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## Mentholated Cigarettes and Cardiovascular and Pulmonary Diseases: A Population-Based Study

Cigarettes labeled as "mentholated" contain substantially higher levels of menthol than regular cigarettes, to produce a characteristic mint flavor and cooling sensation. Potential noncancer adverse health effects of added menthol to cigarettes are largely unknown. Epidemiologic data on the risks of cardiovascular and pulmonary diseases among smokers of mentholated vs nonmentholated cigarettes are extremely limited.[1,2] The purpose of this study was to determine if cardiovascular and pulmonary disease risk was different between mentholated cigarette smokers and nonmentholated cigarette smokers.

**Methods.** A multiyear, cross-sectional, population-based design was used. A total of 5167 current smokers at least 20 years old from the 2001-2008 US National Health and Nutrition Examination Surveys (NHANES)[3] formed the study group. Mentholation status of the cigarettes "usually" smoked was ascertained for 5028 individuals (97.3%). For 3791 individuals (75.4%), cigarette mentholation status was determined by survey administrator examination of smokers' usual cigarette packages. For 1237 individuals (24.6%), cigarette mentholation status was determined by asking participants whether cigarettes they usually smoked were mentholated. Health professional–diagnosed, self-reported hypertension, myocardial infarction, congestive heart failure, stroke, and chronic obstructive pulmonary disease (COPD) were the outcomes examined. Descriptive statistics and multiple logistic regression were use to examine the association between mentholated cigarette smoking and cardiovascular and pulmonary diseases. Given previously reported sex,[3,4] race,[3,5] and age group[3] discrepancies between mentholated and nonmentholated cigarette smokers, fully stratified analyses by sex (women vs men), race (African Americans vs non–African Americans), and age group (≥70 years vs < 70 years) were performed to look for potential differences in outcomes among subgroups of interest. To account for the complex sampling design of NHANES, all point estimates were appropriately weighted, and variance estimates were adjusted by Taylor linearization procedures.

**Results.** A total of 1286 of 5028 respondents (25.6%) usually smoked mentholated cigarettes, and 3742 of 5028 (74.4%) usually smoked nonmentholated cigarettes. After adjusting for sex, age, race, education level, total household income, body mass index, and smoking quantity and duration, mentholated cigarette smokers were found to have significantly increased odds of stroke compared with nonmentholated cigarette smokers (odds ratio [OR], 2.25; 95% CI, 1.33-3.78), and in particular women (OR, 3.28; 95% CI, 1.74-6.19) and non–African American smokers (OR, 3.48; 95% CI, 1.70-7.13) (**Table**). There were no significant associations between mentholated cigarette smoking and hypertension, myocardial infarction, congestive heart failure, and COPD. After also controlling for health professional–diagnosed, self-reported hypertension, diabetes mellitus, and dyslipidemia, the odds of stroke remained significantly increased among all (OR,

**Table. Adjusted[a] Odds of Cardiovascular and Pulmonary Diseases Among Current Mentholated Cigarette Smokers vs Current Nonmentholated Cigarette Smokers From the 2001-2008 NHANES, Stratified by Race, Sex, and Age Group**

| | OR (95% CI)[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| Disease | All (n = 5028) | Women (n = 2289) | Men (n = 2739) | African Americans (n = 606) | Non–African Americans (n = 4422) | Age ≥70 y (n = 181) | Age <70 y (n = 4848) |
| Hypertension | 1.17 (0.84-1.62) | 1.28 (0.81-2.05) | 1.04 (0.63-1.72) | 1.61 (0.75-3.48) | 1.03 (0.68-1.56) | 1.52 (0.21-11.06) | 1.09 (0.80-1.47) |
| MI | 0.89 (0.40-1.99) | 0.47 (0.15-1.44) | 1.81 (0.59-5.49) | 1.19 (0.42-3.41) | 0.68 (0.20-2.39) | 1.08 (0.20-5.74) | 0.80 (0.26-1.79) |
| CHF | 1.32 (0.56-3.15) | 0.86 (0.26-2.83) | 2.48 (0.73-8.44) | 2.41 (0.38-15.37) | 0.53 (0.12-2.44) | 3.05 (0.11-84.59) | 1.20 (0.45-3.18) |
| Stroke | 2.25 (1.33-3.78) | 3.28 (1.74-6.19) | 0.92 (0.36-2.37) | 0.60 (0.22-1.67) | 3.48 (1.70-7.13) | 5.82 (0.58-58.41) | 1.90 (0.95-3.79) |
| COPD | 1.06 (0.50-2.22) | 1.16 (0.54-2.50) | 0.78 (0.19-3.21) | 0.37 (0.07-2.13) | 1.29 (0.56-2.95) | 1.82 (0.36-9.35) | 0.92 (0.44-1.93) |

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Surveys[3]; OR, odd ratio.

[a] Adjusted for age, sex, race, highest education level attained, total household income, body mass index, average number of cigarettes smoked in the past 30 days, average number of days respondent smoked in the past 30 days, and the age the respondent started smoking regularly.



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2.19; 95% CI, 1.05-4.58), women (OR, 3.54; 95% CI, 1.60-7.84), and non–African American (OR, 3.02; 95% CI, 1.24-7.34) mentholated cigarette smokers vs respective nonmentholated cigarette smokers.

**Comment.** To my knowledge this is the first study to report that smokers of mentholated cigarettes, and in particular women and non–African Americans, have significantly increased odds of stroke compared with nonmentholated cigarette smokers. Although potential causal links cannot be established and further research is required to confirm the findings, the association between mentholated cigarette smoking and stroke is noteworthy, given that the results are based on large population-level data, with data spanning nearly a decade, and given that the relationship is independent of multiple sociodemographic, smoking behavior, and health status confounders. The mentholated cigarette–stroke association may even be underestimated because this analysis included only current smokers and not former smokers. Increased cigarette particulate matter entering the lungs because of facilitation of reflex breath-holding through menthol-induced upper airway cold receptor stimulation[6] serves as a potential mechanism for how mentholated cigarettes might potentially cause increased stroke over nonmentholated cigarettes. It is curious why smoking mentholated cigarettes would not result in an increase in forms of cardiovascular disease, other than stroke, like myocardial infarction and hypertension. A possible explanation is that mentholated cigarettes exert some selective effects on the cerebrovascular system. Potentially in support of this theory, smoking mentholated cigarettes has been found to result in increased carotid artery stiffness compared with smoking nonmentholated cigarettes,[7] whereas equal decreases in coronary artery reserve flow[8] were observed between the 2 cigarettes types.

Other potential explanations for the mentholated cigarette–stroke relationship deserve mention. First, smokers with stroke may have a greater predisposition for smoking mentholated cigarettes than regular cigarettes (ie, reverse causality). Second, confounders not included in the analysis may potentially explain the association (eg, the presence or not of medical therapy). Third, the mentholated cigarette–stroke relationship may be erroneous, as a result of several sources of potential bias associated with the analysis (eg, recall bias, prevalence bias). Finally, there is less than 5% probability that the association found between mentholated cigarette smoking and stroke is one of chance. The fact that multiple disease outcomes were examined increases to some degree the finding of a "chance" association.

These results highlight the need for further review of the last legally allowed tobacco additive in North America, given that mentholated cigarettes may be placing individuals at even greater risk of potentially devastating cerebrovascular disease than regular cigarettes.

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## Use of Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers and Cardiovascular Outcomes in Chronic Dialysis Patients: A Population-Based Cohort Study

Routine use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) for the treatment of cardiovascular disease is well established.[1,2] However, because most randomized controlled trials have excluded patients with advanced chronic kidney disease,[3] the role of ACEIs/ARBs in chronic dialysis patients remains poorly defined. Our objective was to determine whether ACEI/ARB use is associated with a reduction in mortality and major adverse cardiovascular events in older chronic dialysis patients.

**Methods.** We conducted a retrospective, population-based cohort study using linked health care databases in Ontario, Canada. To minimize bias, we used a new-user study design.[4] The study population was composed of older chronic dialysis patients in Ontario (age ≥66 years) who were newly treated with ACEIs/ARBs, calcium channel blockers (CCBs), or statins between July 1, 1991, and July 31, 2007. We selected new treatment with ACEIs/ARBs as the exposure group and treatment with CCBs or statins only as the comparator groups to minimize confounding by indication and because CCBs and statins have not been shown to be clearly beneficial in this population. We excluded patients with missing demographic information or incomplete drug records.



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