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Stroke risk among menthol versus non-menthol cigarette smokers in the United States: Analysis of the National Health and Nutrition Examination Survey (NHANES)

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ABSTRACT

Though available evidence is relatively consistent in showing no additional health effects among smokers due to menthol in cigarettes, two studies reported conflicting results for stroke risk using different subsets of NHANES data. We investigated reasons for the differences in these reports by analyzing NHANES cycles conducted between 1999 and 2012, combined and in subsets. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) from three different survey logistic regression models compare risk of reported stroke diagnoses among menthol and non-menthol cigarette smokers. Depending on time-frame, about 1150 to 8000 U.S. adults (aged ≥ 20 years) who smoked on ≥ 1 of the last 30 days had complete data for cigarette type and all covariates included in each model. Results were not much affected by which covariates were included in the models, but depended strongly on the NHANES cycles included in the analysis. Using NHANES 1999–2012 data combined, AORs and 95% CIs for stroke comparing menthol with non-menthol cigarette smokers were 0.95 (95% CI: 0.65, 1.37), 0.85 (95% CI: 0.59, 1.23) or 0.86 (95% CI: 0.59, 1.25). Collectively, findings illustrate the need for fully reporting research and analytical methods, especially when analyses are meant to develop evidence intended for regulatory decision-making.

1. Introduction

Regardless of type (i.e., menthol or non-menthol), cigarette smoking is associated with a variety of adverse health effects, including increased risks of cardiovascular and non-cancer pulmonary disease (Centers for Disease Control and Prevention (CDC), 2008). These diseases are among the leading causes of death in the United States (U.S.), and account for approximately 31% and 6% of all deaths, respectively (Xu et al., 2016). In 2010, an estimated 20.7 million U.S. smokers reported use of menthol cigarettes (Substance Abuse and Mental Health Services Administration (SAMHSA), 2011), and in 2012 menthol cigarettes accounted for an estimated 31% of the cigarette market (Federal Trade Commission (FTC), 2015). Evidence suggests that in the U.S., women, young adults, and African Americans prefer menthol cigarettes (Curtin et al., 2014; Substance Abuse and Mental Health Services Administration (SAMHSA), 2011).

The U.S. Food and Drug Administration (FDA) has examined differences between menthol and non-menthol cigarettes in terms of palatability, addictiveness, and the potential for health risks (Food and Drug Administration (FDA), 2011). Reliable evidence on adverse effects of menthol related to these areas could lead the FDA to restrict or ban menthol in cigarettes. There are limited data available, however, that allow comparisons regarding the risks for these health effects among smokers of menthol compared to non-menthol cigarettes, and the few studies that have been conducted suggest little or no difference in risks due to cigarette type. For example, three prospective cohort studies revealed no increased

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mortality from cardiovascular disease or heart disease (Jones et al., 2013a; Murray et al., 2007), coronary calcification, or decreased pulmonary function (Pletcher et al., 2006) among menthol compared to non-menthol cigarette smokers. There were no statistically significant differences in risks reported in cross-sectional analyses comparing the prevalence of peripheral artery disease (Jones et al., 2013b), chronic obstructive pulmonary disease (COPD), or other comorbid outcomes including cardiovascular disease, congestive heart failure (CHF), peripheral vascular disease (Park et al., 2015), or asthma (Mendiondo et al., 2010). Clinical studies of acute heart and vascular function have generally reported similar smoking-related effects among menthol and non-menthol cigarette smokers, with the exception of a few cardiovascular parameters (e.g., ventricular tissue Doppler velocities, relaxation and contraction indices, systolic blood pressure, heart rate, rate-pressure product, and measures involving the elastic properties of the carotid artery) with uncertain clinical relevance (Ciftci et al., 2008a, 2008b, 2009; Pickworth et al., 2002). In 2013, the FDA presented a preliminary evaluation of the available literature on the public health effects of menthol in cigarettes, including whether use of menthol compared to non-menthol cigarettes increases the risk of smoking-attributable disease Food and Drug Administration (FDA) (2013). Consistent with the data summarized above, Food and Drug Administration (FDA) (2013) reported that "the weight of evidence supports the conclusion that menthol in cigarettes is not associated with an increase in disease risk to the user compared to non-menthol cigarette smokers."

In contrast to the generally consistent messages identified above, two recent publications reported contradictory findings from analyses of data from the National Health and Nutrition Examination Survey (NHANES). Vozoris reported a statistically significantly increased odds of stroke diagnosis among menthol compared to non-menthol cigarette smokers, in particular among non-African Americans (Vozoris, 2012), while Rostron did not detect a difference in stroke risk among smokers of menthol compared with non-menthol cigarettes (Rostron, 2014). These estimates employed different cycles of the NHANES. The purpose of these analyses is to examine reasons for the differences in these two sets of results (Rostron, 2014; Vozoris, 2012) by first replicating the methods reported by each author, and then by providing results from "cross-model validation", whereby each author's model was applied to the data used by the other. In addition, this paper presents findings from a new model estimating the odds of stroke among menthol compared to non-menthol cigarette smokers, using data from all NHANES cycles conducted between 1999 and 2012. Collectively, findings from these analyses illustrate the need for clear reporting of research methods in the peer-reviewed literature. This need may be especially critical within the context of developing evidence that is intended to be used for policy and/or regulatory decision-making.

2. Methods

NHANES is a nationally representative survey of U.S. non-institutionalized civilians. It is conducted in two year cycles, with approximately 10,000 individuals in each cycle. Interviews elicit information on demographic characteristics (e.g., age, gender, race/ethnicity), smoking habits, and whether a health professional had ever diagnosed the participant with certain medical conditions, including cardiovascular and pulmonary diseases. Cycles of the NHANES can be combined, or they can be analyzed individually. Because NHANES employs a complex, multistage sampling strategy, survey statistics must be used to analyze the data and to generalize findings to the U.S. population. In this case, we used the SURVEYLOGISTIC procedure of SAS/STAT© version 9.4 to perform logistic regression accounting for the complex sampling design. Specifically, we used the masked variance pseudo-primary sampling unit (SMDVPSU) and the masked variance pseudo-stratum (SDMVSTRA) variables, the adjusted 2 year interview weight (WTINT2YR), and used Taylor series linearization to estimate the covariance matrix. Weights were adjusted for the inclusion of multiple surveys (Johnson et al., 2013) by dividing the WTINT2YR variable by the number of cycles used in each analysis. We additionally ran all models within strata defined by age, race/ethnicity, and gender using the SAS DOMAIN statement to specify these subpopulations and to ensure the variance and standard errors were calculated correctly.

Following both Vozoris and Rostron, we defined current smokers as those who had smoked on $\geq$ 1 of the last 30 days and who were $\geq$20 years old at the time of the interview. Covariates included: age, gender, race/ethnicity, education level, body mass index, the ratio of family income to the poverty threshold (PIR, an indication of income), average number of cigarettes smoked in the last 30 days, number of days smoked in the last 30 days, age the respondent started smoking regularly, and tobacco products use in the last five days (yes/no). Cases were identified by their self-reported diagnoses according to the question "has a doctor or other health professional ever told you that you had [high blood pressure, a heart attack, congestive heart failure, a stroke, or COPD (emphysema or chronic bronchitis)]" (yes/no). Outcomes other than stroke were selected to support additional analyses (reported in Van Landingham et al., 2017; Data in Brief, in press). All other responses were considered to be a non-response and were set to missing. Variables we used are presented in Table 1 of Van Landingham et al. Data in Brief, in press.

We attempted to replicate the analyses described by Vozoris (2012) and Rostron (2014) using the same survey cycles and covariates they reported. Vozoris (2012) reported analyzing NHANES 2001 to 2008, and Rostron (2014) reported analyzing NHANES 1999 to 2010. Both used as covariates age, gender, race/ethnicity, and body mass index. Vozoris (2012) included educational attainment and total household income, while Rostron (2014) used PIR. For indicators of cigarette smoking, Rostron computed pack-years of smoking (i.e., number of cigarettes smoked per day/20 cigarettes per pack $\times$ duration of smoking), where Vozoris (2012) used average number of cigarettes smoked per day in the last 30 days, the number of days the respondent smoked in the last 30 days, and the age the respondent started smoking. Neither author specified the criteria used to select covariates. To determine if differences in the results reported by Vozoris (2012) and Rostron (2014) were due to the NHANES cycles analyzed or to the covariates included, we reran the models specified by each author using data from the NHANES cycles analyzed by the other author. We additionally ran the models described by Vozoris (2012) and Rostron (2014) using all NHANES cycles from 1999 through 2012.

We used purposeful selection of covariates to identify appropriate terms to include in a new model of stroke risk, using data combining NHANES cycles from 1999 to 2012 (Hosmer et al., 2013). A preliminary model consisted of cigarette type (menthol or non-menthol) and all potentially relevant covariates in addition to cigarette type, which we forced to remain in all models (Table 1, Van Landingham et al. Data in Brief, in press). We identified covariates other than cigarette type, with a p-value of greater than 0.05, dropped the covariate with the largest p-value, and refit the model. We repeated this process until only cigarette type and covariates with p-values of 0.05 or less remained (i.e. the main effects). We added back to the model each covariate that had been dropped, individually, and calculated the relative percent change in the regression coefficient for cigarette type as compared with the model containing only statistically significant covariates. If

including a given covariate resulted in a relative percent change in the regression coefficient (Eq. (1)) that was greater than 15%, we retained that covariate in the model.

$$relative\ \%\ change = \left|1 - original\ estimate/_{new\ estimate}\right| \times 100 \quad (1)$$

Once we determined the set of main effects, we explored all the possible interactions between the covariates (excluding cigarette type). We added all interaction terms with p-values less than or equal to 0.1 to the model individually, along with the main effect terms, and retained them if the interaction term and one or both of the main effects in the fully adjusted model were statistically significant (with p-values of 0.05 or less). We used domain variables to define strata according to race/ethnicities, genders, and age groups, but did not repeat the model building process. Finally, we re-ran all models for individual cycles of the NHANES in order to determine if there were anomalous or secular patterns in risk of stroke that might be missed in the combined analysis.

3. Results

Table 1 shows the unweighted numbers of observations we identified from the 2001–2008 surveys, as described by Vozoris (2012); data we identified from the combined 1999–2010 surveys, as used by Rostron (2014); and, data combined from the 1999–2012 survey cycles. It also shows the numbers of observations with complete data for the covariates included in each author's model for the survey cycles analyzed by that author. There are slight differences in counts between the data sets reported here and the counts reported in Vozoris (2012) and Rostron (2014) that cannot be explained.

Attempts to replicate the Vozoris (2012) analyses were unsuccessful. When we applied the model described by Vozoris (2012) to the 2001–2008 dataset, there was no evidence of the reported increase in adjusted odds ratios (AOR) comparing risk of stroke diagnosis among menthol compared to non-menthol cigarette smokers. We subsequently learned that the results reported in the publication (Vozoris, 2012) were based only on the 2007–2008 NHANES survey data (Vozoris, N., personal communication June 7 t h, 2014), and that the counts reported were weighted counts adjusted by the individual record weight divided by the overall mean of the weights. As shown in Table 2, limiting the replication to this one cycle produced point estimates generally similar to those reported in the publication. Specifically, when we ran the model using the 2007–2008 cycle of NHANES, stroke risk was elevated overall (AOR = 2.22, 95% confidence interval [CI]: 1.30, 3.79), among women (AOR = 3.33, 95% CI: 1.62, 6.84), among non-African-Americans (AOR = 3.59, 95% CI: 1.39, 9.24) and among respondents ages 20–70 years (AOR = 1.71, 95% CI: 0.87, 3.36). All other point estimates were less than one and had wide confidence intervals. Among participants ages ≥70 years, the odds of stroke among smokers of menthol cigarettes were 90% lower compared with smokers of non-menthol cigarettes, with a wide confidence interval (AOR = 0.10, 95% CI: 0.01, 1.74), whereas Vozoris (2012) reported an adjusted odds ratio of 5.82 (95% CI:0.58, 58.41). We have no explanation for this difference.

When we applied the model from Vozoris (2012) to the combined 1999–2010 data sets analyzed by Rostron (2014), or to the data combing NHANES cycles for 1999–2012, all point estimates became less extreme, i.e., were closer to 1.0, and all confidence intervals included 1.0 (Table 2). Of particular note, the odds of stroke among non-African Americans who smoked menthol compared with non-menthol cigarettes was 1.16 (95% CI: 0.72, 1.86) using the data from 1999 to 2010, and 1.02 (95% CI: 0.66, 1.60) using the data from 1999 to 2012. Among those ages ≥70 years, odds of stroke were 0.62 (95% CI: 0.21, 1.81) among menthol versus non-menthol cigarette smokers in the 1999–2010 data, and 0.46 (95% CI: 0.19, 1.12) in the 1999–2012 data (Table 2).

We ran the model described by Rostron using data from NHANES 1999–2010, as reported (Rostron, 2014), and found similar results compared to our estimates (Table 3). There was no statistically significant difference in odds of stroke diagnosis among menthol compared to non-menthol cigarette smokers overall or in any stratum defined by Rostron (2014), except among non-Hispanic Blacks. In this group, menthol cigarette smokers were statistically significantly less likely to report stroke diagnoses compared with non-menthol cigarette smokers (AOR = 0.52, 95% CI: 0.28, 0.97). The association was no longer statistically significant when we ran

Table 1
Unweighted Counts of Records in NHANES cycles.

	NHANES cycle(s)					
	2001–2008		1999–2010		1999–2012	
	Stroke	No stroke	Stroke	No stroke	Stroke	No stroke
Smokers 20 years and older	172	4526	255	6785	320	7828
Indication of Menthol use	165	4393	243	6503	301	7468
With Body Mass Index	172	4526	255	6785	320	7828
With Family Poverty to Income Ratio	172	4526	255	6785	320	7828
With Household Income Level[a]	172	4526	255	6785	320	7828
	Vozoris (2012) [c]		Rostron (2014) [d]		Van Landingham et al. (2017)[e]	
	Stroke	No stroke	Stroke	No stroke	Stroke	No stroke
With all covariates in author's model[b]	52	1101	195	5562	247	6434

[a] Includes observations with codes 77 = Refused and 99 = Don't know.
[b] Unweighted counts with complete data for all covariates included in the model described by each author.
[c] Counts are for records with complete data in the 2007–2008 NHANES. Covariates consist of age, gender, race, highest education level attained, total household income, body mass index, average number of cigarettes smoked in last 30 days, days smoked in last 30, age started smoking regularly (Vozoris, N. (2012). "Mentholated cigarettes and cardiovascular and pulmonary diseases: a population-based study." Archives of Internal Medicine 172(7): 590–591.
[d] Counts are for records with complete data in the 1999–2010 NHANES. Covariates consist of age, gender, race/ethnicity, pack years of smoking, body mass index (BMI), poverty:income ratio (PIR) (Rostron, B. (2014). "Menthol Cigarette Use and Stroke Risk Among US Smokers: A Critical Reappraisal." JAMA Internal Medicine 174(5): 808–809).
[e] Counts are for records with complete data in the 1999–2012 NHANES. Covariates resulting from purposeful selection consist of: age, BMI, PIR, education, gender*race/ethnicity, education*race/ethnicity, education*gender.

Table 2
Model described in Vozoris (2012) [a]: Adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) comparing risk of stroke among smokers of menthol and non-menthol cigarettes.

			Current analyses of NHANES cycle(s)					
	Described in Vozoris (2012) [a,b]		2007–2008		1999–2010		1999–2012	
Stratum:	AOR	(95% CI)	AOR	(95% CI)	AOR	(95% CI)	AOR	(95% CI)
All	2.25	(1.33, 3.78)	2.22	(1.30, 3.79)	1.03	(0.69, 1.56)	0.95	(0.65, 1.37)
Women	3.28	(1.74, 6.19)	3.33	(1.62, 6.84)	1.04	(0.62, 1.74)	0.97	(0.61, 1.54)
Men	0.92	(0.36, 2.37)	0.68	(0.30, 1.56)	0.94	(0.56, 1.60)	0.88	(0.56, 1.41)
African-Americans	0.60	(0.22, 1.67)	0.55	(0.14, 2.15)	0.68	(0.35, 1.30)	0.75	(0.44, 1.28)
Non-African Americans	3.48	(1.70, 7.13)	3.59	(1.39, 9.24)	1.16	(0.72, 1.86)	1.02	(0.66, 1.60)
Non-Hispanic Black	c	c	0.55	(0.14, 2.15)	0.68	(0.35, 1.30)	0.75	(0.44, 1.28)
Non-Hispanic White	c	c	3.18	(0.99, 10.2)	0.96	(0.54, 1.70)	0.89	(0.52.1.51)
Mexican-American	c	c	d	d	0.98	(0.19, 5.08)	0.67	(0.14, 2.28)
Ages ≥ 70 years	5.82	(0.58, 58.41)	0.10	(0.01, 1.74)	0.62	(0.21, 1.82)	0.46	(0.19, 1.12)
Ages 20 to < 70 years	1.90	(0.95, 3.79)	1.71	(0.87, 3.36)	0.95	(0.58, 1.55)	0.87	(0.55, 1.34)

[a] Vozoris, N. (2012). "Mentholated cigarettes and cardiovascular and pulmonary diseases: a population-based study." Archives of Internal Medicine 172(7): 590–591.
[b] Model controls for age, gender, race/ethnicity, and body mass index, total household income, average number of cigarettes smoked per day in the last 30 days, number of days smoked in the last 30 days, age started smoking, highest education level obtained.
[c] Strata included for comparability with Rostron (2014) analyses; not included in Vozoris (2012). Note: African-Americans are the same as Non-Hispanic Black.
[d] Not calculated: there were no cases of stroke among Mexican American smokers of menthol.

Table 3
Model described in Rostron (2014) [a]: Adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) comparing risk of stroke among smokers of menthol and non-menthol cigarettes.

			Current analyses of NHANES cycle(s)					
	Reported by Rostron (2014) [a,b]		2007–2008		1999–2010		1999–2012	
Stratum	AOR	(95% CI)	AOR	(95% CI)	AOR	(95% CI)	AOR	(95% CI)
All	0.95	(0.63, 1.44)	2.04	(1.27, 3.27)	0.95	(0.63, 1.42)	0.85	(0.59, 1.23)
Women	1.02	(0.61, 1.72)	3.17	(1.81, 5.54)	1.04	(0.62, 1.73)	0.92	(0.58, 1.46)
Men	0.74	(0.42, 1.33)	0.59	(0.22, 1.57)	0.74	(0.42, 1.29)	0.72	(0.44, 1.16)
African-Americans	c	c	0.47	(0.17, 1.33)	0.52	(0.28, 0.97)	0.61	(0.36, 1.05)
Non-African Americans	c	c	3.00	(1.28, 7.06)	1.10	(0.68, 1.78)	0.79	(0.46, 1.37)
Non-Hispanic Black	0.52	(0.28, 0.99)	0.47	(0.17, 1.33)	0.52	(0.28, 0.97)	0.61	(0.36, 1.05)
Non-Hispanic White	0.87	(0.48, 1.58)	3.00	(1.28, 7.06)	0.88	(0.49, 1.58)	0.79	(0.46, 1.37)
Mexican-American	1.12	(0.26, 4.77)	d	d	1.11	(0.23, 5.38)	0.75	(0.15, 3.85)
Ages ≥ 70 years	c	c	2.42	(0.31, 19.07)	0.38	(0.10, 1.54)	0.45	(0.16, 1.25)
Ages 20 to < 70 years	c	c	2.10	(1.17, 3.75)	1.00	(0.62, 1.61)	0.87	(0.56, 1.36)

[a] Rostron, B. (2014). "Menthol Cigarette Use and Stroke Risk Among US Smokers: A Critical Reappraisal." JAMA Internal Medicine **174**(5): 808–809.
[b] Model controls for age, gender, race/ethnicity, and body mass index, PIR, pack-years of smoking.
[c] Strata included for comparability with Vozoris (2012) analyses; not included in Rostron (2014). Note: African-Americans are the same as Non-Hispanic Black.
[d] Not calculated: there were no cases of stroke among Mexican American smokers of menthol cigarettes, and one case among smokers of non-menthol cigarettes.

the model from Rostron (2014) on the data set consisting of NHANES cycles from 1999 through 2012 (AOR = 0.61, 95% CI: 0.36, 1.05). In all other strata, point estimates were smaller and 95% confidence intervals narrower when we ran the model from Rostron (2014) using data from 1999 through 2012. Additionally, all point estimates were near or less than one, and all confidence intervals included one.

For comparability with Vozoris (2012), we also stratified these analyses according to respondent age. Among respondents ages ≥70 years, the adjusted odds ratio comparing stroke risk among smokers of menthol versus non-menthol cigarettes was 0.38 (95% CI: 0.10, 1.54) in the 1999–2010 data set and 0.45 (95% CI: 0.16, 1.25) in the 1999–2012 data set (Table 3). Among respondents ages 20–70 years, odds of stroke among smokers of menthol versus non-menthol cigarettes were 1.00 (95% CI: 0.62, 1.61) in the 1999–2010 data set and 0.87 (95% CI: 0.56, 1.36) in the 1999–2012 data set (Table 3).

Running the model from Rostron (2014) on data for NHANES for only the 2007–2008 cycle, as was done by Vozoris (2012), produced point estimates that were statistically significantly elevated in the same or similar strata that produced elevated point estimates using that model: overall (AOR = 2.04, 95% CI: 1.27, 3.27); women (AOR = 3.17, 95% CI: 1.81, 5.54); non-Hispanic White (AOR = 3.00, 95% CI: 1.28, 7.06); ages ≥ 70 years (AOR = 2.42, 95% CI: 0.31, 19.07) and ages 20–70 years (AOR = 2.10, 95% CI: 1.17, 3.75). Like the estimates produced by Vozoris (2012), these estimates were markedly higher in almost every stratum compared with the estimates based on data sets that combined multiple cycles of the NHANES data.

Table 4 shows the results of the logistic regression models we developed with purposeful selection techniques using data from the 1999 through 2012 cycles of the NHANES, combined. Similar to the results produced using the models from Vozoris (2102) and Rostron (2014) with these data, the odds of self-reported stroke diagnoses were not statistically significantly associated with cigarette type, nor meaningfully different from 1.0, overall or in most of the subgroups. Among non-Hispanic Blacks, menthol cigarette smokers had lower odds of stroke than non-menthol cigarette smokers (AOR = 0.62, 95% CI: 0.36, 1.05). Odds of stroke were also lower among menthol versus non-menthol cigarette smokers who were at least 70 years old (AOR = 0.51, 95% CI: 0.18, 1.44).

Fig. 1 shows the effect of restricting analyses to single cycles of

Table 4
Model determined by purposeful selection of covariates[a]Adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) comparing risk of stroke among smokers of menthol and non-menthol cigarettes.

NHANES cycles 1999–2012, combined		
Stratum:	AOR	(95% CI)
All	0.86	(0.59, 1.25)
Women	0.91	(0.57, 1.46)
Men	0.74	(0.45, 1.22)
African-Americans[b]	0.62	(0.36, 1.05)
Non-African Americans	0.93	(0.58, 1.46)
Non-Hispanic White	0.78	(0.45, 1.34)
Mexican-American	0.67	(0.12, 3.68)
Ages ≥ 70 years	0.51	(0.18, 1.44)
Ages 20 to < 70 years	0.95	(0.63, 1.43)

[a] Model controls for age, BMI, PIR, education, gender*race/ethnicity, education*race/ethnicity, education*gender.
[b] African-Americans comprise non-Hispanic Blacks.

1999–2010 cycles of NHANES (Vozoris, 2012; Rostron, 2014). However, using data only from the 2007–2008 cycle of NHANES, as actually analyzed by Vozoris (2012), all three models (i.e., the Vozoris model, the Rostron model, and our model) suggested statistically significant increases in the odds of self-reported diagnosis of stroke for smokers of menthol versus non-menthol cigarettes. This seems to be due to some underlying difference in the 2007–2008 NHANES data compared with data from other cycles, and highlights the importance of using the most complete available data when the purpose of the analysis is to draw causal inferences, as opposed to describing a population at a particular point in time.

Clarity and reproducibility of methods is considered a hallmark of good science, and is particularly important in carrying out research that is intended to influence public policies and regulations. These goals are more easily achieved when using publically available data, like the NHANES, whose accessibility facilitates

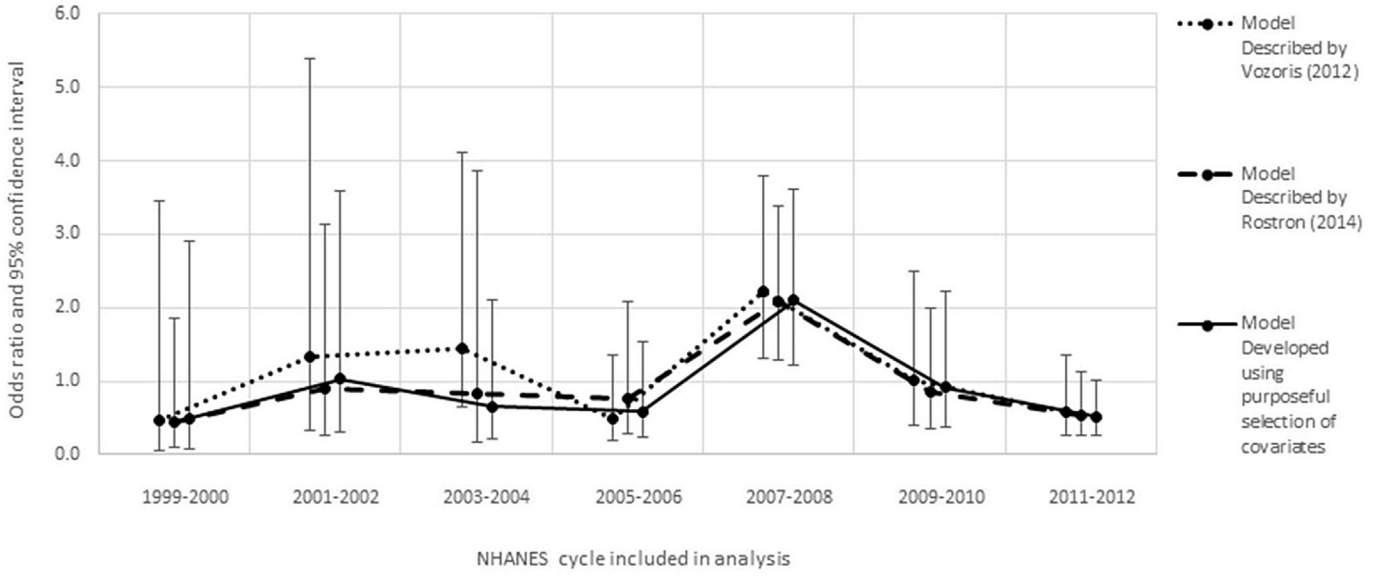

Fig. 1. Adjusted odds ratio and 95% confidence intervals: Risk of stroke among all smokers of menthol versus non-menthol cigarettes according to three different models using individual cycles of the NHANES from 1999 through 2012.

the NHANES. We applied each of the three models to estimate risk of stroke among all smokers of menthol versus non-menthol cigarettes in individual data sets: NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012. While confidence intervals are wide, the point estimates produced by the three models are generally similar to one another. All three models produce anomalously high risk estimates for the 2007–2008 cycle as compared with estimates from the other cycles of the NHANES.

4. Discussion

We examined whether reported differences in stroke risk comparing smokers of menthol and non-menthol cigarettes using different subsets of data from the 1999–2012 NHANES cycles were due to differences in the data sets or to modeling approaches. We found no evidence of higher adjusted odds of stroke among smokers of menthol compared to non-menthol cigarettes based on a model built using purposeful selection of covariates and data combining the 1999–2012 cycles of NHANES, nor when we applied models specified by other authors to data sets comprising the replication of published results. Each researcher must correctly and accurately report the data used (e.g., combination of survey cycles), any calculations used to create variables or categories in the analyses, and the methods by which the data were analyzed. The analyses reported here show that replication of results can be difficult to achieve if the methods used and adjustments made to the data are not completely or clearly reported. The results of these direct replication and cross-model validation efforts serve to highlight the importance of full and accurate disclosure of methods, including equations for key calculations, as well as the value of including descriptive results, such as the unweighted sample counts, to show the true sample sizes in survey data sets.

Overall, the results from the three models were consistent with each other when applied to the same data sets. The analyses employing the largest, most robust data sets (i.e., combining NHANES cycles 1999–2010 or 1999–2012) were consistent with each other and with the literature in suggesting no substantial increases in the risk of stroke among smokers of menthol compared with non-menthol cigarettes. Analyses of individual cycles of the NHANES survey show that the 2007–2008 cycle was different from the other cycles in the 1999–2012 period (Fig. 1). Only in this cycle

are the odds of stroke elevated. Starting with the 2007–2008 cycle, NHANES oversamples all Hispanics where previously only Mexican Americans were oversampled. However, since there were no strata that isolated Hispanics, this would not explain the difference in estimated risks. The NHANES 2007–2008 sample also included a larger percentage of respondents in the 40–59 and 60 + age groups than were seen in 2005–2006 (Centers for Disease Control and Prevention (CDC) 2009), but this would not explain why the risks estimated from later or earlier cycles differed from 2007 to 2008.

Including data from all available cycles of the NHANES serves to maximize the statistical power of the analyses, although there were still sparse numbers in some subgroups, even when data from all seven available cycles were combined, and some results were unreliable due to small numbers of cases. We propose that the most appropriate analyses should include all available, pertinent data; and, that models should be built empirically, using purposeful selection methods to produce models with the optimum set of covariates, reducing the risk of over-fitting the model and maximizing the power to detect true differences in the risk of the outcome, if they exist (Hosmer et al., 2013). Collectively, these analyses indicate that the choice of survey cycles influenced the results, and illustrate the importance of carefully and fully documenting all research and analysis methods.

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Declaration of interest

Dr. Sulsky, Ms. Van Landingham, Dr. Fuller and Mr. Mariano are all employees of Ramboll Environ where they have multiple projects with multiple clients including other tobacco companies and projects with RAIS that are outside the scope of this collaborative work. Dr. Curtin and Dr. Marano are employees of RAIS.

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References

Centers for Disease Control and Prevention (CDC), 2008. Cigarette smoking among adults—United States, 2007. Morb. Mortal. Wkly. Rep. (MMWR). 57, 1221–1226. Report date: Nov 14. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5745a2.htm.

Centers for Disease Control and Prevention (CDC), 2009. National Health and Nutrition Examination Survey, 2007-2008 Data Documentation, Codebook and Frequencies Demographic Variables and Sample Weights. http://wwwn.cdc.gov/Nchs/Nhanes/Search/DataPage.aspx?Component=Demographics%26CycleBeginYear=2007.

Ciftci, O., Caliskan, M., Gullu, H., Yildirir, A., Muderrisoglu, H., 2008. Mentholated cigarette smoking induced alterations in left and right ventricular functions in chronic smokers. Anadolu kardiyoloji dergisi AKD = Anatol. J. Cardiol. 8, 116–122.

Ciftci, O., Topcu, S., Caliskan, M., Gullu, H., Erdogan, D., Yildirim, E., Yildirir, A., Muderrisoglu, H., 2008. Smoking mentholated cigarettes impairs coronary microvascular function as severely as does smoking regular cigarettes. Acta Cardiol. 63, 135–140. http://dx.doi.org/10.2143/AC.63.2.2029518.

Ciftci, O., Gullu, H., Caliskan, M., Topcu, S., Erdogan, D., Yildirir, A., Yildirim, E., Muderrisoglu, H., 2009. Mentholated cigarette smoking and brachial artery, carotid artery, and aortic vascular function. Turk Kardiyol. Dernegi arsivi. Turk Kardiyol. Derneginin yayin organidir. 37, 234–240.

Curtin, G., Sulsky, S., Van Landingham, C., Marano, K., Graves, M., Ogden, M., Swauger, J., 2014. Patterns of menthol cigarette use among current smokers, overall and within demographic strata, based on data from four U.S. government surveys. Regul. Toxicol. Pharmacol. 70 (1), 189–196. http://dx.doi.org/10.1016/j.yrtph.2014.06.018.

Federal Trade Commission (FTC), 2015. Federal Trade Commission Cigarette Report for 2012. https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-cigarette-report-2012/150327-2012cigaretterpt.pdf.

Food and Drug Administration (FDA), 2011. Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes. http://www.fda.gov/downloads/UCM361598.pdf.

Food and Drug Administration (FDA), 2013. Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes. http://www.fda.gov/downloads/UCM361598.pdf.

Hosmer Jr., D., Lemeshow, S., Sturdivant, R., 2013. Applied Logistic Regression, third ed. John Wiley & Soncs, Inc, Hoboken, New Jersey.

Johnson, C., Paulose-Ram, R., Ogden, C., Carroll, M., Kruszon-Moran, D., Dohrmann, S., Curtin, L., 2013. National health and nutrition examination survey: analytic guidelines, 1999-2010. Natl. Cent. Health Statistics. Vital Health Stat 2 (161). http://www.cdc.gov/nchs/nhanes/survey_methods.htm.

Jones, M.R., Tellez-Plaza, M., Navas-Acien, A., 2013. Smoking, menthol cigarettes and all-cause, cancer and cardiovascular mortality: evidence from the National Health and Nutrition Examination Survey (NHANES) and a meta-analysis. PloS one 8, e77941. http://dx.doi.org/10.1371/journal.pone.0077941.

Jones, M.R., Apelberg, B.J., Samet, J.M., Navas-Acien, A., 2013b. Smoking, menthol cigarettes, and peripheral artery disease in U.S. adults. Nicotine Tob. Res. 15, 1183–1189. http://dx.doi.org/10.1093/ntr/nts253.

Mendiondo, M.S., Alexander, L.A., Crawford, T., 2010. Health profile differences for menthol and non-menthol smokers: findings from the national health interview survey. Addict. (Abingdon, Engl). 105 (124–140) http://dx.doi.org/10.1111/j.1360-0443.2010.03202.x.

Murray, R.P., Connett, J.E., Skeans, M.A., Tashkin, D.P., 2007. Menthol cigarettes and health risks in lung health study data. Nicotine Tob. Res. 9, 101–107. http://dx.doi.org/10.1080/14622200601078418.

Park, S.J., Foreman, M.G., Demeo, D.L., Bhatt, S.P., Hansel, N.N., Wise, R.A., Soler, X., Bowler, R.P., 2015. Menthol cigarette smoking in the COPDGene cohort: relationship with COPD, comorbidities and CT metrics. Respirol. Carlt. Vic.) 20, 108–114. http://dx.doi.org/10.1111/resp.12421.

Pickworth, W.B., Moolchan, E.T., Berlin, I., Murty, R., 2002. Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery. Pharmacol. Biochem. Behav. 71, 55–61. http://dx.doi.org/10.1016/s0091-3057(01)00623-2.

Pletcher, M.J., Hulley, B.J., Houston, T., Kiefe, C.I., Benowitz, N., Sidney, S., 2006. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function: the coronary artery risk development in young adults (CARDIA) study. Archives Intern. Med. 166, 1915–1922. http://dx.doi.org/10.1001/archinte.166.17.1915.

Rostron, B., 2014. Menthol cigarette use and stroke risk among US smokers: a critical reappraisal. JAMA Intern. Med. 174 (5), 808–809. http://dx.doi.org/10.1001/jamainternmed.2013.9600.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2011. The NSDUH Report: recent Trends in Menthol Cigarette Use. Center for Behavioral Health Statistics and Quality, Rockville. MD November 18. http://www.samhsa.gov/data/sites/default/files/WEB_SR_088/WEB_SR_088/WEB_SR_088.htm.

Van Landingham, C., Fuller, W., Mariano, G., Marano, K., Curtin, G., Sulsky, S., 2017. Comparing risk of cardiovascular and pulmonary diseases among smokers of menthol and non-menthol cigarettes using data from the National Health and Nutrition Examination Survey (NHANES), 1999-2012. Regul. Toxicol. Pharmacol. Data in Brief (submitted).

Vozoris, N., 2012. Mentholated cigarettes and cardiovascular and pulmonary diseases: a population-based study. Archives Intern. Med. 172 (7), 590–591. http://dx.doi.org/10.1001/archinternmed.2012.320.

Xu, J., Murphy, S., Kochanek, K., Bastian, B., 2016. Deaths: final Data for 2013. National Vital Statistics Reports, vol.64. Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (2). http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf.