Center for Regulatory Effectiveness (CRE) assessment of the following research report:

"Menthol Cigarettes, Smoking Cessation, Atherosclerosis and Pulmonary Function"

By:

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<div align="center">Reference:</div>

Research Report: "Menthol Cigarettes, Smoking Cessation, Atherosclerosis, and Pulmonary Function" *Arch Intern Med. 2006;166:1915-1922*, by Dr. *Mark J. Pletcher*, et al.

Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation (quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference was identified for review and public discussion due to its focus on young adults' mentholated cigarette use in relation to race (African Americans versus European Americans), smoking cessation behavior, and tobacco-related morbidity (coronary calcification and change in pulmonary function). The study used 1985 to 2000 data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. The CARDIA Study is a longitudinal study of risk factors for coronary artery disease in 5115 African American and European American women and men aged 18 to 30 years and healthy at the time of enrollment in 1985. Participants underwent a baseline examination and then follow-up examinations at years 2, 5, 7, 10, and 15, with 74% retention of the surviving cohort at year 15. For this investigation, the researchers identified CARDIA smokers and measured associations between menthol/nonmenthol exposure and smoking cessation behaviors during follow-up, the prevalence of coronary calcification in 2000, and changes in pulmonary function test results between 1985 and 1995. The following timeline generally illustrates the time points when variables were measured.

Measures	Baseline (1985)	Years after baseline				
		2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
Menthol smoking status	X	X	X	X	X	X
Smoking cessation behaviors						
Not currently smoking	X	X	X	X	X	X
Recent quit attempt	X	X	X	X	X	X
Cessation if recent quit attempt	X	X	X	X	X	X
Sustained smoking cessation			X	X	X	X
Documented relapse						X
Tobacco-related coronary calcification						X
Pulmonary function	X				X	

The researchers presented the following primary results:

- African American smokers were statistically significantly more likely to be menthol cigarette users than European American smokers (89% versus 29%, $p < 0.001$);
- Menthol smokers had statistically nonsignificant lower cessation and recent quit attempt rates and a statistically significantly higher risk of relapse than nonmenthol smokers (odds ratios [95% confidence interval] for cessation, recent quit attempt, and risk of relapse, in order, were 0.71[0.49, 1.02], 0.77[0.56, 1.06], 1.89[1.17, 3.05]), after adjusting for ethnicity, demographics, and social factors.
- There were no statistically significant differences from menthol in tobacco related coronary function or 10-year pulmonary function decline, after for ethnicity, demographics, and social factors.

The researchers therefore concluded that "Menthol and nonmenthol cigarettes seem to be equally harmful per cigarette smoked in terms of atherosclerosis and pulmonary function decline, but menthol cigarettes may be harder to quit smoking."

The CRE conducted a limited assessment which comprised a review of the report.

Summary of Findings and Issues

1. *Is the measurement of menthol exposure accurate and adequate?*

The independent variable, menthol exposure, was defined as cumulative exposure to menthol pack-years and nonmenthol pack-years using information on current smoking, number of cigarettes smoked per day, menthol preference, and past years of smoking at baseline, assuming that participants smoked only menthol or nonmenthol cigarettes at any one time. This assumption needs to be justified. Intervals between two measurement points were two to five years; switch from menthol to nonmenthol cigarettes or vice versa is likely to happen. It was reported that younger smokers were highly likely to switch to menthol cigarettes (Sidney et al 1989). Therefore, this assumption potentially underestimated menthol pack-years.

In addition, menthol exposure was measured as a binary variable at every time point, as well as two independent numeric variables (menthol pack-years and nonmenthol pack-years). The study only explicitly described how the two numeric variables were defined and how they were analyzed in the logistic regression models with coronary calcification and change in pulmonary function as outcomes. There were no such descriptions regarding how menthol exposure was defined in logistic regression models with smoking cessation behavior variables as outcomes. From the title of Table 2, the reader learnt that only menthol preference at baseline was assessed in terms of its relationship with smoking cessation behavior variables. An advanced appropriate way is to treat it as time-dependent binary variable.

2. *Problems with measurements of smoking cessation behaviors.*

There were five measurements of smoking cessation behaviors. The definitions of those measurements were overlapped and confused. For example, the measurement cessation if recent quit attempt is a sub-group of recent quit attempt; it would be more efficient to define the two separate

binary variables as one categorical variable with 3-levels: no recent quit attempt/recent quit attempt but no cessation/recent quit attempt and cessation. The definitions of sustained smoking cessation and documented relapse in this study are confusing. By the definitions of this study, those two opposite behaviors (the former is considered as a positive smoking cessation behavior while the latter a negative behavior) can be obtained for one case. Suppose a subject had longitudinal smoking behaviors recorded as the following:

Measures	Baseline (1985)	Years after baseline				
		2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
smoking status at the time (1=yes,0=no)	1	0	0	0	0	1

Based on the definition of sustained smoking cessation (no current smoking the past 2 times they were examined), the case was in sustained smoking cessation at time 1992, 1995, and 2000. Based on the definition of documented relapse (baseline smokers who reported no current smoking at a subsequent examination and then current smoking the final time they were examined), the case was also in documented relapse at time 2000. In addition, the definition of documented relapse didn't capture all the patterns for relapse over the time course of this study. For example, if a case with behavioral pattern as the following:

Measures	Baseline (1985)	Years after baseline				
		2 (1987)	5 (1990)	7 (1992)	10 (1995)	15 (2000)
smoking status at the time (1=yes,0=no)	1	0	0	1	1	0

should it be accounted as a documented relapse? However, by the definition of relapse in this study, it's a non relapse case.

3. *Was the logistic regression with 1 observation per participant adequate for sustained smoking cessation?*

Based on the definition of sustained smoking cessation (no current smoking the past 2 times they were examined), a case should have as many as 4 measurements for this variable at times 1990, 1992, 1995, and 2000. But the researcher used logistic regression with 1 observation per participant for this outcome. Should repeated-measure analyses be conducted instead?

4. *Missing data and sensitivity analysis*

In this study, over a quarter of data (26%) were missed on key information such as coronary calcification. The researcher used a weight approach to adjust for the missing data and a sensitivity analysis showed that unweighted and weighted analyses had approximately equal results. Other alternatives are to conduct sensitivity analysis with Multiple Imputation (MI), Maximum Likelihood (ML), and Weighted Estimating Equation (WEE), especially when dealing with large proportion of missing data.

Detailed Technical Issues

1) On page 1917, in first sentence in section Study sample and menthol preference, (30%) can be added after the number 1544.
2) On page 1917, in the sentence "Before adjustment, menthol smokers were less likely to be noncurrent smokers at follow-up examinations…" in section Smoking cessation behavior, double negatives were used. It would be easier to understand if changing the sentence to '…menthol smokers were more likely to be current smokers at follow-up examinations…'.
3) Redundant information regarding statistical significance (both 95% CI and p-value) was presented all over the research paper. For example, on page 1915, in the Results section of the abstract, it presented "odds ratio [OR], 0.71;95%confidence interval [CI], 0.49-1.02; *P*=.06".

Reference:

Sidney et al 1989. "**Mentholated Cigarette Use among Multiphasic Examinees, 1979-86**" *Am J Public Health. 1989 Oct;79(10):1415-6*, by Drs. Sidney S, Tekawa I, and Friedman GD.