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Evaluation of a reduced nicotine product standard: moderating effects of and impact on cannabis use*

Lauren R. Pacek[1,2,**], **Ryan Vandrey**[2], **Sarah S. Dermody**[3], **Rachel L. Denlinger**[4], **Andrine Lemieux**[5], **Jennifer W. Tidey**[4], **F. Joseph McClernon**[1], **Ananta S. Bangdiwala**[6], **David J. Drobes**[7], **Mustafa al'Absi**[5], **Andrew A. Strasser**[8], **Joseph S. Koopmeiners**[9], **Dorothy K. Hatsukami**[10], and **Eric C. Donny**[11]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA 27705

[2]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA 21224

[3]Centre for Addiction and Mental Health, Toronto, ON, Canada

[4]Center for Alcohol and Addiction Studies, Brown University, Providence, RI, USA 02912

[5]Department of Biobehavioral Health and Population Sciences, University of Minnesota Medical School, Duluth, MN, USA 55812

[6]Biostatistics and Bioinformatics Core, Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA 55455

[7]Department of Health Outcomes and Behavior, Moffitt Cancer Center, Tampa FL, USA 33612

[8]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA 19104

[9]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA 55455

[10]Masonic Cancer Center and Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA 55455

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**Corresponding author – Address: 2608 Erwin Road Suite 300 Durham, NC, USA 27705; Telephone: 919-684-5437; Fax: 919-681-1600; lauren.pacek@duke.edu.

Contributors

Authors Pacek and Vandrey conceptualized the research question Authors Pacek, Bangdiwala, and Koopmeiners conducted the statistical analyses. Author Pacek wrote the first draft of the manuscript. All authors contributed to, have critically reviewed and revised, and have approved of the final manuscript.

Conflict of Interest

Dr. Drobes reports other support from law firms (on behalf of individual plaintiffs) outside the submitted work, while Dr. McClernon reports previous grant support from Pfizer, Inc., outside the submitted work. Dr. Vandrey reports being a consultant for Zynerba Pharmaceutials outside the submitted work. The authors have no other conflicts of interest to declare.

[11]Department of Psychology, University of Pittsburgh, Pittsburgh PA, USA 15260

Abstract

Introduction—The Family Smoking Prevention and Tobacco Control Act authorized the FDA to reduce the nicotine content in cigarettes. Research is needed to guide proposed regulations, including evaluation of consequences to public health. This study evaluated how a reduced nicotine product standard might be moderated by and impact cannabis use.

Methods—Secondary analysis of a controlled clinical trial examining the effects of nicotine content in cigarettes in adult daily smokers. Linear regression assessed whether baseline cannabis use moderated behavioral, subjective, or physiological effects of smoking very low nicotine content (VLNC) versus normal nicotine content (NNC) cigarettes. Repeated measures analysis of associations between nicotine condition and prevalence and frequency of cannabis use was completed using generalized estimating equations (GEE).

Results—Among cannabis users and non-users, smokers randomized to VLNC cigarettes reported lower nicotine dependence, cigarettes per day, biomarkers of nicotine exposure, and craving compared to smokers randomized to NNC cigarettes. Non-cannabis using smokers randomized to VLNC cigarettes also reported lower smoking dependence motives and had lower tobacco-specific nitrosamine exposure and total puff volume versus smokers randomized to NNC cigarettes. For cannabis users, smokers randomized to VLNC cigarettes reported decreased positive affect. Cannabis use did not moderate most effects of VLNC cigarettes. VLNC cigarette use did not impact the prevalence or frequency of cannabis use.

Discussion—Findings provide evidence that nicotine reduction in cigarettes could have beneficial effects on cigarette smoking regardless of cannabis use. Results suggest that transitioning to VLNC cigarettes is unlikely to alter current rates of cannabis use.

Keywords

nicotine; cigarette; smoking; cannabis; marijuana; co-use; comorbidity

1. INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act (FSPTCA; U.S. Congress, 2009) granted the Food and Drug Administration (FDA) the authority to enact product standards that reduce the nicotine content in cigarettes. This reduction is congruent with the hypothesis that reducing the nicotine in cigarettes to a level below an addiction threshold should no longer support dependence, and reduce the public health burden of tobacco (Benowitz and Henningfield, 1994, 2013).

In a 6-week randomized multisite trial (Donny et al., 2015), participants assigned to smoke cigarettes with a nicotine content of 2.4 mg per g of tobacco or lower reported smoking fewer cigarettes per day (CPD) and had decreased biomarkers of nicotine exposure relative to participants who smoked cigarettes with normal nicotine content (NNC; i.e., 15.8 mg/g). Though these findings indicate that VLNC cigarettes may have a positive impact on smokers

generally, it remains unknown how reduced nicotine standards would impact smokers who also use cannabis.

Cannabis is the most widely used illicit drug globally; as of 2012, 10.2% and 2.1% of the U.S. population were non-daily and daily users, respectively (Pacek et al., 2015). Cannabis and tobacco are commonly used concurrently: most cannabis users smoke tobacco, and up to half of tobacco smokers use cannabis (Peters et al., 2012). In addition to concurrent use, there is evidence for these substances substituting for one another. Some co-users report increasing tobacco use to cope with withdrawal during cannabis abstinence (Allsop et al., 2014; Levin et al., 2010). Preclinical evidence indicates that THC may reduce nicotine withdrawal (Balerio et al., 2004), suggesting a negative reinforcement pathway that would promote cannabis use during tobacco abstinence. Thus, cannabis users may be differentially impacted by the effects of nicotine reduction on smoking, and reducing nicotine in cigarettes may impact cannabis use.

The present study examines how: 1) baseline cannabis use impacts responses to VLNC cigarettes; and 2) use of VLNC cigarettes impacts cannabis use. We hypothesized that cannabis users would smoke more CPD and experience more withdrawal and craving as a consequence of nicotine reduction. We hypothesized that participants assigned to VLNC cigarettes would be more likely to report cannabis use, and to report using cannabis on a greater proportion of days, as compared to participants assigned to NNC cigarettes, to compensate for the lower nicotine content and manage withdrawal symptoms.

2. METHODS

2.1 Participants

Eligible participants (*N*=839) were adult, daily smokers who: smoked ≥5 CPD, had expired carbon monoxide (CO) >8 ppm or urine cotinine >100 ng/ml; did not intend to quit smoking in next 30 days, regularly use other tobacco products or binge drink (i.e., >9 of past 30 days), have unstable medical/psychiatric conditions, positive illicit drug toxicology screen other than cannabis, exclusively use “roll your own” cigarettes, and were not pregnant/ breastfeeding.

2.2 Procedure

Methods for the 7-arm, double-blind, 10-site, randomized parent study are described elsewhere (Donny et al., 2015). After a 2-week baseline period, participants were randomly-assigned to smoke, for 6 weeks, cigarettes of varying nicotine content (15.8, 5.2, 2.4, 1.3, 0.4 mg/g) or their usual brand cigarettes. Tar yields were 8-10 g, but one of the 0.4 mg/g conditions was 13 g. At weekly visits, participants received a free 14-day cigarette supply, were instructed not to use other cigarettes, and received brief counseling to increase compliance. Menthol or non-menthol cigarettes were provided based on participant's preference. Study cigarettes were supplied by NIDA (NOT-DA-14-004).

2.3 Measures

Participants completed an assessment battery at each visit. Cannabis use was measured at baseline via self-report (i.e., past 30 day use) and urine toxicology. Timeline follow-back (TLFB) assessed on which days cannabis was used between experimental visits (Sobell and Sobell, 1992). Participants reported CPD (study and non-study cigarettes) from the prior day via an Interactive Voice Response (IVR) system that automatically called daily. Weekly averages of daily CPD were computed. Smoking topography was assessed at baseline for usual brand cigarettes, and at Weeks 2 and 6 for experimental cigarettes, using the handheld, portable version of the Clinical Research Support System (CReSS; Borgwaldt, KC Inc., Richmond, VA). Participants smoked one cigarette during each topography session; number of puffs, total puff volume, and mean puff volume were measured.

Participants provided expired breath CO samples at the beginning of each session, immediately prior to, and 15 minutes following smoking topography assessments. CO readings assess recent smoking, and the CO boost from pre- to post-smoking. Liquid chromatography with tandem mass spectrometry was used to determine nicotine exposure at baseline, Week 2, and Week 6, via urinary total nicotine equivalents (TNE), baseline salivary nicotine metabolite ratio (NMR), and urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL; Carmella et al., 2013; Murphy et al., 2014, 2013).

Nicotine dependence was assessed via the Fagerström Test for Nicotine Dependence at baseline, Week 2, and 6 (FTND; Heatherton et al., 1991) and the 37-item version of the Wisconsin Index of Smoking Dependence Motives at baseline and Week 6 (WISDM; Smith et al., 2010). Weekly assessments measured withdrawal symptoms using the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami, 1986), and craving using the Questionnaire on Smoking Urges–Brief scale (QSU; Cox et al., 2001). The QSU has two factors: craving for positive reinforcing effects (Factor 1) and craving to reduce abstinence-related negative affect (Factor 2).

At baseline and Week 6, the Center for Epidemiological Studies–Depression (CES-D) Scale assessed depression symptoms (Radloff, 1977). At baseline, Weeks 2 and 6, the Perceived Stress Scale-4 (PSS-4 (Cohen et al., 1983) assessed stress related to current, objective events, and the Positive and Negative Affect Scale (PANAS) measured positive and negative affect (Watson et al., 1988).

2.4 Statistical analyses

To maximize statistical power, the two NNC conditions (i.e., usual brand, 15.8 mg/g) were combined and compared with four VLNC conditions (0.4–2.4 mg/g), as these conditions had similar effects in the parent study (Donny et al., 2015). The 5.2 mg/g condition was excluded due to inconsistent effects in the overall sample (e.g., compared to 15.8 mg/g, it resulted in similar CPD but reduced nicotine exposure (Donny et al., 2015)), and to remain consistent with prior secondary analyses (Tidey et al., In press). This lead to a sample size of n=717 for this analysis.

Linear regression examined the effects of baseline cannabis use and nicotine condition on Week 6 outcome measures. Baseline cannabis use was defined as self-reported past 30 day

use and/or a THC-positive urine sample. Models controlled for baseline levels of each variable (i.e., unadjusted model), and adjusted models further controlled for sex, age (continuous), race (Caucasian, African American, other), education (<12; ≥12 years), nicotine condition, FTND, and NMR. Interactions between baseline cannabis use and nicotine condition were examined using the same methods. Standardized treatment effects were also calculated for both of the aforementioned analyses. Using identical methods, sensitivity analyses assessed whether heaviness of baseline cannabis use (<15 days/month; ≥15 days/month) differentially impacted associations between nicotine condition and outcome measures.

Repeated measures analyses using generalized estimating equations (GEE) modeled cannabis use throughout the study. A longitudinal logistic model assessed whether prevalence of cannabis use was associated with nicotine condition, while Poisson regression —offset by the number of days between visits—assessed whether the proportion of days using cannabis was associated with nicotine condition. Unadjusted models included: nicotine condition, baseline use, visit, and a nicotine condition-by-visit interaction. Non-significant interaction terms were removed. P-values <0.05 were considered statistically significant. Analyses were conducted using STATA statistical software version 14.0 (StataCorp, 2015) and SAS software version 9.4 (SAS, 2013).

3. RESULTS

3.1 Baseline characteristics of cannabis users versus non-users

At baseline, 28.9% participants were current cannabis users. Of these, 71.5% reported cannabis use and tested positive for THC; 16.4% reported use but tested negative for THC; 12.1% tested positive for THC but did not report use. Current cannabis users self-reported using cannabis on 11.3 days/past month (*SD* = 11.7). Relative to non-users, cannabis users were more likely to be male χ^2 (1, *N*=717)=8.8, *p*=0.003; Caucasian χ^2 (2, *N*=717)=8.0, *p*=0.018; younger *t*(715)=10.2, *p*<0.001; had higher PANAS negative affect scores *t*(714)= −2.0, *p*=0.045; smoked fewer CPD *t*(711)=2.1, *p*=0.033; and lower FTND scores *t*(715)=3.9, *p*<0.001 (Table 1). During baseline *ad libitum* smoking, cannabis users had smaller total puff volumes *t*(648)=2.3, *p*=0.022 and smaller mean puff volumes *t*(648)=3.6, *p*<0.001 versus non-cannabis users.

3.2 Baseline characteristics of participants in NNC versus VLNC conditions

There were no differences between NNC participants versus VLNC participants on sociodemographic characteristics (Supplementary Table 1[1]). NNC condition participants had lower baseline CO readings *t*(715)=2.8, *p*=0.006; higher QSU scores *t*(715)=2.5, *p*=0.012; fewer puffs *t*(648)=−2.1, *p*=0.039; and lower total puff volumes *t*(648)=−2.3, *p*=0.022 compared with VLNC participants.

[1]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

3.3 Impact of baseline cannabis use on outcomes

VLNC cigarettes significantly decreased CPD, FTND scores, QSU scores, and TNE in cannabis users and non-users (Table 2). VLNC cigarettes significantly decreased WISDM, total NNAL, total puff count, and total puff volume among non-cannabis users, while significantly decreasing PANAS positive affect scores among cannabis users. Cannabis use significantly moderated the effect of VLNC cigarettes on QSU Factor 1 scores: cannabis users exhibited greater decreases in QSU Factor 1 scores than non-cannabis users (p=0.049). Standardized treatment effects are reported in Supplementary Table 2[2]. Sensitivity analyses indicated that baseline heaviness of cannabis use did not moderate the effect of VLNC cigarettes on Week 6 outcomes (Supplementary Table 3[3]).

3.4 Effect of nicotine condition on cannabis use

At Week 6, 33.1% of the remaining 768 were cannabis users: 79.5% of these self-reported use and tested positive for THC, and 20.5% self-reported past-month use but tested negative. When comparing baseline cannabis use to self-reported use via the TLFB during the study, 44 (9%) individuals appeared to initiat cannabis use during the course of the study. However, in adjusted analyses, the odds of cannabis use in the VLNC group was not significantly different than the odds of cannabis use in the NNC group (aOR=0.89; 95% CI=0.57-1.38; p=0.600; not shown). Furthermore, assignment to VLNC versus NNC cigarettes was not associated with days of cannabis use (adjusted multiplicative change in proportion=0.87; 95%=CI 0.67-1.12; p=0.280; not shown).

4. DISCUSSION

Findings indicate that effects of smoking VLNC cigarettes in cannabis users are largely similar to those in non-cannabis users. Cannabis users and non-users experienced reductions in CPD, nicotine dependence, craving, and TNEs. Though differences between cannabis and non-cannabis users were observed on the WISDM, PANAS, and smoking topography during the experimental cigarette period, the lack of significant interactions indicate that baseline cannabis use did not moderate the effect of VLNC cigarettes on these outcomes. One exception emerged: cannabis users experienced greater reductions in Factor 1 scores than non-users, though this was marginally statistically significant and likely to be of limited clinical significance.

Nicotine condition did not impact the prevalence of or proportion of days using cannabis during the experimental cigarette use period. When considering a change in policy regarding the level of nicotine in cigarettes it is important to consider unintended consequences in subgroups who may be at risk of increased harm. In this case, nicotine reduction did not increase cannabis use.

Study limitations include participants' non-compliance with study cigarettes (Nardone et al., 2016). Though nicotine reduction has not led to compensatory drinking (Dermody et al., 2016), we are unable to examine the impact on other substances because individuals testing

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[3]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

positive for other illicit substances were excluded from the study. The duration of the trial was only 6 weeks, thus the full effects of VLNC cigarettes may not have been actualized. Longer trials, and trials that include substance users, will address these limitations.

This investigation had several strengths including the longitudinal and prospective examination of this topic, and the large multisite design with a diverse population of smokers. Findings indicate that cannabis use does not have a negative impact on smoking outcomes following 6 weeks of exposure to VLNC cigarettes, nor does VLNC cigarette use have an impact on cannabis use. Though additional research is needed to investigate other vulnerable populations, this work demonstrates that cigarette reduced nicotine product standards are unlikely to differentially impact cannabis users with regards to smoking, or have an unintended impact on cannabis use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Cannabis users and non-users differed on demographic and smoking characteristics
- Cannabis use did not moderate most effects of very low nicotine content cigarettes
- Very low nicotine content cigarette use did not significantly impact cannabis use

Table 1

Baseline sociodemographic and mental health characteristics of current cannabis users versus non-cannabis users (n=717)

Characteristic	Non-cannabis users (n=510) Mean (SD)	Cannabis users (n=207) Mean (SD)	p-value
Male – n (%)	**276 (54.1)**	**137 (66.2)**	**0.003**
Age	**44.6 (12.4)**	**34.2 (12.5)**	**<0.001**
Race – n (%)			
Caucasian	**253 (49.6)**	**117 (56.5)**	**0.018**
African American	**208 (40.8)**	**62 (29.9)**	
Other	**49 (9.6)**	**28 (13.5)**	
Education – n (%)			
<College	226 (44.3)	87 (42.0)	0.576
Attended college	284 (55.7)	120 (58.0)	
Treatment condition – n (%)			
NNC	166 (32.5)	71 (34.3)	0.652
VLNC	344 (67.5)	136 (65.7)	
CESD Score	8.6 (7.1)	9.5 (6.3)	0.108
PSS Score	4.4 (2.8)	4.7 (2.7)	0.142
PANAS positive affect	34.7 (7.8)	34.1 (7.3)	0.369
PANAS negative affect	**15.6 (5.7)**	**16.5 (5.6)**	**0.045**
CPD	**15.8 (7.8)**	**14.5 (6.8)**	**0.033**
FTND Score	**5.3 (2.2)**	**4.6 (2.3)**	**<0.001**
CO	15.1 (7.6)	15.3 (8.8)	0.796
QSU Total Score	30.2 (14.8)	30.0 (14.5)	0.894
QSU Factor 1	19.5 (9.3)	19.5 (9.1)	0.975
QSU Factor 2	10.7 (6.6)	10.5 (6.6)	0.802
MNWS Score	6.5 (5.1)	7.1 (4.7)	0.127
WISDM	42.0 (13.2)	40.7 (11.4)	0.241
TNE*	41.7 (45.7)	42.2 (42.8)	0.876
NNAL*	1.1 (1.6)	1 (1.4)	0.165
Number of puffs	15.3 (5.7)	15.4 (5.3)	0.706
Total puff volume	**774.7 (316.5)**	**713.1 (301.4)**	**0.023**
Mean puff volume	**53.0 (17.5)**	**47.6 (16.4)**	**<0.001**

Note: Bolded text indicates statistically significant findings p<0.05

Abbreviations: NNC=normal nicotine content; VLNC=very low nicotine content; CESD=Centers for Epidemiological Studies of Depression Scale; PSS=Perceived Stress Scale; PANAS=Positive and Negative Affect Scale; CPD=cigarettes per day; FTND=Fagerström Test for Nicotine Dependence; CO=carbon monoxide; QSU=Questionnaire of Smoking Urges; MNWS=Minnesota Nicotine Withdrawal Scale; WISDM=Wisconsin Inventory of Smoking Dependence Motives; TNE=total nicotine equivalents; NNAL=a biomarker of [NNK] exposure

*Geometric means are presented for TNE and NNAL

Table 2

Mean differences between VLNC and NNC conditions at the post-randomization Week 6 visit in cannabis users versus non-users, and p-values for tests of interactions between baseline cannabis use status and nicotine content.

	Unadjusted Model[a]			Adjusted Model[b]		
Outcome	**No Cannabis Use**	**Cannabis Use**	**Interaction *p*-value**	**No Cannabis Use**	**Cannabis Use**	**Interaction *p*-value**
FTND	**−0.92 (−1.22, −0.62)**	**−0.57 (−1.00, −0.13)**	0.202	**−0.94 (−1.25, −0.64)**	**−0.58 (−1.01, −0.14)**	0.246
QSU total score	**−4.53 (−6.90, −2.15)**	**−9.14 (−12.56, −5.73)**	0.072	**−4.49 (−6.92, −2.07)**	**−8.96 (−12.49, −5.42)**	0.069
QSU Factor 1	**−3.29 (−4.75, −1.84)**	**−5.93 (−8.10, −3.75)**	0.065	**−3.22 (−4.70, −1.73)**	**−5.89 (−8.12, −3.66)**	**0.049**
QSU Factor 2	**−1.36 (−2.41, −0.31)**	**−3.21 (−4.73, −1.69)**	0.124	**−1.40 (−2.47, −0.32)**	**−3.04 (−4.62, −1.46)**	0.166
MNWS	−0.61 (−1.45, 0.23)	−0.05 (−1.26, 1.16)	0.457	−0.74 (−1.58, 0.10)	−0.14 (−1.43, 1.14)	0.511
CESD	−0.36 (−1.81, 1.08)	0.09 (−2.22, 2.40)	0.732	−0.54 (−2.01, 0.92)	0.35 (−2.09, 2.78)	0.564
PSS	−0.22 (−0.72, 0.29)	−0.02 (−0.82, 0.78)	0.685	−0.22 (−0.74, 0.29)	0.02 (−0.80, 0.83)	0.631
PANAS positive affect	−0.24 (−1.56, 1.09)	−1.85 (−3.90, 0.21)	0.181	−0.28 (−1.63, 1.06)	**−2.25 (−4.33, −0.17)**	0.106
PANAS negative affect	0.05 (−0.96, 1.07)	−0.65 (−2.34, 1.04)	0.512	−0.14 (−1.14, 0.86)	−0.61 (−2.36, 1.15)	0.559
WISDM	**−4.13 (−6.00, −2.26)**	−0.51 (−3.38, 2.35)	**0.042**	**−4.37 (−6.20, −2.53)**	−0.94 (−3.84, 1.96)	0.074
CO	−0.64 (−2.07, 0.78)	−1.49 (−3.64, 0.67)	0.377	−0.56 (−2.01, 0.89)	−1.69 (−3.93, 0.55)	0.298
CPD	**−6.08 (−7.51, −4.64)**	**−6.68 (−8.89, −4.48)**	0.734	**−6.19 (−7.63, −4.74)**	**−6.54 (−8.82, −4.26)**	0.748
TNE[c]	**−0.80 (−1.04, −0.56)**	**−0.61 (−1.00, −0.22)**	0.395	**−0.76 (−1.00, −0.52)**	**−0.61 (−1.02, −0.20)**	0.458
NNAL[c]	**−0.30 (−0.46, −0.13)**	−0.22 (−0.48, 0.04)	0.641	**−0.28 (−0.45, −0.11)**	−0.19 (−0.46, 0.08)	0.560
Puff count	**−1.55 (−2.38, −0.73)**	−0.97 (−2.44, 0.51)	0.468	**−1.58 (−2.42, −0.73)**	−1.04 (−2.6, 0.52)	0.572
Total puff volume	**−107.85 (−154.73, −60.98)**	−51.48 (−123.92, 20.96)	0.250	**−97.81 (−145.25, −50.37)**	−66.96 (−144.26, 10.34)	0.574
Mean puff volume	−1.12 (−4.02, 1.79)	−0.8 (−5.40, 3.81)	0.853	−0.57 (−3.51, 2.36)	−1.59 (−6.34, 3.16)	0.773

Note: Bolded text indicates statistically significant findings p<0.05

Outcomes are expressed as differences between the VLNC and NNC conditions. Negative values indicate that those in the VLNC condition reported lower scores on a measure relative to those in the NNC condition.

Abbreviations: NNC=normal nicotine content; VLNC=very low nicotine content; CESD=Centers for Epidemiological Studies of Depression Scale; PSS=Perceived Stress Scale; PANAS=Positive and Negative Affect Scale; CPD=cigarettes per day; FTND=Fagerström Test for Nicotine Dependence; CO=carbon monoxide; QSU=Questionnaire of Smoking Urges; MNWS=Minnesota Nicotine Withdrawal Scale; WISDM=Wisconsin Inventory of Smoking Dependence Motives; TNE=total nicotine equivalents; NNAL=a biomarker of [NNK] exposure

[a] Adjusted for baseline value only

[b] Adjusted for age, race, sex, education, and NMR, along with baseline value

[c] Findings are expressed as odds ratios - Associations between nicotine content and TNE and NNAL were summarized by the ratio of the geometric mean from the VLNC condition relative to the geometric mean from the NNC condition