Appendix A6.2.3.1: Draft Manuscript: Menthol Cigarettes, Time to First Cigarette, and Smoking Cessation

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Abstract

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 displayed a small but statistically significant shorter TTFC≤5 min (random-effects OR = 1.12; 95%CI, 1.04-1.21), while 17 independent estimates provided a non-significant difference for TTFC≤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.

Keywords

Smoking cessation; time to first cigarette; menthol; socioeconomic status

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Introduction

The considerable negative impact of cigarette smoking on individual and public health (US Department of Health and Human Services, 2010) and the benefits of smoking cessation (Fagerström, 2002) 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 considerable attention in many parts of the world including the US is the mentholated cigarette. In 2013 the US Food and Drug Administration (FDA) issued an independent analysis of the published literature on nine different topics related to smoking and health focusing on menthol and non-menthol cigarettes (FDA, 2013). Two of these are of particular interest; namely, dependence and ease of cessation, for both of which the FDA reported a difference between menthol and non-menthol smokers. The authors of the FDA report concluded that the best measure of dependence is time to first cigarette (TTFC), and they also concluded that "menthol smokers are more likely to smoke their first cigarette within 5 minutes of waking", suggesting that menthol smokers are more dependent than are non-menthol smokers. Consistent with the TTFC finding, the FDA report goes on to conclude that "the weight of evidence supports the conclusion that menthol in cigarettes is likely associated with reduced success in smoking cessation, especially among African American menthol smokers."

FDA's findings were based on a "weight of scientific evidence" analysis of the available literature. This type of approach tends to provide equal weight to each study, even though it is well known that large studies are likely to better reflect the presence or absence of an association than are small studies (Turner et al., 2013). This publication reports the results of

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a meta-analysis, a quantitative approach of all available published data addressing the two questions: (1) are menthol smokers more likely to smoke their first cigarette of the day sooner than non-menthol smokers, and (2) is there an association between menthol smoking and cessation rates? A critical evaluation of the application of TTFC as an indicator of cessation is also included.

Methods

Identification of Relevant Studies

For TTFC the initial basis for the literature selection was all of the references cited in the FDA report (FDA, 2013). 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 (Foulds et al., 2010; Hoffman and Miceli, 2011), and a search was performed in PubMed for “similar articles” to check for completeness.

All papers published up 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.

Selection of Estimates

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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 Supplementary Text 1 and 2). 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 the exception noted in the next point.

2. The one exception to point number 1 is that cessation estimates for which an adjustment for TTFC or a dependence index that includes TTFC, such as the Heaviness of Smoking Index (HSI) (Heatherton et al., 1989) or the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991), were not included in any of the meta-analyses. These estimates were excluded to avoid over-adjustment (Weitkunat and Wildner, 2002; Schisterman et al., 2009). This point was also made in the FDA report (FDA, 2013, p. 124).

3. For clinical studies, all estimates are based on intention to treat 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

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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 (1999). This methodology uses weighting by inverse standard error and provides both fixed-effect and random-effects pooled results. Given that ORs are not normally distributed, the meta-analyses were conducted on the ln(ORs). Standard errors of ln(OR) were calculated 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 (2011) 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 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 percent 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)

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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 criteria. These papers are listed in *Appendix A*, 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. (2002) for which about 10% of the subjects were Canadian. The 30 non-overlapping estimates taken from these 18 publications that were used for the meta-analyses are listed in *Table 1*. Explanation of the choice of estimates to be included is provided in Supplementary Text 1, 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.

[Insert *Table 1* around here]

Overall, 5 meta-analyses were performed on the appropriate data from the selected 20 TTFC studies. 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, (>1000 subjects, N = 12) or small studies (<1000 subjects, N = 8). The results of these meta-analyses are reported in *Table 2*.

[Insert *Table 2* around here]

For the overall meta-analysis both fixed-effect and random-effects 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 $\leq$5 min alone, the estimates also indicate that menthol cigarette smokers were more likely to smoke their

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first cigarette within 5 minutes of waking as compared to non-menthol 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 minutes of waking, neither the fixed-effect nor the random-effects pooled estimate was statistically significant. The difference between the two fixed-effect estimates (≤5 min and ≤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 (≤5 or ≤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 baseline data from subjects who participated in clinical studies. Setting N=1000 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=1343-77183). 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 TTFC data stratified for both menthol and race.

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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 C1*, *Appendix C*). 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 are consistent with the conclusion reached in the FDA report that menthol cigarette smokers have a tendency to smoke their first cigarette in the morning earlier than do non-menthol smokers. However, the increase in 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. The FDA report suggested that a decrease in TTFC associated with menthol smokers would indicate a concomitant increase in difficulty in smoking cessation for menthol smokers, and they followed this suggestion up by performing an analysis of studies relevant to this question. This analysis will follow the same course.

Smoking Cessation

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, two of which presented data on two different studies. These

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papers are listed in *Appendix B*, 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. (2002). Of the 29 studies listed in *Appendix B*, 13 were randomized controlled trials (RCT), 10 were cross-sectional, 5 were prospective studies, and 1 was a retrospective cohort study. There were three studies that analyzed data from the National Health Interview Survey Cancer Control Supplement (NHIS-CCS), and four 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 Supplementary Text 2.

[Insert *Table 3* around here]

Table 3 contains the 43 estimates derived from non-overlapping 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) 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.

[Insert *Table 4* around here]

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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 non-menthol 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 quit 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=1343-65,316), 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 clinical 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

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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 clinical 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 clinical 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 clinical studies also clearly support a greater difficulty for menthol smokers to quit compared to non-menthol 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 by cigarette type.

We also investigated possible publication bias for cessation results, and the relevant funnel plot is shown in *Figure C2*, *Appendix C*. 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.

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Effect of Residual Confounding

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. non-menthol), 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) 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 of an unrealistic magnitude.

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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 (FDA, 2013) and on a higher prevalence of smoking in this sociocultural subpopulation, although this difference is not large (Cokkinides et al., 2009). However, even after conditioning the analyses on race (by stratification), cessation rates remain lower in African American menthol cigarette smokers compared to African American non-menthol 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 (Reid et al., 2010) as well as the fact that African Americans are more likely to be socially, economically, and educationally disadvantaged than are Caucasians (Dimou et al., 2009). Such differences may also play a role with respect to smoking cessation of African American menthol cigarette smokers.

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

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subjects, clinical 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 clinical ORs were no longer statistically significant; however, this result was based on only three estimates. Although not shown in *Table 5*, I^2 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.

[Insert *Table 5* around here]

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 meta-analyses 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;

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namely, education, employment and income. With respect to education, 6 studies indicated that menthol cigarette smokers had less education than non-menthol 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. These results, although not unidirectional, show that menthol cigarette smokers are more likely to have lower SES "scores" than non-menthol cigarette smokers.

[Insert *Table 6* around here]

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 minutes 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.

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355 **Discussion**

356 The major strengths of this analysis are: 1) a comprehensive literature search was conducted
357 that appears to have identified all relevant published studies, and 2) a quantitative analysis
358 was undertaken as opposed to the qualitative analysis reported in the FDA report.

359 The meta-analyses provide some indication that smokers of menthol cigarettes have a small
360 tendency to smoke their first cigarette of the morning sooner after waking than do non-
361 menthol cigarette smokers. This difference, however, does not appear to translate into a
362 difference between menthol and non-menthol cigarette smokers with respect to smoking
363 cessation. As a consequence, it is of interest to examine more closely the claim that TTFC is
364 a valid marker of ease of smoking cessation.

365 The FDA report (2013) suggests that TTFC is the best measure of nicotine dependence,
366 primarily citing a study by Baker et al. (2007). Based on five studies conducted in the US,
367 Baker et al. indicated that the specific question regarding TTFC in the FTND (question 1)
368 was the best predictor of smoking cessation success at both 1 week and 6 months. In
369 addition they reported that smokers whose TTFC was <5 min were more likely to experience
370 difficulty in quitting than those whose TTFC was between 5 and 30 min. It should be noted
371 that none of these studies compared cessation results separately for menthol and non-
372 menthol cigarette smokers.

373 There are other studies that have examined the relationship between TTFC and smoking
374 cessation. Haddock et al. (1999) reported that the TTFC question in the FTND was strongly
375 related to 1 year of smoking cessation. Toll et al. (2007) suggested that TTFC was strongly
376 related to cigarette craving, and that craving, in turn, was a strong predictor of the tendency

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of smokers to relapse following cessation. Sweitzer et al. (2013) 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, 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. (2011) 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 (2010) reported that although the HSI was a significant predictor of success of smoking cessation at 8 days, at 31 days this index could explain only 1-3% of the variance in smoking cessation. A recent paper similarly suggests a lack of correlation between TTFC and smoking cessation for longer cessation periods (Rohsenow et al., 2013). 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 the association 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 go some way to explaining the

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inconsistency in the analyses on cessation (see *Table 4*). For example, the differences in findings between the large longitudinal or cross-sectional studies and smaller clinical studies may be explained in part by the difference in smoking cessation periods, with clinical 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 clinical 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.

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The result of the investigation of the possible impact of socioeconomic effects with respect to smoking cessation merits further discussion. Three clinical studies provide further support for the importance of adjustment for SES factors. Foulds et al. (2006) 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. (2011) 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. (2013) reported that 14.1% of smokers earning ≥$1800/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

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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.

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 (2013) took the position that smoking restrictions have led to this marker being less reliable as a measure of dependence, although Baker et al. (2007) reported mixed results for the association of CPD with smoking cessation. Given that only three estimates in the data set

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466 corrected for CPD, and that there is some question as to the importance of CPD as a marker
467 of dependence, it was decided to retain these three estimates. With respect to duration of
468 smoking, Sweitzer et al. (2013) examined the association between years of smoking and
469 time to first relapse and reported an OR of 1.07 (95%CI, 1.00-1.14). Given the weakness of
470 this association it was felt appropriate to retain the estimates that adjusted for this covariate.
471 There is little information in the literature regarding "confidence in quitting smoking" and
472 successful quitting. Two studies have been published reporting that individuals who have a
473 high level of confidence with respect to quitting smoking are more likely to be successful
474 (Marino et al., 2010; Khan et al., 2012). On the other hand, confidence in quitting was
475 closely related to "self-efficacy" (Etter et al., 2000), which has been extensively investigated.
476 In a meta-analysis by Gwaltney et al. (2009), all published results through 2006, consisting of
477 189 analyses drawn from 54 publications, were pooled and it was concluded that "the
478 relationship between SE [self-efficacy] and subsequent smoking was reliable and statistically
479 significant, but small, accounting for only 2% of the variance in outcome…" Furthermore, the
480 outcome was substantially lower among studies examining a pre-quit self-efficacy measure,
481 which was the case for the two estimates included in this meta-analysis. As a consequence,
482 these two estimates were retained.

483 A further weakness of this analysis was that it relied solely on published data. The FDA
484 report (FDA, 2013) cites several secondary data analyses with respect to TTFC that the
485 authors of this report could not access. With respect to cessation, however, the only
486 unpublished analysis discussed was an independent analysis of the 2006-2007 CPS-TUS
487 data, which was covered by other studies included in this analysis. The Delnevo et al. (2011)
488 analysis used in this report provided an OR for Caucasian smokers that was somewhat

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higher than the one provided in the FDA analysis, an OR for African American smokers that was somewhat lower, and an OR for Hispanic smokers that was essentially identical. It should also be noted that the Delnevo et al. analysis also included data taken from the 2003 CPS-TUS.

Conclusions

In conclusion, meta-analysis of the available data on TTFC and menthol cigarette smokers does not completely support the FDA position that menthol cigarette smokers have shorter TTFC than non-menthol cigarette smokers. 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 meta-anaylses 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 likely, 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. As noted in the introduction, any change that can be made with respect to current tobacco products that will increase the ability of smokers to quit smoking must be

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considered as positive. The evidence presented herein strongly suggests, however, that eliminating menthol cigarettes would not achieve that goal.

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.

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Table 1. Results (US) for Time to First Cigarette (TTFC).

Est. No.	Pub. No.	First Author	Year	Sample Size	%Menth. Smokers	TTFC range (mins)	Number of smokers in TTFC range (%)		Covariates Adjusted for [a]	OR and 95%CI
							Menthol	Non Menthol		
1	1	Hyland	2002	13,268 [b]	24.0	<10	947 (29.7%)	3338 (33.1%)	s, a, r, edu, cpd, other [c]	0.90, 0.81-0.99
2	1	Hyland	2002	13,268 [b]	24.0	≤30	1699 (56.0%)	6520 (63.9%)	None	0.72, 0.66-0.78 [d]
3	2	Okuyemi	2003	600	78.5	≤30	385 (81.7%)	90 (69.8%)	None	1.94, 1.25-3.02 [d]
4	3	Collins	2006	572	92.8	≤5	239 (45%)	12 (29%)	None	1.98, 0.99-3.96 [d]
5	3	Collins	2006	572	92.8	≤30	398 (75%)	27 (66%)	None	1.55, 0.79-3.05 [d]
6	4	Fu	2008	1343	25.5	≤30	256 (75%)	791 (79%)	None	0.79, 0.59-1.05 [d]
7	5	Gandhi	2009	1664	46,1	≤5	187 (24.3%)	178 (19.9%)	None	1.30, 1.03-1.64 [d]
8	5	Gandhi	2009	1664	46.1	≤30	622 (81.0%)	744 (83.0%)	None	0.87, 0.68-1.12 [d]
9	6	Muscat	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	2010	3541	33.0	≤5			a, r, edu, inc, occ, aoo, dur, ss-12	0.94, 0.60-1.47
11	7	Fagan, 6-10 cpd	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

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12	7	Fagan, 11-19 cpd	2010	6405	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	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	2010	3541	33.0	≤30	a, r, edu, inc, occ, aoo, dur, ss-12	1.20, 0.96-1.50
15	7	Fagan, 6-10 cpd	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	2010	6405	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	2010	23,496	22.0	≤30	a, r, edu, mar, inc, occ, reg, met, yr, aoo, dur, ss-12, itq(30)	1.05, 0.95-1.16
18	8	Ahijevych, daily smokers	2010	2241	29.9	≤30	s, r, edu, occ, hsr [e]	1.16, 0.98-1.38 [f]
19	8	Ahijevych, non-daily smokers	2010	688	25.7	≤30	s, r [e]	2.03, 1.09-3.78 [f]

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20	10	Faseru	2011	540	83.7	≤30	330 (73.0%)	60 (68.2%)	None	1.26, 0.77-2.07 [d]
21	11	Reitzel	2011	244	50.5	≤5	90 (73.2%)	101 (83.5%)	None	0.54, 0.29-1.01 [d]
22	12	D'Silva	2012	6257	18.7	≤5	543 (46.3%)	2192 (43.1%)	None	1.14, 1.00-1.29 [d]
23	13	Rosenbloom	2012	928	36.1	≤5	164 (49.0%)	213 (36.0%)	None	1.71, 1.30-2.25 [d]
24	16	Rojewski	2014	166	36.7	≤30	47 (82.4%)	83 (79.8%)	None	1.19, 0.52-2.74 [d]
25	17	Frost-Pineda	2014	3341	31.2	≤5	337 (33.8%)	661 (30.1%)	None	1.19, 1.01-1.39 [d]
26	17	Frost-Pineda	2014	3341	31.2	≤30	782 (74.9%)	1636 (71.2%)	s, a, r, edu, tar	1.17, 0.96-1.42
27	18	Curtin [g]	2014	77,183	32.0	≤5	5383 (21.8%)	10457 (19.9%)	other [h]	1.12, 1.08-1.16 [d]
28	18	Curtin [g]	2014	77,184	32.0	≤30	13231 (53.5%)	27643 (52.7%)	other [h]	1.03, 1.00-1.06 [d]
29	18	Curtin [i]	2014	4759	31.6	≤5	492 (32.7%)	1007 (30.9%)	other [h]	1.08, 0.95-1.24 [d]
30	18	Curtin [i]	2014	4759	31.6	≤30	910 (60.5%)	1970 (60.5%)	other [h]	1.00, 0.88-1.13 [d]

[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; ss-12 - smoking status 12 months ago; tar - tar yield; yr - survey year

[b] Includes 1382 Canadian smokers

[c] 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

[d] Calculated from data provided using 2x2 table

[e] Covariates that were significant in the multivariate model

[f] OR and 96%CI calculated from the binary logit model coefficient and standard error

[g] Data were obtained from the 2001-2009 National Survey on Drug Use and Health (NSDUH)

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[h] Demographic variables, not specified

[i] Data were obtained from NHANES, 2001-2010

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Table 2. Meta-analytic Results for TTFC.

Description of Group (N)	Fixed-Effect OR (95%CI)	Random-Effects OR (95%CI)	I^2
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

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

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Table 3. Results (US) for Cessation.

Esti-mate No.	Publ. No.	First Author	Year	Race stratification [a]	Group Size	Menthol	Non-ment.	Cessation rate (no.)		Relevant time period	Method used for calculation [b]	Covariates adjusted for [c]	OR, 95%CI	Comments
								Menthol	Non-menthol					
1	2	Muscat	2002	C	17,639	2350	15289	43.7% (1027)	52.9% (8088)	19 years	ulr	s, a, edu, ccs, dur, cpd	1.1, 1.0-1.3	
2	2	Muscat	2002	AA	1906	655	1251	29.4% (194)	35.7% (447)	19 years	ulr	s, a, edu, ccs, dur, cpd	1.1, 0.8-1.4	
3	3	Okuyemi	2003	AA	600	471	129	18.5% (87)	23.2% (30)	6 months	2x2	None	0.75, 0.47-1.20	[d][e][f][g]
4	4	Pletcher .	2006	none	1535	972	563	31% (301)	46% (259)	15 years	lr	s, a, eth, edu, mar, occ, ins	0.71, 0.49-1.02	[h][i]
5	5	Foulds	2006	none	1021	418	595	24.9% (104)	35.8% (213)	26 weeks	2x2	None	0.59, 0.44-0.77	[j][k]
6	6	Okuyemi	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	[d]
7	6	Okuyemi	2007	AA ≥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	[d]
8	7	Murray	2007	none	5734	1191	4543	15.4% (183)	16.6% (752)	5 years	2x2	None	0.92, 0.77-1.10	[i]

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9	8	Fu	2008	none	1343	342	1001	n.a.	n.a.	About 6 months	n.a.	None	1.14, 0.85-1.53	[d][k]
10	10	Gandhi	2009	C	1086	348	738	29% (101)	31% (229)	6 months	mh	None	0.88, 0.66-1.10	[d][k][ ][m]
11	10	Gandhi	2009	AA	374	302	72	19% (57)	36% (26)	6 months	mh	None	0.40, 0.23-0.70	[d][k][ ][m]
12	10	Gandhi	2009	H	149	99	50	9% (9)	27% (14)	6 months	mh	None	0.32, 0.13-0.77	[d][k][ ]
13	11	Cropsey	2009	C	109	53	56	13.5% (7)	8% (4)	12 months	2x2	None	1.98, 0.54-7.19	[d][l]
14	11	Cropsey	2009	AA	124	117	7	14% (16)	8% (1)	12 months	2x2	None	0.95, 0.11-8.42	[d][l]
15	13	Stahre	2010	none	12004	3215	8789	47.1% (1515)	50.4% (4434)	≥12 months	2x2	None	0.87, 0.81-0.95	
16	13	Stahre	2010	C	10079	2092	7987	52.4% (1096)	50.7% (4051)	≥12 months	2x2	None	1.07, 0.97-1.18	[n]
17	13	Stahre	2010	AA	1434	1017	417	35.7% (363)	50.4% (210)	≥12 months	2x2	None	0.55, 0.43-0.69	[o]
18	13	Stahre	2010	H	1491	348	1143	39.9% (139)	44.6% (510)	≥12 months	2x2	None	0.82, 0.65-1.05	
19	15	Rose	2010	none	809	269	540	19.7% (53)	25.0% (135)	6 months	2x2	None	0.74, 0.51-1.05	[d][p]

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20	17	Reitzel	2011	none	244	123	121	n.a.	n.a.	26 weeks post partum	crl	None	0.79, 0.50-1.24	[i][q]
21	17	Reitzel	2011	C	88	20	68	6% (1)	24% (16)	26 weeks post partum	2x2	None	0.17, 0.02-1.38	[i][l][r]
22	17	Reitzel	2011	AA	81	70	11	17% (12)	35% (4)	26 weeks post partum	2x2	None	0.36, 0.09-1.43	[i][l][r]
23	17	Reitzel	2011	H	75	33	42	27% (9)	18% (8)	26 weeks post partum	2x2	None	1.59, 0.54-4.72	[i][l][r]
24	18	Delnevo	2011	none	65316 (17,703 / 47,613)	17703	47613	n.a.	n.a.	5 years	mlr	s, a, r, occ, inc, y, m	0.92, 0.88-0.97	[l][s]
25	18	Delnevo	2011	C	55,347	n.a.	n.a.	n.a.	n.a.	5 years	mlr	s, a, edu, inc, y, m	0.95, 0.90-1.00	[l]
26	18	Delnevo	2011	AA	5448	n.a.	n.a.	n.a.	n.a.	5 years	mlr	s, a, edu, inc, y, m	0.78, 0.64-0.95	[l]
27	18	Delnevo	2011	H	4521	n.a.	n.a.	n.a.	n.a.	5 years	mlr	s, a, edu, inc, y, m	0.97, 0.82-1.14	[l]

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28	19.1	Blot	2011	C (retrospective)	16522	4358	12164	49.6% (2162)	40.3% (4905)	6.5 years	ulr	s, a, edu, inc, rec, BMI	1.55, 1.41-1.70	
29	19.1	Blot	2011	AA (retrospective)	34342	28676	5666	29.7% (8521)	41.4% (2347)	6.5 years	ulr	s, a, edu, inc, rec, BMI	1.03, 0.96-1.11	
30	19.2	Blot	2011	none prospective	12373	7886	4487	n.a.	n.a.	4.3 years	ulr	s, a, r, edu, inc, rec, BMI, pyb, tel	1.02, 0.89-1.16	[t][u]
31	20	Steinberg	2011	none	692	331	361	19.9% (66)	26.0% (94)	6 months	2x2	None	0.71, 0.49-1.01	[d][r][v]
32	21	D'Silva	2012	none	715	120	595	17.3% (21)	13.8% (82)	7 months	2x2	None	1.33, 0.78-2.24	[r][w]
33	22	Faseru	2013	AA	540	452	88	10.0% (45)	20.4% (18)	26 weeks	2x2	None	0.43, 0.24-0.78	[x]
34	23	Reitzel	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	[i]
35	23	Reitzel	2013	C	95	18	77	n.a.	n.a.	3 weeks	crl	s, a, r, edu, inc, occ, par, stg	0.21, 0.05-0.98	[i]
36	23	Reitzel	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	[i]
37	24	Rojewski	2014	none	166	61	105	13% (8)	30% (32)	26 weeks	lr	a	0.40, 0.17-0.96	[d]

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38	25	Lewis	2014	none	1582	454	1128	20.3% (92)	26.2% (296)	≥1 year	cph	None	0.79, 0.64-0.99	[y]
39	25	Lewis	2014	AA	189	103	86	17.0% (18)	18.5% (16)	≥1 year	2x2	None	0.93, 0.44-1.95	[y]
40	26	Smith	2014	none	1439	625	814	29.9% (187)	35.9% (292)	26 weeks	gee	t, trt	0.71, 0.59-0.86	[d][z]
41	26	Smith	2014	C	1253	439	814	32.6% (143)	35.9% (292)	26 weeks	2x2	None	0.86, 0.68-1.10	[d]
42	27	Sulsky	2014	C	n.a.	n.a.	n.a.	n.a.	n.a.	1-3 years	lr	men, cpd, dur	0.90, 0.84-0.96	[aa]
43	27	Sulsky	2014	AA	n.a.	n.a.	n.a.	n.a.	n.a.	1-3 years	lr	men, sia, dur	0.84, 0.67-1.05	[aa]

[a] AA = African American; C = Caucasian; H = Hispanic; none = subjects not stratified by race

[b] 2x2 = calculated from 2x2 table; 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; n.a. = not available

[c] 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 = 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; r= 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= year;

[d] Based on 7-day point prevalence

[e] Based on the statement that attrition rates were equal for menthol and non-menthol smokers, since only rates were provided

[f] 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

[g] Reported ORs were restricted to < and >50 years of age, for 6-week cessation, and were adjusted for TTFC

[h] Apparently based on N = 1260 with no obvious explanation for the difference between this number and the total sample of 1535.

[i] Based on sustained quitters

[j] Apparently there were 8 smokers who could not be classified as menthol or non-menthol

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[k] Reported ORs using multiple logistic regression were adjusted for TTFC

[l] Results obtained graphically

[m] Cessation rates as a function of employment were presented

[n] The reported OR for Caucasian smokers was the reference

[o] The reported OR for African American smokers was based on a reference OR of 1.00 for Caucasian smokers

[p] Results were obtained from a meeting abstract

[q] The reported unadjusted OR was used since TTFC was a covariate used in the adjusted OR

[r] Reported ORs were adjusted for TTFC

[s] Numbers of menthol and non-menthol smokers are based on the percentages for the total sample

[t] Overall cessation rate was 21%; cessation rates were not specified for menthol and non-menthol smokers

[u] Cessation was defined as a current smoker at baseline reporting non-smoking at a follow-up interview

[v] Although not apparently stated in the publication, 61 subjects did not specify menthol or non-menthol

[w] Based on 30-day point prevalence

[x] The reported adjusted OR was for 7 weeks of cessation

[y] Cessation defined by no cigarette purchase for a period of 1 year

[z] Data were analyzed using a "marginal or 'population average' model that permit inferences about the effects of covariates on populaton and subpopulation 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. (2007)

[aa] Data obtained from the 2010/2011 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) for regular and former smokers

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781 Table 4. Meta-analytic Results for Smoking Cessation.

782 Description of Group (N)	Fixed-Effect OR (95%CI)	Random-Effects OR (95%CI)	I^2
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
Clinical 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

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

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Table 5. Meta-analytic Results for Smoking Cessation Effect of Adjustment for SES.

Description of Group (N)	Fixed-Effect OR (95%CI)	Random-Effects OR (95%CI)
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)
Clinical estimates (*Table 4*) (17)	0.73 (0.65-0.81)	0.70 (0.60-0.82)
Clinical estimates, adjusted for SES (3)	0.96 (0.50-1.82)	0.89 (0.54-1.48)
Clinical 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)

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

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Table 6. Comparison of SES Factors Menthol (M) and Non-Menthol (NM) Smokers.

Study	Measure of Education			Measure of Employment			Measure of Income		
	%M	%NM	p	%M	%NM	p	%M	%NM	p
Okuyemi, 2003	≥High school graduate			Employed			Monthly income >$1800		
	50.7%	47.3%	p = 0.487	*78.3%*	*65.9%*	*p = 0.004*	45.4%	45.3%	p = 0.977
Pletcher, 2006	Some college			Employed full time			NS[a]		
	35.3%	**53.5%**	**p<0.001**	**45.5%**	**62.2%**	**p<0.001**			
Okuyemi, 2007	≥High school education			Employed			Monthly income ≥$1800		
	83.2%	84.8%	p = 0.705	47.5%	49.3%	p = 0.707	40.4%	43.9%	p = 0.494
Murray, 2007	Education (years)			NS			NS		
	13.8%	13.6%							
Fu, 2008	Some college or more			NS			NS		
	61%	*39%*	*p<0.001*						
Gandhi, 2009	Bachelors or higher			Full-time employed			NS		
	14.9%	**30.8%**	**p<0.001**	**41.2%**	**48.8%**	**p<0.001**			
Stahre, 2010	Some college/degree			NS			NS		
	38.7%[b]	**44.3%[b]**	**p = 0.025**						
Reitzel, 2011	<High school/GED			NS			≥$20,000/year		
	23.6%	**13.2%**	**p = 0.037**				**56.0%**	**75.9%**	**p = 0.002**
Delnevo, 2011	BA/BS or more			NS			≥$75,000		
	15.4%	*11.1%*					**15.2%**	**18.6%**	
D'Silva, 2012	Less than high school			NS			NS		
	14.4%	**8.9%**							
Reitzel, 2013	>High school diploma			Employed			≥$20,000		
	60.2%	73.0%	p = 0.067	**43.4%**	**58.0%**	**p = 0.049**	47.5%	58.6%	p = 0.14
Rojewski, 2014	NS			Employed			NS		
				78.7%	80.0%				
Smith, 2014	>High school diploma			Employed			NS		

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	63.9%	**76.9%**	**p<0.0001[c]**	**75.8%**	**80.2%**	**p = 0.0056[c]**

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

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Supplementary Text 1

Explanation of Choice of TTFC Study Where More than One Study Was Based on the Same Data Set

All publications providing data that met inclusion and exclusion criteria for the meta-analysis of TTFC for menthol smokers compared to non-menthol smokers are listed in *Appendix A*. Three publications reported results for the 2003 and 2006/2007 Tobacco Use Supplement to the US Current Population Survey (TUS-CPS). Fagan et al. (2010, publication 7, *Appendix A*) reported results for both TTFC ≤5 min and ≤30 min, and their results were adjusted for a large number of covariates. Lawrence et al. (2010, publication 9) provided a result for ≤30 min. Although their result was adjusted, the adjustment factors were not specified. Lastly, Curtin et al. (2014, publication 18) reported results for both ≤5 and ≤30 min, but their results were unadjusted. As a consequence, the Fagan et al. results were used in the meta-analysis for both ≤5 and ≤30 min. Lastly, Ahijevych and Ford (2010, publication 8) 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 = 3129, subjects).

Two studies reported results for data obtained from the National Health and Nutrition Examination Survey (NHANES). Jones et al. (2013 publication 15) reported on TTFC results for ≤5 min from NHANES 2001-2010, while Curtin et al. (2014, publication 18) 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. (2096 vs. 4759 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. (2014 publication 14) reported on NSDUH 2008-2009, whereas Curtin et al. (2014, publication 18) 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 given the larger number of subjects.

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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. (2010) with TTFC ≤5 min as a function of cigarettes per day (cpd). These range from 0.94-1.22. The OR obtained by Curtin et al. for TTFC ≤5 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 ≤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. (2010) 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. (2014) 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. (2014), the selected study, reported an OR=1.08 (95%CI, 0.95-1.24) for TTFC ≤5 min, whereas Jones et al. (2012), 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. (2014) reported an OR= 1.03 (95%CI, 1.00-1.06) for TTFC ≤30 min based on NSDUH data, while the OR reported by Hickman et al. (2014 was 1.05 (95%CI, 1.00-1.10). Once again, these two results are not significantly different.

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Appendix A. Papers with Results Dealing with Time to First Cigarette (TTFC)

Publication Information			General Study Design							
No.	Author	Year	Study Design [a]	Total Sample Size	Mean Age (±SD) or Age Range	Percent Male	Race Distribution % [a]	% Menthol Smokers (by race) [a]	Number (%) for given Time to First Cigarette by smoker type [a]	Comments
1	Hyland et al.	2002	X-S	13,268	25-64	49.2		24 (C23; AA57)	<10 min: 947M (29.7%); 3338NM (33.1%) ≥10 min: 2231M (70.3%), 6704NM (66.9%)	[b][c][d]
2	Okuyemi et al.	2003	X-S	600	44.2±10.0	29.3	AA100	78	≤30 min: 385M (81.7%), 90NM (69.8%) >30 min: 86M (18.3%), 30NM (30.2%)	
3	Collins and Moolchan	2006	X-S	572	15.6±1.6	44.9	EA48.2; AA46.9; other4.9	92.8	≤5 min: 239M (45%), 12NM (29%) >5 min: 292M (55%), 29NM (71%)	[e][f]
4	Fu et al.	2008	X-S	1343	56.0±10.3	94	C73; AA14; other12	25.5 (C19; AA62; other25)	≤30 min: 256M (75%), 791NM (79%) >30 min: 86M (25%), 210NM (21%)	[g]
5	Gandhi et al.	2009	RCT	1688	41.5±13.3	41.9	C64.3; AA22.2; H8.8; other4.7	46.1 (C32.0; AA80.7; H66.4; other36.7)	≤5min: 187M (24.3%), 178NM (19.9%) >5min: 581M (75.6%), 718NM (80.2%)	[h][i]
6	Muscat et al.	2009	X-S	525	n.a.	49.2	C54.8; AA45.1	54.1 (C27.8; AA86.1)	≤30 min: M (34%), NM (21%) >30 min: M (66%), NM (79%)	[j]

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7	Fagan et al.	2010	X-S	45,315	≥18	44.3		25.80%	≤5 min: M (22.27%) 95%CI, 21.30-23.27 NM (22.17%) 95%CI, 21.57-22.79	[k][ ][m][n][o]
8	Ahijevych and Ford	2010	X-S	3129 (d-2241; nd-688)	d-21.5±1.9; nd-21.8±1.8	d-48.9; nd-48.8		d-29.9; nd25.7	d: ≤30 min, 1127 (50.3%) >30 min, 1114 (49.7%) nd: ≤30 min, 67 (9.7%) >30 min, 621 (90.3%)	[p][q]
9	Lawrence et al.	2010	X-S	63,193	≥18	52.1		25.8 (nhC20.6; nhAA73.2; H28.0; AI18.8; AS35.1; MR29.1)	≤30 min: 8139M (51.5%), 24823NM (54.3%) >30 min: 7675M (48.5%), 20907NM (45.7%)	[r][s][t]
10	Faseru et al.	2011	X-S	540	46.5±11.3	33.9	AA100	83.7	≤30 min: 330M (73.0%), 60NM (68.2%) >30 min: 122M (27.0%), 28NM (31.8%)	
11	Reitzel et al.	2011	X-S	244	24.6±5.3	0	C36.1; AA81; L30.7	50.4 (C29.4; AA86.4; L44.0)	≤5 min: 33M (26.8%), 20NM (16.5%) >5 min: 90M (73.2%), 101NM (83.5%)	
12	D'Silva et al.	2012	X-S	6257	≥18	30.8	nhC83.4; nhAA7.3; H3.3; other6.0	18.7 (nhC14.6; nhAA64.2; H19.6; other28.0)	≤5 min: 543M (46.3%), 2192NM (43.1%) >5 min: 629M (53.7%), 2893NM (56.9%)	

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13	Rosenbloom et al.	2012	X-S	928	41.0±10.1	0	C78.7; AA21.3	36.1	≤5 min: 164M (49.0%), 213NM (36.0%) >5 min: 171M (51.0%), 380NM (64.0%)	
14	Hickman et al.	2014	X-S	24,157	≥18	51.4	nhC68.2; nhAA10.8; H12.5; ASA2.1; other6.4	38.1 (nhC29.0; nhAA86.4; H43.4; ASA40.7; other41.1)	≥30 min: 4085M (44.4%), 6457NM (43.2%) >30 min: 5113M (55.5%), 8502NM (56.8%)	[u][v]
15	Jones et al.	2013	X-S	4603	41.7±0.4 (SE)	57.1	C57.7; AA24.8; H18.6	25.7 (C19.1; AA69.0; H12.0)	≤5 min: 227M (35.1%), 470NM (32.4%) >5 min: 420M (64.9%), 979NM (67.6%)	[w][x][y]
16	Rojewski et al.	2014	X-S	166	44.3±10.6	28.3	C90.3; AA7.7; other1.9	36.1 (C40.0; AA25.0; other33.3	≤30 min: 47M (82.4%), 83NM (79.8%) >30 min: 10M (17.5%), 21NM (20.2%)	[z][aa]
17	Frost-Pineda et al.	2014	X-S	3341	41.9 (21-80)	42.4	C81.6; AA18.4	31.2 (C21.8; AA73.0)	≤5 min: 337M (32.5%), 661NM (28.8%) >5 min: 701M (67.5%),1633NM (71.1%)	[f][ab]
18.1	Curtin et al.	2014	X-S	4759	≥20	55	nhC56.0; nhAA23.1; other20.9	31.6 (nhC20.1; nhAA69.8; other20.3)	≤5 min: 492M (32.7%), 1007NM (30.9%) >5 min: 1012M (67.3%), 2248NM (69.1%)	[f][ac]
18.2	Curtin et al.	2014	X-S	57,058	≥15	47.5	nhC81.2; nhAA7.8; other10.9	25.7 (nhC20.7; nhAA73.8; other28.6)	≤5 min: 2995M (20.4%), 9125NM (21.5%) >5 min: 11693M	[f][ad]

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									(79.6%), 33263NM (78.5%)	
18.3	Curtin et al.	2014	X-S	77,183	≥20	50.4	nhC73.8; nhAA10.0; other16.2	32.0 (nhC23.9; nhAA84.1; other37.1)	≤5 min: 5383M (21.8%), 10457NM (19.9%) >5 min: 19358M (78.2%), 41985NM (80.0%)	[f][ae]

[a] abbreviations: AA = African American; AI = American Indian; AS = Asian; ASA = 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; nhAA = non-hispanic African American; NM = smokers of non-menthol cigarettes; RCT = Randomized Control Trial; X-S = Cross-sectional

[b] 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.

[c] 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

[d] Data were also provided for TTFC at >10-30 min, 31-60 min, and >60 min

[e] All subjects were adolescents

[f] Data were also provided for TTFC at 6-30 min, 31-60 min, and >60 min

[g] All subjects were relapsed smokers

[h] Time to first cigarette data based on 1664 total subjects - 768 menthol smokers and 896 non-menthol smokers

[i] Data were also provided for TTFC at 6-30 min, and >30 min

[j] 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.

[k] 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.

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[l] 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.

[m] 82.2% non-Hispanic Caucasian, 7.5% non-Hispanic African American, 7.5% Hispanic, 1.3% American Indian, 1.3% Asian, 2.1% other

[n] 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

[o] Data were also provided for TTFC at 6-10 min, 11-15 min, and >16 min

[p] Data were obtained from the TUS-CPS; however, this paper analyzed data for young smoking adults, aged 18-24 years

[q] 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

[r] 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

[s] 80.0% non-Hispanic Caucasian, 8.2% non-Hispanic African American, 6.2% Hispanic, 1.5% American Indian, 1.8% Asian, 2.2% multiple races

[t] TTFC based on a sample size of 61,549 because of elimination of 1649 individuals with varying TTFC

[u] 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.

[v] Based on unweighted data

[w] 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

[x] TTFC data was based on NHANES 2001-2010 with a total of 2096 individuals, of which 647 were menthol and 1449 non-menthol smokers

[y] Data were also provided for TTFC at 6-30 min, 31-60 min, and >60 min

[z] Race distribution and percent menthol based on a total sample of 155

[aa] TTFC based on a total sample of 161

[ab] TTFC based on a sample size of 3332 (1039 menthol smokers and 2293 non-menthol smokers)

[ac] Data were obtained from NHANES, 2001-2010. Data from this data base were analyzed by Jones et al., publication 15

[ad] 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

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[ae] 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

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Supplementary Text 2

Explanation of Choice of Cessation Study Where More than One Study Was Based on the Same Data Set

All publications providing data that met inclusion and exclusion criteria for the meta-analysis of cessation rates for menthol smokers compared to non-menthol smokers are listed in *Appendix B*. Three publications provided results drawn from the 2005 National Health Interview Survey Cancer Control Supplement (NHIS-CCS); namely, Gundersen et al. (2009) (publication 9), Stahre et al. (2010) (publication 13), and Sulsky et al. (2014) (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, 7815 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 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. 2010 (publication 12), Fagan et al. 2010 (publication 14), Levy et al. 2011 (publication 16) and Delnevo et al. 2011 (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. (2011) and Levy et al. (2011) have approximately equal sample sizes. However, Delnevo et al. (2011) 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. (2011) analyses did not make this exclusion. Moreover, the analysis presented only a single estimate; namely for all subjects irrespective

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of race. Given these considerations, the results of the Delnevo et al. (2011) 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. (2010) (publication 13) was chosen to represent the NHIS-CCS data. Results reported by Gundersen et al. (2009) (publication 9) and Sulsky et al. (2014) (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. (2011) (publication 18). Levy et al. (2011) (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. (2010) (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. (2010) (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.

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Appendix B. Publications with Results Dealing with Cessation

Publication Information			General study characteristics									
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
1	Hyland et al.	2002	p [a]	13,268	25-64	49.2	[b]	24 (C23; AA57)	5y	24	None	[c]
2	Muscat et al.	2002	x-s [d]	19,545	>45-<65	70.0	C 90.2; AA 9.8	15.4 (C13.3; AA34.4)	19y	49.9	None	None
3	Okuyemi et al.	2003	RCT	600 [e]	44.2±10.0	30.0	AA 100	78.5	6m	21.0M, 27.0NM (based on a total of 518 subjects remaining) [f]	Exhaled CO	Treatment group received bupropion; all subjects received psychological counseling
4	Pletcher et al.	2006	p	1535 [g]	25.0±3.7	47.4	C 42.8; AA 57.2	63.3 (C19.4; AA80.5)	15y	31M, 46NM sustained abstinence	None	None
5	Foulds et al.	2006	RCT	1021	43 (15-80)	40.5	C 65.6; AA 21.4; H 7.8; other 5.1	40.9	26w [h]	31.3 (24.9M; 35.8NM)	Exhaled CO	[i]

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6	Okuyemi et al.	2007	RCT [j]	753 [k]	43.4±10.3	67.1	AA 100	81.7	26w [l]	11.2M and 18.8NM	Salivary cotinine and exhaled CO	[j]
7	Murray et al.	2007	p	5883 [m]	48.5±6.9	62.9	AA 3.5	20.7	5y	15.4M; 16.6NM [n]	Not specified	[o]
8	Fu et al.	2008	x-s [p]	1343	56.0±10.3	94	C 73; AA 14; other 12	25.5 (C18.8; AA63.7; other 25.5)	About 6m		Self report	[q]
9	Gunderson et al.	2009	x-s [r]	7815 82.7%	49.1±0.23 (SE)	50.2	C 82.7; AA 8.9; H 8.4	26.5	Not applicable	56.9M; 61.5NM	Self-report	Not specified
10	Gandhi et al.	2009	RCT [s]	1688	41.5±13.3	41.9	C 64.3; AA 22.2; H 8.8; other 4.7	46.1 (C32.0; AA80.7; H66.4; other 36.7)	6m [t]	22M, 32NM [u]	Exhaled CO	[v]
11	Cropsey et al.	2009	RCT	233	33.9±8.9	0	C 46.8; AA 53.2	73.1 (C48.5; AA94.7)	12m	13.7M; 8NM [w]	Exhaled CO	Psychological support and nicotine patch [x]
12	Trinidad et al.	2010	x-s [y]	73,691 [z]	20-65	[aa]	[aa]	25.8	Not applicable	5.1M, 5.5NM	Self report	Not specified

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13	Stahre et al.	2010	x-s [ab]	12,004 [ac]	>18	51	C 84.0; AA 11.9; AI 0.8; AS 1.8 [ad]	26.8 (C20.8; AA71.0; AI21.5; AS31.5; H23.3)	Not applicable	49.6 (47.1M; 50.4NM)	Self report	About 32% of current smokers and 25% of past smokers reported using quit aids
14	Fagan et al.	2010	x-s [ae]	45,315 [af]	>18	44.3	nhC 82.2; nhAA 7.5; H 5.1; AI 1.3; AS 1.7; other 2.1	25.8 (nhC21.0; nhAA74.0; H29.5; AI17.9; AS33.4; other 28.4)	Not applicable	10.6 (10.8M; 10.5NM)	Self report	Not specified
15	Rose and Behm	2010	RCT [ag]	809	n.a.	n.a.	n.a.	33.2	6m [ah]	23.2 (19.7M, 5.0NM)	Not specified	At least NRT
16	Levy et al.	2011	x-s [ai]	65,510	>18	n.a.	n.a.	25.8	5y	20.8 (18.6M; 21.2NM)	Self report	Not specified
17	Reitzel et al.	2011	RCT [aj]	244	24.6±5.3	0	C 36.1; AA 33.2; H 30.7	50.4 (C22.7; AA86.4; H44.0)	40-47w (26w post-partum) [ak]	[al]	Exhaled CO or salivary cotinine	Psychological counselling for the intervention groups (N = 136)
18	Delnevo et al.	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 (C21.0;	5y	23.4	Self report	Not specified

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								AA71.8; H28.1)				
19.1	Blot et al.	2011	r [ao]	50,864	40->60	48.9	C 32.5; AA 67.5	64.9 (C26.4; AA83.5)	6.5y	35.3 (32.3M; 40.6NM)	Self-report	Not specified
19.2	Blot et al.	2011	p [ao]	12,373	n.a.	n.a.	n.a.	36.3	4.3y	21	Self report	Not specified
20	Steinberg et al.	2011	RCT	723	45 (16-78)	47	C 59; AA 23; H 14; other 5	48	6m	23 (18M; 26% (NM)	Exhaled CO	A large variety of pharmaco-logical treat-ments, NRT, and pychological support
21	D'Silva et al.	2012	RCT [ap]	715	[aq]	[aq]	[aq]	16.8	7m	14.4 (17.3M; 13.8NM)	Self-report	Both NRT (4 weeks) and psychological support were made available.
22	Faseru et al.	2013	RCT	540 [k]	46.5±11.3	33.9	AA 100	83.7 [ar]	26w [as]	14.1M; 20.4NM	Salivary cotinine	Treatment group: 7 weeks bupropion SR; control group, placebo; both groups received psychological support

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23	Reitzel et al.	2013	RCT	183	46.4±9.71	42.62	nhC 51.91; nhAA 48.09	45.4 (nhC18.9; nhAA73.9)	3w [at]	15.9 (12.1M; 19.0NM) [au]	Exhaled CO	NRT (4 weeks) and access to counseling sessions
24	Rojewski et al.	2014	RCT	166	44.3±10.6	28.9	C 90.3; AA 7.7; other 1.9 [av]	36.7 (C40.0; AA25.0; other 33.3)	26w [aw]	13M; 30NM	Exhaled CO	Intervention group received naltrexone; all subjects received nicotine patches and counseling
25	Lewis et al.	2014	p[ax]	1582 house-holds	60..01± 10.43	26.7 [ay]	AA 11.9; nAA 88.1	28.7 (AA54.5; nAA25.2)	≥1y	24.5(20.3M; 26.2NM)	Lack of cigarette purchase for at least one year	Not specified
26	Smith et al.	2014	RCT [az]	1439	44.7±11.1	41.1	C 87.1; AA 12.9	43.4 (C35.3; AA100)	26w [ba]	33.3 (29.9M, 35.9NM)	Exhaled CO	[bb]
27.1	Sulsky et al.	2014	x-s[bc]	[bd]	>20	55.6	nhC 79.3; nhAA 9.4; other 11.2 [be]	27.1 (nhC21.4; nhAA74.1; other 28.1)[be]	Not specified	50.8(47.1M; 52.2NM)[be]	Self-report	Not specified
27.2	Sulsky et al.	2014	x-s [bf]	[bd]	>20	54.4	nhC 78.8; nhAA 8.9; other 12.3 [be]	27.5 (nhC22.2; nhAA73.5; other 28.3) [be]	[bg]	51.2 (45.2M; 53.4NM) [be]	Self-report	Not specified

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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 clinical trial; w = weeks; x-s = cross-sectional; y = years

[a] 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.

[b] 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%.

[c] 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 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 communities.

[d] 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

[e] Intention to treat

[f] See Ahluwalia et al. (2002) for details

[g] Number of smokers with known menthol or non-menthol preference at baseline

[h] Four-week cessation data were also provided

[i] Multiple types of support were made available to all participants including psychological support, nicotine replacement therapy (NRT), and treatment with bupropion

[j] 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. (2006) for details. All groups have been combined

[k] All smokers were "light" smokers - smokers of <10 cig/day

[l] Eight-week cessation data were also provided

[m] Usual care (UC) and smoker intervention (SI) groups combined

[n] Based on 5734 participants; the percentage of menthol smokers remained constant

[o] 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.

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[p] This intervention study was conducted in five US Veterans Administration medical centers. Details of the study are provided in Partin et al. (2006). All subjects were relapsed smokers who had previously quit.

[q] All participants received NRT or bupropion; the intervention group received psychological counseling

[r] 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 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 not indicate that they had attempted to quit were also excluded

[s] Analysis of 1688 consecutive patients who attended a smoking cessation clinic between 2001 and 2005

[t] Four-week cessation data were also provided

[u] Calculations of ORs were based on 1609 subjects rather than 1688 subjects

[v] Both psychological support and/or FDA-approved tobacco-dependence treatment were made available

[w] Percentages obtained graphically; graphical cessation data were also provided for each week up to 9 weeks and at 3 and 6 months

[x] In the orginal study (Cropsey et al. (2008)) 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.

[y] 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

[z] 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 who reported smoking either essentially only menthol or only non-menthol. It is not clear if smokers who had quit for less than 6 months (12,583) were included as current smokers or were excluded

[aa] 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

[ab] 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

[ac] This number includes current and former smokers who specified smoking either menthol or non-menthol

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[ad] 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

[ae] 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

[af] 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.

[ag] A retropsective analysis of two RCT conducted at the Duke Medical Center; no details provided

[ah] Four-week cessation data were also provided

[ai] 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

[aj] Subjects were women who quit smoking during pregnancy or no more than 2 months before becoming pregnant. The measured end point was relapse.

[ak] Eight-week post-partum data were also provided

[al] 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 Americans - 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

[am] 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

[an] 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

[ao] Southern Community Cohort Study

[ap] 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 = 6257). No quit information was obtained. The second evaluated quit rates in a smaller survey (N = 715), but no demographic information was presented.

[aq] 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

[ar] Taken from Cox et al. (2012)

[as] Three-week and 7-week cessation data were also provided; menthol was not a factor in the regression model at 26 weeks

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[at] One and 2-week cessation data were also provided

[au] Data were also provided for 7-day point prevalence abstinence, which can change from week to week

[av] Based on 155 subjects

[aw] Fourteen-week cessation data were also provided

[ax] 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.

[ay] Based on the 566 households with either single female or single male occupancies

[az] Based on a clinical study; see Piper et al. (2009)

[ba] Four-week and 8-week cessation data were also provided

[bb] 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

[bc] 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

[bd] Total sample size not provided - only weighted frequency based on the US population

[be] Based on weighted frequencies for regular and former smokers

[bf] Data were obtained for regular smokers from the 2010-2011 TUS-CPS

[bg] Former smokers were restricted to short-term former smokers; i.e., those who had quit for 1-3 years

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Appendix C. Funnel Plots for TTFC Point Estimates <5 Min (N = 13) and Cessation Point Estimates not Stratified by Race (N = 20)

[Insert *Figure C1* here]

Figure C1. 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 (vertical line not shown), 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).

[Insert *Figure C2* here]

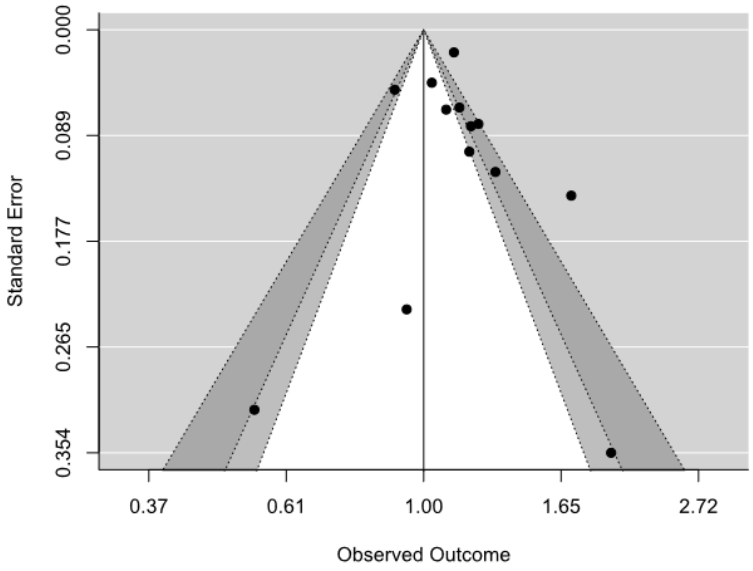
Figure C2. Funnel plot of included point estimates for all included cessation studies not stratified by race (N = 30).

There are quite a few studies missing to the right of the point estimate of 0.87 (vertical line not shown) 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).

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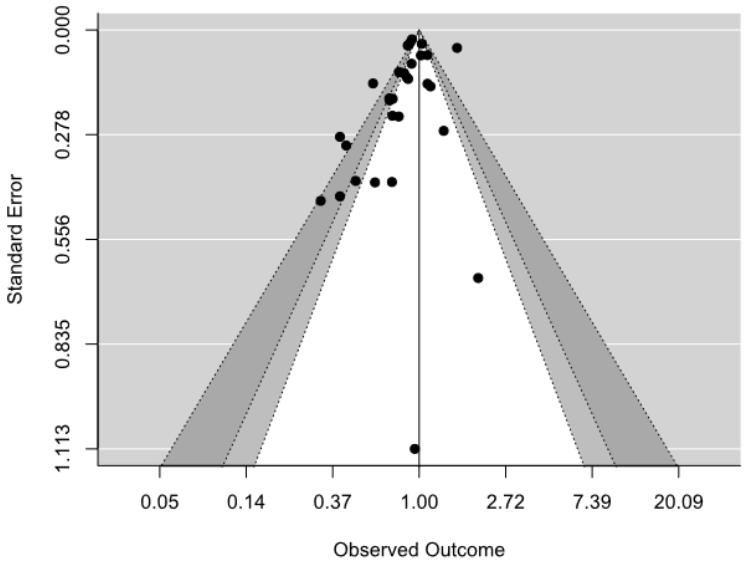
Figure C1 :



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Figure C2 :



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Highlights

- Meta-analysis suggests that smokers of menthol cigarettes have a shorter time to first cigarette than non-menthol smokers.
- An association of menthol cigarette smoking with reduced success at cessation was restricted to non-Caucasian subjects.
- Differences in socioeconomic status seems to explain the anomaly between Caucasian and non-Caucasian subjects.

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