 187 M (24.3%), 178 NM (19.9%) > 5min: 581 M (75.6%), 718 NM (80.2%)	≤ 30 min: M (34%), NM (21%) > 30 min: M (66%), NM (79%)	≤ 5 min: M (22.27%) 95% CI, 21.30–23.27 NM (22.17%) 95% CI, 21.57–22.79	d: ≤ 30 min, 1,127 (50.3%) > 30 min, 1,114 (49.7%) nd: < 30 min 67 (9.7%)	 > 30 min, 621 (90.3%) ≤ 30 min: 8,139 M (51.5%), 24,823 NM (54.3%) > 30 min: 7,675 M (48.5%), 20,907 NM (45.7%) 	≤ 30 min: 330 M (73.0%), 60 NM (68.2%) > 30 min: 122 M (27.0%), 28 NM (31.8%)
eneral study design	% Menthol smokers (by race) [a]	24 (C 23; AA 57)	78	92.8	25.5 (C 19; AA 62; other 25)	46.1 (C 32.0; AA 80.7; H 66.4; other 36.7)	54.1 (C 27.8; AA 86.1)	25.80%	d-29.9; nd-25.7	25.8 (nhC 20.6; nhAA 73.2; H 28.0; AI 18.8; AS 35.1; MR 29.1)	83.7
U	% Race distribution [a]		AA 100	EA 48.2; AA 46.9; other 4.9	C 73; AA 14; other 12	C 64.3; AA 22.2; H 8.8; other 4.7	C 54.8; AA 45.1				AA 100
	% Male	49.2	29.3	44.9	94	41.9	49.2	44.3	d-48.9; nd-48.8	52.1	33.9
	Mean age (± SD) or age range	25–64	44.2 ± 10.0	15.6 ± 1.6	56.0 ± 10.3	41.5 ± 13.3	n.a.	≥ 18	d-21.5 ± 1 .9; nd-21.8 ± 1.8	ي 8	46.5 ± 11.3
	Total sample size	13,268	600	572	1,343	1,688	525	45,315	3,129 (d–2241; nd–688)	63,193	540
-	Study design [a]	S-X	S-X	S-X	S-X	RCT	S-X	S-X	s.×	S-X	X-S
Ľ	Year	2002	2003	2006	2008	2009	2009	2010	2010	2010	2011
Publication informatio	Author	НҮLAND <i>et al.</i> (12)	Ок∪ҮЕМІ <i>et al.</i> (31)	Collins and Moolchan (32)	F∪ <i>et al.</i> (33)	GANDHI <i>et al.</i> (34)	MUSCAT <i>et al.</i> (35)	FAGAN <i>et al.</i> (36)	AHUEVYCH and FORD (37)	LAWRENCE <i>et al.</i> (58)	FASERU <i>et al.</i> (38)
	No.	-	2	e	4	2J	9	~	ω	ი	10

Appendix B. Papers with results dealing with time to first cigarette (TTFC)

	Publication information	uc					Ge	eneral study design		
No.	Author	Year	Study design [a]	Total sample size	Mean age (± SD) or age range	% Male	% Race distribution [a]	% Menthol smokers (by race) [a]	Number (%) for given time to first cigarette by smoker type [a]	Comments
7	Rептzец <i>et al.</i> (39)	2011	X-S	244	24.6 ± 5.3	0	C 36.1; AA 33.2; L 30.7	50.4 (C 29.4; AA 86.4; L 44.0)	≤ 5 min: 33 M (26.8%), 20 NM (16.5%) > 5 min: 90 M (73.2%), 101 NM (83.5%)	
12	D'SILVA <i>et al.</i> (40)	2012	S-X	6,257	د 18	30.8	nhC 83.4; nhAA 7.3; H 3.3; other 6.0	18.7 (nhC 14.6; nhAA 64.2; H 19.6; other 28.0)	≤ 5 min: 543 M (46.3%), 2,192 NM (43.1%) > 5 min: 629 M (53.7%), 2,893 NM (56.9%)	
13	Rosenbloom <i>et al.</i> (41)	2012	X-S	928	41.0 ± 10.1	0	C 78.7; AA 21.3	36.1	≤ 5 min: 164 M (49.0%), 213 NM (36.0%) > 5 min: 171 M (51.0%), 380 NM (64.0%)	
4	HICKMAN <i>et al.</i> (60)	2014	S-X	24,157	≥ 18	51.4	nhC 68.2; nhAA 10.8; H 12.5; ASA 2.1; other 6.4	38.1 (nhC 29.0; nhAA 86.4; H 43.4; ASA 40.7; other 41.1)	≤ 30 min: 4,085 M (44.4%), 6,457 NM (43.2%) > 30 min: 5,113 M (55.5%), 8,502 NM (56.8%)	[ʌ] [ŋ]
15	JONES <i>et al.</i> (59)	2013	S-X	4,603	41.7 ± 0.4 (SE)	57.1	C 57.7; AA 24.8; H 17.4 (25.7 C 19.1; AA 69.0; H 12.0)	≤ 5 min: 227 M (35.1%), 470 NM (32.4%) > 5 min: 420 M (64.9%), 979 NM (67.6%)	[v] [x] [v]
16	RoJEWSKI <i>et al.</i> (42)	2014	S-X	166	44.3 ± 10.6	28.3	C 90.3; AA 7.7; other 1.9	36.1 (C 40.0; AA 25.0; other 33.3)	≤ 30 min: 47 M (82.4%), 83 NM (79.8%) > 30 min: 10 M (17.5%), 21 NM (20.2%)	[z] [aa]
17	Frost-Pineda <i>et al.</i> (43)	2014	X-S	3,341	41.9 (21–80)	42.4	C 81.6; AA 18.4	31.2 (C 21.8; AA 73.0)	≤ 5 min: 337 M (32.5%), 661 NM (28.8%) > 5 min: 701 M (67.5%), 1,633 NM (71.1%)	[f] [ab]
18.1	Сиктім <i>et al.</i> (44)	2014	X-X	4,759	≥ 20	55	nhC 56.0; nhAA 23.1; other 20.9	31.6 (nhC 20.1; nhAA 69.8; other 20.3)	≤ 5 min: 492 M (32.7%), 1,007 NM (30.9%) > 5 min: 1,012 M (67.3%), 2,248 NM (69.1%)	[f] [ac]
18.2	: CURTIN <i>et al.</i> (44)	2014	S-X	57,058	≥ 15	47.5	nhC 81.2; nhAA 7.8; other 10.9	25.7 (nhC 20.7; nhAA 73.8; other 28.6)	s 5 min: 2,995 M (20.4%), 9,125 NM (21.5%) > 5 min: 11,693 M (79.6%), 33,263 NM (78.5%)	[f] [ad]
18.3	. CURTIN <i>et al.</i> (44)	2014	X-X	77,183	≥ 20	50.4	nhC 73.8; nhAA 10.0; other 16.2	32.0 (nhC 23.9; nhAA 84.1; other 37.1)	≤ 5 min: 5,383 M (21.8%), 10,457 NM (19.9%) > 5 min: 19,358 M (78.2%), 41,985 NM (80.0%)	[f] [ae]

Appendix B. Continued

7	2	5
ć	1	5
		ŝ
2		2
		-
4		5
\$		-
ĩ	-	5
2	1	:
ç		,
	I	
Ξ.		
2	2	5
7		-
2		1
5		-
	1	2
\$	1	2
ē		2
1	l	7
5	1	Ļ

- Abbreviations: AA = African American; AI = American Indian; AS = Asian American; C = Caucasian; d= daily smokers; EA = European Americans; H = Hispanic; L = Latina; M = smokers of menthol cigarettes; MR = multiple races; nd = non-daily smokers; nhC =non-hispanic Caucasian; nhA = non-hispanic African American; NM = smokers of non-menthol cigarettes; RCT = Randomized Controlled Trial; X-S = Cross-sectional. ø
- 11 matched pairs of communities utilized 10 in the US, 1 in Canada. Each matching pair consisted of a intervention community and a control community.
- Samples from US (89.58%) and Canada (10.42%): For the US sample, race distribution was 84.17% Caucasian (non-Hispanic); 7.39% African American (non-Hispanic); 1.15% Asian; 0.97% American Indian, 5.83% Hispanic; 0.35% other; and 0.14% apparently unknown. ල ව
 - Data were also provided for TTFC at >10–30 min, 31–60 min, and > 60 min.
- All subjects were adolescents.
- Data were also provided for TTFC at 6–30 min, 31–60 min, and > 60 min.
- All subjects were relapsed smokers.
- Time to first cigarette data based on 1,664 total subjects 768 menthol smokers and 896 non-menthol smokers.
- Data were also provided for TTFC at 6–30 min, and > 30 min.
- There appears to be a problem with Table 3 where these results were tabulated. The numbers of menthol smokers were identical to the numbers of non-menthol smokers for both time periods (98 and 26, respectively). As a consequence, only the percentages are given.
 - Data were obtained from the 2003 and 2006/2007 TUS-CPS. This is the same data set that was analyzed by Lawrence et al., publication 9, and and by Curtin et al., publication 18.
 - The total sample was 46,271. The sample listed above has been reduced by 958 current or former smokers who reported smoking neither menthol or non-menthol as their primary product.
 - 22% non-Hispanic Caucasian, 5.1% non-Hispanic African American, 7.5% Hispanic, 1.3% American Indian, 1.7% Asian, 2.1% other.
- Percentage menthol by race is as follows: 21.0% non-Hispanic Caucasian, 74.0% non-Hispanic African American, 29.5% Hispanic, 17.9% American Indian, 33.4% Asian, 28.4% other.
 - Data were also provided for TTFC at 6–10 min, 11–15 min, and > 16 min.
- Data were obtained from the TUS-CPS; however, this paper analyzed data for young smoking adults, aged 18–24 years.
- Daily smokers: 79.9% Caucasian, 6.4% African American, 7.0% Hispanic, 6.7% other; non-daily smokers: 69.4% Caucasian, 8.1% African American, 14.5% Hispanic, 8.0% other.
 - Data were obtained from the 2003 and 2006/2007 TUS-CPS. This is the same data set that was analyzed by FAGAN et al., publication 7, and by CURTIN et al., publication 18.
 - 30.0% non-Hispanic Caucasian, 8.2% non-Hispanic African American, 6.2% Hispanic, 1.5% American Indian, 1.8% Asian, 2.2% multiple races.
- TTFC based on a sample size of 61,549 because of elimination of 1,649 individuals with varying TTFC.
- Data were obtained from the 2008 and 2009 National Survey on Drug Use and Health (NSDUH). Data from this database were analyzed by CURTIN *et al.*, publication 18. This study, however, analyzed a subset of the data where individuals indicated the presence of psychological distress.
- Based on unweighted data.
- Data were obtained from NHANES data, 1999-2010 but for current smokers only. Data from this data base were analyzed by CURTIN et al., publication 18.
- TTFC data was based on NHANES 2001–2010 with a total of 2096 individuals, of which 647 were menthol and 1449 non-menthol smokers.
- Data were also provided for TTFC at 6–30 min, 31–60 min, and > 60 min.
- Race distribution and percent menthol based on a total sample of 155. $\Xi \boxtimes \Xi \boxtimes \Xi$
 - TTFC based on a total sample of 161. aa]
- TTFC based on a sample size of 3,332 (1,039 menthol smokers and 2,293 non-menthol smokers). [ab]
- Data were obtained from NHANES, 2001–2010. Data from this data base were analyzed by JONES et al., publication 15. [ac]
- Data were obtained from the 2003 and 2006/2007 TUS-CPS. This is the same data set that was analyzed by FAGAN et al., publication 7, and by LAWRENCE et al., publication 9. [ad]
 - Data were obtained from the 2001-2009 National Survey on Drug Use and Health (NSDUH). Data from this database were also analyzed by HickMAN et al., publication 14.

APPENDIX C

Explanation of choice of cessation study where more than one study was based on the same data set.

All publications providing data that met the inclusion criterion for the meta-analysis of cessation rates for menthol smokers compared to non-menthol smokers are listed in Appendix D. Three publications provided results drawn from the 2005 National Health Interview Survey Cancer Control Supplement (NHIS-CCS); namely, GUNDERSEN et al. (61) (publication 9), STAHRE et al. (50) (publication 13), and SULSKY et al. (13) (publication 27). The STAHRE et al. analysis was based on 12,004 subjects, whereas GUNDERSEN et al. reported data on a much smaller sample size; namely, 7,815 subjects. The primary reason for the difference in sample size is that GUNDERSEN et al. restricted their analysis to current and former smokers who indicated that they had ever attempted to quit smoking. Not only is the STAHRE et al. sample size larger, but applying the restriction used by GUNDERSEN et al. could bias the results. SULSKY et al. analyzed not only the NHIS-CCS 2005 data but also the NHIS-CCS 2010 data. There is, however, a major issue with the SULSKY et al. results in that the sample size was not specified. The only information given was the frequency data for current smokers and former smokers based on the US population. As a consequence, the STAHRE et al. results were chosen for the meta-analysis.

The second set of multiple results drawn from the same database includes four studies that used data from the 2003 and 2006–2007 Tobacco Use Supplement (TUS), a module that is periodically added to the US Current Population Survey (CPS). These four studies were TRINIDAD et al. (62) (publication 12), FAGAN et al. (36) (publication 14), LEVY et al. (63) (publication 16) and DELNEVO et al. (52) (publication 18). The sample sizes for each of these four studies are 73,691, 45,310, 65,510, and 65,319 subjects, respectively. The FAGAN et al. sample was considerably smaller than the other three samples; therefore, the results from this publication were not selected for meta-analysis. Although it would appear that TRINIDAD et al. have analyzed the largest sample, this sample size represents only ever smokers who specified either menthol or non-menthol as their usual type of cigarette. The total number of ever smokers was 125,369. Not only does this sample size appear to be out of line compared to the other three studies, but the number of ever smokers who had no usual type of cigarette, 41,349, also appears to be out of line. As a consequence, this study was not selected. Both DELNEVO et al. and LEVY et al. have approximately equal sample sizes. However, DELNEVO et al. used five different

sample restrictions. One of these, sample restriction 2, eliminated all current and former smokers who reported using other tobacco products. As a consequence, these results refer exclusively to the cessation of cigarette smoking. The LEVY *et al.* analyses did not make this exclusion. Moreover, the analysis presented only a single estimate; namely for all subjects irrespective of race. Given these considerations, the results of the DELNEVO *et al.* analysis were used in the meta-analysis.

It is important to evaluate if the choices that were made would have materially changed the results obtained. As noted above, STAHRE et al. (50) (publication 13) was chosen to represent the NHIS-CCS data. Results reported by GUNDERSEN et al. (61) (publication 9) and SULSKY et al. (13) (publication 27) were also based on NHIS-CCS data. The ORs for smoking cessation reported by GUNDERSEN et al. were noticeably higher for all subjects (OR = 1.14), Caucasian subjects (OR = 1.17), and African American subjects (OR = 0.78) compared to those reported by STAHRE et al. (see Table 3). On the other hand, the OR reported by GUNDERSEN et al. for Hispanic subjects (OR = 0.61) was somewhat lower. Likewise, SULSKY *et al.* also reported higher ORs for both Caucasian regular smokers (OR = 1.07) and African American regular smokers (OR = 1.12). As a consequence, selection of the STAHRE et al. data clearly did not bias the meta-analysis in favor of menthol cigarette smokers finding it easier to quit. The situation is somewhat more complicated for studies based on the 2003 and 2006-2007 TUS-CPS data in that there were four such studies. The estimates used in the meta-analysis were derived from the DELNEVO et al. (52) (publication 18). LEVY et al. (63) (publication 16) provided an OR only for all subjects (OR = 1.09), and this result was larger than that of DELNEVO et al. (see Table 3). FAGAN et al. (36) (publication 14) provided four estimates based on CPD category, and those for all subjects (1.03, 0.97, 1.05, 0.93) were all somewhat greater than that provided by DELNEVO et al. The results for TRINIDAD et al. (62) (publication 12) were extremely different from the other three studies based on 2003 and 2006–2007 TUS data. The ORs were 0.28 for Caucasian smokers, 0.23 for African American smokers, and 0.48 for Hispanic smokers. Therefore, as noted above, not only are the number of subjects and the number of smokers designated as having "no usual type" of cigarette widely different from the results presented by the other three study groups that analyzed the 2003 and 2006–2007 TUS-CPS data, but the results are widely different as well. There is no obvious explanation for these differences, but given its inconsistencies with three other studies, it would appear that the decision not to utilize this study to represent the TUS-CPS data is justified.

	Publication informat	ion					-	General study char	acteristics			
No.	Author	Year	Study design	Total sample size	Mean age (+SD) or age range	% Male	% Race distribution	% Menthol smokers (by race)	Study duration	% Smoking cessation	Type of validation	Type of support
-	HYLAND <i>et al.</i> (12)	2002	a [a]	13,268	25-64	49.2	[q]	24 (C 23; AA 57)	5y	24	None	୍ର
2	MUSCAT <i>et al.</i> (45)	2002	X-S [d]	19,545	46–64	70.0	C 90.2; AA 9.8	15.4 (C 13.3; AA 34.4)	19y	49.9	None	None
ი	OkuYEMI <i>et al.</i> (31)	2003	RCT	600 [e]	44.2 ± 10.0	30.0	AA 100	78.5	бm	21.0 M, 27.0 NM (based on a total of 518 subjects remaining) [f]	Exhaled CO t	Treatment group received upropion; all subjects received psychological counseling
4	PLETCHER <i>et al.</i> (46)	2006	٩	1,535 [g]	25.0±3.7	47.4	C 42.8; AA 57.2	63.3 (C 19.4; AA 80.5)	15y \$	31 M, 46 NM sustained abstinence	None	None
5	Foulds <i>et al.</i> (24)	2006	RCT	1,021	43 (15–80)	40.5	C 65.6; AA 21.4; H 7.8; other 5.1	40.9	26w [h]	31.3 (24.9 M; 35.8 NM)	Exhaled CO	E
9	Ок∪ҮЕМІ <i>et al.</i> (47)	2007	RCT []	753 [k]	43.4 ± 10.3	67.1	AA 100	81.7	26w []	11.2 M and 18.8 NM	Salivary cotinine and exhaled CO	0
2	Микка <i>y et al.</i> (48)	2007	٩	5,883 [m]	48.5 ± 6.9	62.9	AA 3.5	20.7	5y	15.4 M; 16.6 NM [n]	Not specified	[0]
ω	Fu <i>et al.</i> (33)	2008	X-S [d]	1,343	56.0 ± 10.3	94	C 73; AA 14; other 12	25.5 (C 18.8; AA 63.7; other 25.5)	About 6m		Self report	[6]
6	GUNDERSEN <i>et al.</i> (61)	2009	S-X [F]	7,815	49.1 ± 0.23 (SE)	50.2	C 82.7; AA 8.9; H 8.4	26.5	Not applicable	56.9 M; 61.5 NM	Self report	Not specified
10	GANDHI <i>et al.</i> (34)	2009	RCT [s]	1,688	41.5 ± 13.3	41.9	C 64.3; AA 22.2; H 8.8; other 4.7	46.1 (C 32.0; AA 80.7; H 66.4; other 36.7)	6m [t]	22 M, 32 NM [u]	Exhaled CO	Σ
7	CROPSEY <i>et al.</i> (49)	2009	RCT	233	33.9 ± 8.9	0	C 46.8; AA 53.2	73.1 (C 48.5; AA 94.7)	12m	13.7 M; 8 NM [w]	Exhaled CO	Psychological support and nicotine patch [x]
12	Trinidad <i>et al.</i> (62)	2010	S-X [y]	73,691 [z]	20–65	[aa]	[aa]	25.8	Not applicable	5.1 M, 5.5 NM	Self report	Not specified
13	STAHRE <i>et al.</i> (50)	2010	X-S [ab]	12,004 [ac]	× 18	51	C 84.0; AA 11.9; AI 0.8; AS 1.8 [ad]	l 26.8 (C 20.8; AA 71.0; Al 21.5; AS 31.5; H 23.3)	Not applicable	49.6 (47.1 M; 50.4 NM)	Self report	About 32% of current smokers and 25% of past smokers reported using quit aids

Appendix D. Publications with results dealing with cessation.

1	Publication informa	tion					-	General study char	acteristics			
No.	Author	Year	Study design	Total sample size	Mean age (+SD) or age range	% Male	% Race distribution	% Menthol smokers (by race)	Study duration	% Smoking cessation	Type of validation	Type of support
4	Fagan <i>et al.</i> (36)	2010	X-S [ae]	45,315 [af]	v 18	44.3	nhC 82.2; nhAA 7.5; H 5.1; AI 1.3; AS 1.7; other 2.1	25.8 I (nhC 21.0; nhAA 74.0; H 29.5; Al 17.9; AS 33.4; other 28.4)	Not applicable	10.6 (10.8 M; 10.5 NM)	Self report	Not specified
15	Rose and BEHM (51)	2010	RCT [ag]	809	n.a.	n.a.	n.a.	33.2	6m [ah]	23.2 (19.7 M, 5.0 NM)	Not specified	At least NRT
16	LEVY <i>et al.</i> (63)	2011	X-S [ai]	65,510	× 18	n.a.	n.a.	25.8	5y	20.8 (18.6 M; 21.2 NM)	Self report	Not specified
17	REITZEL <i>et al.</i> (39)	2011	RCT [aj]	244	24.6 ± 5.3	0	C 36.1; AA 33.2; H 30.7	50.4 (C 22.7; AA 86.4; H 44.0)	40–47w (26w post- partum) [ak]	[a]]	Exhaled CO or salivary cotinine	Psychological counselling for the intervention groups (N = 136)
18	DELNEVO <i>et al.</i> (52)	2011	X-S [am]	65,319 [an]	× 18	n.a.	C 84.7; AA 8.3; H 6.9	27.9 cs; 24.5 fs (C 21.0; AA 71.8; H 28.1)	5y	23.4	Self report	Not specified
191	ВLOT <i>et al.</i> (53)	2011	r [ao]	50,864	40->60	48.9	C 32.5; AA 67.5	64.9 (C 26.4; AA 83.5)	6.5y	35.3 (32.3 M; 40.6 NM)	Self report	Not specified
192	ВLOT <i>et al.</i> (53)	2011	p [ao]	12,373	n.a.	n.a.	n.a.	36.3	4.3y	21	Self report	Not specified
20	STEINBERG <i>et al.</i> (25)	2011	RCT	723	45 (16–78)	47	C 59; AA 23; H 14; other 5	48	өт	23 (18 M; 26 NM)	Exhaled CO	A large variety of pharmaco- logical treatments, NRT, and psychological support
5	D'SILVA <i>et al.</i> (40)	2012	RCT [ap]	715	[aq]	[aq]	[aq]	16.8	2m	14.4 (17.3 M; 13.8 NM)	Self report	Both NRT (4 weeks) and psychological support were made available.
52	FASERU <i>et al.</i> (26)	2013	RCT	540 [k]	46.5 ± 11.3	33.9	AA 100	83.7 [ar]	26w [as]	14.1 M; 20.4 NM	Salivary cotinine	Treatment group: 7 weeks bupropion SR; control group, placebo; both groups received psychological support
23	REITZEL <i>et al.</i> (54)	2013	RCT	183	46.4 ± 9.71	42.62	nhC 51.9; nhAA 48.1	45.4 (nhC 18.9; nhAA 73.9)	3w [at]	15.9 (12.1M; 19.0 NM) [au]	Exhaled CO	NRT (4 weeks) and access to counseling sessions

Continued
ы.
Appendix

- 10
ā
Ē
=
÷
_
- T
C
-
Δ
~
≏
8
ē
۳
0
Q

	Type of support	Intervention group received naltrexone; all subjects received nicotine patches and counseling	Not specified	[qq]	Not specified	Not specified
	Type of validation	Exhaled CO	Lack of cigarette purchase for at least one year	Exhaled CO	Self report	Self report
	% Smoking cessation	13 M; 30 NM	24.5 (20.3 M; 26.2 NM)	33.3 (29.9 M, 35.9 NM)	50.8 (47.1 M; 52.2 NM) [be]	51.2 (45.2 M; 53.4 NM) [be]
acteristics	Study duration	26w [aw]	≥ 1 ح	26w [ba]	Not specified	[6q]
General study char	% Menthol smokers (by race)	36.7 (C 40.0; AA 25.0; other 33.3)	28.7 (AA 54.5; nAA 25.2)	43.4 (C 35.3; AA 100)	27.1 (nhC 21.4; nhAA 74.1; other 28.1) [be]	27.5 (nhC 22.2; nhAA 73.5; other 28.3) [be]
	% Race distribution	C 90.3; AA 7.7; other 1.9 [av]	AA 11.9; nAA 88.1	C 87.1; AA 12.9	nhC 79.3; nhAA 9.4; other 11.2 [be]	nhC 78.8; nhAA 8.9; other 12.3 [be]
	% Male	28.9	26.7 [ay]	41.1	55.6	54.4
	Mean age (+SD) or age range	44.3 ± 10.6	60.01 ± 10.43	44.7 ± 11.1	> 20	> 20
	Total sample size	166	1,582 households	1,439	[pq]	[pq]
	Study design	RCT	p [ax]	RCT [az]	X-S [bc]	X-S [bd]
tion	Year	2014	2014	2014	2014	2014
Publication information	Author	RoJEWSKI <i>et al.</i> (42)	LEWIS <i>et al.</i> (55)	SMITH <i>et al.</i> (55)	SULSKY <i>et al.</i> (13)	SuLskY <i>et al.</i> (13)
-	No.	24	25	26	27.1	27.2

Abbreviations:

AA = African American; AI = American Indian; AS = Asian; C = Caucasian; cs = current smokers; fs = former smokers; H = Hispanic; M = Menthol; m = months; n.a. = not available; nAA = non African American; nhAA = non-hispanic African American; nhC = non-hispanic Caucasian; NM = Non Menthol; p = prospective (longitudinal); r = retrospective cohort; RCT = randomized controlled trial; w = weeks; X-S = cross-sectional; y = years.

- Randomized long-term community intervention trial consisting of 11 matched pairs of communities 10 in the US, 1 in Canada. Each matching pair consisted of an intervention community and a control community. മ
- For the US sample, race distribution was 84.17% non-Hispanic Caucasian, 7.39% non-Hispanic African American, 1.15% Asian, 0.97% American Indian, 5.83% Hispanic, 0.35% other, and 0.14% apparently unknown. The distribution of US and Canadian subjects was 89.58 and 10.42%. g
- coordination was provided by the NCI (COMMIT Research Group, 1996). All data in the HYLAND et al. study, and all results summarized herein combine both intervention and control Intervention in each of the 11 intervention communities was conducted locally within the community. Community coordination was provided by a trial coordinating center, and overall communities. ы
- Subjects were current and former smokers taken from a case-control study of the effect of smoking on lung, head and neck, kidney, and pancreatic cancers. [] [] [] [] []
 - Intention-to-treat.
- See AHLUWALIA et al. (64) for details.
- Number of smokers with known menthol or non-menthol preference at baseline.
- Four-week cessation data were also provided.
- Multiple types of support were made available to all participants including psychological support, nicotine replacement therapy (NRT), and treatment with bupropion.

σ
ā
Ē
Ē
- E
5
5
~~
U
0
_ <u>×</u>
5
~
5
ŏ
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
7
~

- Subjects were randomized into four equal arms: 1) nicotine gum + motivational interviewing (MI) (N = 189), 2) nicotine gum + health education (HE) N = 189), 3) placebo gum + MI (N = 189) and 4) placebo gum + HE (N = 188). See AHLUWALIA et al. (65) for details. All groups have been combined. 5
  - All smokers were "light" smokers smokers of < 10 cig/day
- Eight-week cessation data were also provided.
- Usual care (UC) and smoker intervention (SI) groups combined. Y = E E O
- Based on 5,734 participants; the percentage of menthol smokers remained constant.
- The SI group was originally composed of 2 arms of about equal size. One arm received smoking intervention (psychological support) and a bronchodilator inhaler; the second arm received smoking intervention and a placebo inhaler. The UC arm received no intervention.
- This intervention study was conducted in five US Veterans Administration medical centers. Details of the study are provided in PARTIN et al. (66). All subjects were relapsed smokers who had previously quit. ₫
- All participants received NRT or bupropion; the intervention group received psychological counseling.
- included in the data set analyzed by SULSKY et al., publication 27. All subjects werre current or former cigarette smokers; smokers of other tobacco products were excluded; smokers who did Data were obtained from the 2005 National Health Interview Survey-Cancer Control Supplement (NHIS-CCS). This is the same data set analyzed by STAHRE et al., publication 13, and is not indicate that they had attempted to quit were also excluded. ΞΞ
- Analysis of 1,688 consecutive patients who attended a smoking cessation clinic between 2001 and 2005.
- Four-week cessation data were also provided.
- Calculations of ORs were based on 1,609 subjects rather than 1,688 subjects.
- Both psychological support and/or FDA-approved tobacco-dependence treatment were made available.
- Percentages obtained graphically; graphical cessation data were also provided for each week up to 9 weeks and at 3 and 6 months. ĩ ± ⊐ ∑ ∑ ≍
- In the orginal study (CROPSEY et al. (67)) the initial treatment group consisted of a 71 subject treatment group and a 179 wait list control group. After 6 months, the wait list control group also underwent treatment. Therefore, at 12 months, the entire group of subjects had undergone treatment. The difference between the 233 subjects used in this study and 250 used in the original study stems from the fact that 17 subjects were neither African American nor Caucasian
- Data were obtained from the 2003 and 2006-2007 TUS-CPS. This is the same data set that was analyzed by FAGAN et al., publication 14, LEVY et al., publication 16, and DELNEVO et al., publication 18.  $\leq$
- The sample size specified, 73,691, represents those subjects who were current smokers plus those who had quit for a period of less than 6 months plus those who had quit for a period of more than 6 months plus those who had quit for a period of more than 6 months (12,583) were included as current smokers or were excluded. Ы
- The total sample consisted of 49.1% males and was subdivided into non-Hispanic Whites, African Americans, Hispanics, Asian American, and Native Americans. It was not possible to calculate sex distribution or percentages of each race for the relevant sample. [aa]
- Data were obtained from the 2005 NHIS-CCS. This is the same data set analyzed by GUNDERSEN et al., publication 9, and is included in the data set analyzed by SULSKY et al., publication 27. [ab]
  - This number includes current and former smokers who specified smoking either menthol or non-menthol. [ac]
- The total is only 98.5% indicating a category of other nationalities that was not mentioned. In addition, 12.4% were identified as Hispanics, which clearly overlaps with Caucasian and/or African American subjects.
  - Data were obtained from the 2003 and 2006-2007 TUS-CPS. This is the same data set that was analyzed by TRINIDAD et al., publication 12, LEVY et al., publication 16, and DELNEVO et al., publication 18. [ae]
- The total sample was 46,271. The sample listed above has been reduced by 958 current or former smokers who reported smoking neither menthol or non-menthol as their primary product. [af] [ag]
  - A retropsective analysis of two RCT conducted at the Duke Medical Center; no details provided.
- Four-week cessation data were also provided

σ
Ð
Ξ.
Ē
=
Ξ
ō
õ
0
Δ
J
<u>م</u> .
σ
Ē
Ð
ā
Q
₫
-

- Data were obtained from the 2003 and 2006-2007 TUS-CPS. This is the same data set that was analyzed by TRINIDAD et al., publication 12, FAGAN et al., publication 14, and DELNEVO et al., publication 18. [ai]
- Subjects were women who quit smoking during pregnancy or no more than 2 months before becoming pregnant. The measured end point was relapse [a] [a]
  - Eight-week post-partum data were also provided.
- Continuous abstinance rates by race and cigarette type were as follows: Caucasians 5% at 26 weeks for menthol, 23% at 26 weeks for non-menthol; African American 17% at 26 weeks for menthol and 37% at 26 weeks for non-menthol; Hispanics - 27% at 26 weeks for menthol and 17% at 26 weeks for non-menthol. Data were obtained graphically.
  - Data were obtained from the 2003 and 2006-2007 TUS-CPS. This is the same data set that was analyzed by TRINIDAD et al., publication 12, FAGAN et al., publication number 14, and LEVY et al., publication number 16. [am]
- Five different population definitions were used all leading to different sample sizes. This analysis utilized model 2, which consists of former smokers who quit within the past 5 years and current smokers both of whom do not or did not use other tobacco products. [an]
- Southern Community Cohort Study. [ao]
- Two different types of surveys were conducted. The first evaluated the demographic, smoking, and clinical characteristics of menthol and non-menthol smokers who called a Minnesota quitline (N = 6,257). No quit information was obtained. The second evaluated quit rates in a smaller survey (N = 715), but no demographic information was presented.
  - For reference, demographic information from the first survey is as follows: age > 18, 30.5% male; 63.9% non-Hispanic Caucasian, 25.0% African American, 3.5% Hispanic, 7.6% other
  - Taken from Cox et al. (68). [aq] [ar] [as] [au] [av] [aw]
- Three-week and 7-week cessation data were also provided; menthol was not a factor in the regression model at 26 weeks.
- One and 2-week cessation data were also provided
- Data were also provided for 7-day point prevalence abstinence, which can change from week to week.
- Based on 155 subjects.
- Fourteen-week cessation data were also provided.
- The design of the study was quite unusual. Participants in the Nielsen Homescan Panel were followed between 2004 to 2009. Purchases of cigarettes were monitored. When a household that had been purchaseing cigarettes showed no purchase for a period of one year, cessation was assumed. [ax]
  - Based on the 566 households with either single female or single male occupancies.
- Based on a clinical study; see PIPER *et al.* (69).
- Four-week and 8-week cessation data were also provided.
- Six treatment conditions were evaluated: 1) nicotine lozenge, 2) nicotine patch, 3)bupropion SR, 4) nicotine patch + nicotine lozenge, 5) bupropion SR + nicotine lozenge, and 6) placebo.
- Data were obtained for regular smokers from the 2005 and 2010 NHIS-CCS. The 2005 NHIS-CCS data set was analyzed by GUNDERSEN et al., publication 9, and STAHRE et al., publication 13. Total sample size not provided - only weighted frequency based on the US population. [ay] [ba] [bb] [bd] [bd] [bd]
  - - Data were obtained for regular smokers from the 2010-2011 TUS-CPS. Based on weighted frequencies for regular and former smokers.
- Former smokers were restricted to short-term former smokers; i.e., those who had quit for 1–3 years.

# APPENDIX E

Funnel plots for TTFC point estimates < 5 min (N = 13)and cessation point estimates not stratified by race (N = 30).





Figure E1. Funnel plot of included point estimates for TTFC < 5 min (N = 13).

There are quite a few studies missing to the left of the point estimate of 1.12 (dashed vertical line), the pooled random-effects meta-analytic result for these estimates. This indicates that the estimate being > 1 is at least partially due to publication bias in terms of preference to publish studies with OR > 1. Funnel plot created using R (metafor package).

Figure E2. Funnel plot of included point estimates for all included cessation studies not stratified by race (N = 30).

There are quite a few studies missing to the right of the point estimate of 0.87 (dashed vertical line), the pooled random-effects meta-analytic result for these estimates. This indicates that the estimate being < 1 is very likely at least partially due to publication bias in terms of preference to publish studies with OR < 1. This appears to be especially true for smaller studies (i.e., larger standard errors). Funnel plot created using R (metafor package).