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Original Investigation

Blood Nicotine Predicts the Behavioral Economic Abuse Liability of Reduced-Nicotine Cigarettes

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Abstract

Background: Cigarette smoking continues to be a major health concern and remains the leading preventable cause of death in the US. Recent efforts have been made to determine the potential health and policy benefits of reducing nicotine in combustible cigarettes. The degree to which changes in blood nicotine relate to measures of the abuse liability of reduced-nicotine cigarettes is unknown. The current study examined the relation between blood nicotine and behavioral economic demand measures of cigarettes differing in nicotine content.

Methods: Using a within-subject design, participants smoked a single cigarette during each experimental session. Cigarettes included the participant's usual-brand cigarette and SPECTRUM investigational cigarette differing in nicotine level (mg of nicotine to g of tobacco; 15.8 mg/g, 5.2 mg/g, 2.4 mg/g, 1.3 mg/g, and 0.4 mg/g). During each session, blood was collected at multiple timepoints and behavioral economic demand was assessed. Nonlinear mixed-effects models were used to estimate differences in derived intensity (Q_0) and change in elasticity (α).

Results: Measures of blood nicotine decreased in an orderly fashion related to nicotine level and significantly predicted change in elasticity (α), but not derived intensity. No differences in demand parameters between the usual brand and 15.8mg/g cigarettes were observed. However, α was significantly higher (lower valuation) for 0.4mg/g than 15.8mg/g cigarettes.

Conclusions: The lowest nicotine level (0.4mg/g) corresponded with the lowest abuse liability (α) compared to the full-strength control (15.8mg/g), with the 1.3mg/g level also resulting in low abuse liability.

Implications: This is the first study examining the relative contributions of nicotine content in cigarettes and blood nicotine levels on the behavioral economic demand abuse liability of cigarettes ranging in nicotine content. Our results suggest blood nicotine and nicotine content both predict behavioral economic demand abuse liability. In addition, our results suggest a nicotine content of 1.3mg/g or lower may be effective at reducing cigarette uptake among first-time (naïve) smokers. Our results largely conform to previous findings suggesting a very low nicotine content cigarette maintains lower abuse liability than full-strength cigarettes.

Introduction

Cigarette smoking, the leading preventable cause of death, is associated with a myriad of negative health consequences including cancer and death.[1] Annual US costs associated with cigarette smoking are estimated at over $300 billion.[1] Nicotine is one of the primary addictive constituents in combustible cigarettes.[2] Some have proposed that limiting the amount of nicotine in combustible cigarettes could benefit individuals and society, including decreased dependence and a lower likelihood of initiation among new smokers.[3–5] In 2009, the Food and Drug Administration (FDA) was granted authority to regulate the amount of nicotine in combustible cigarettes. Recently, FDA and scientific inquiry examined the potential impacts of reducing nicotine in combustible cigarettes to nonaddictive levels.[6] The current paper contributes to this body of literature by investigating nicotine levels low enough that may reduce the likelihood of initiation by first-time smokers and help current smokers abstain or transition to harm-reducing alternatives.

Tools from the field of behavioral economics show promise for evaluating the abuse liability of drugs, including alcohol and cigarettes.[7–9] In behavioral economic studies, valuation is measured by a person's willingness to incur escalating costs to obtain the drug or substance of interest[10–12] and this reinforcing efficacy is typically assessed using the Cigarette Purchase Task (CPT[13–15]), a self-report measure whereby participants report the number of cigarettes they would purchase and consume at several different price points. Generally, there is good evidence demonstrating the validity and reliability of the CPT as a valuable tool in understanding cigarette use factors.[16–18] The behavioral economic framework and associated tools could help understand one aspect of the complex relation between proposed nicotine levels in cigarettes and the resulting abuse liability, ultimately informing policy efforts.[8,19] That is, reducing nicotine levels in combustible cigarettes may result in lower valuation, resulting in decreased initiation, dependence, and use.[20]

Several studies have examined reduced-nicotine cigarettes within a behavioral economic paradigm.[21–29] Overall,

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two main findings have emerged. First, behavioral economic measures typically show higher demand valuation (as measured by willingness to pay more) for participants' usual brand cigarettes than any of the research cigarettes, suggesting that usual brand cigarettes maintain higher valuation.[29] Second, behavioral economic measures reflecting significantly lower valuation are typically observed among only the lowest nicotine levels (e.g., 1.3, 0.4 mg/g [mg nicotine per g of tobacco]), suggesting cigarettes with low nicotine content maintain the lowest abuse potential. Furthermore, all the behavioral economic cigarette abuse liability research has examined cigarette demand in relation to the cigarettes' nicotine *content*. We are aware of no studies comparing blood nicotine obtained from reduced-nicotine cigarettes and the associated behavioral economic demand measures, especially within a parametric analysis of nicotine content. Although they did not investigate reduced-nicotine content cigarettes, Higgins and colleagues[30] found nicotine intake, COT+3HC (measured by a combination of cotinine [nicotine metabolite] and 3'-hydroxycotinine), from usual brand cigarettes was significantly related to dependency measures (e.g., Fagerström Test of Nicotine Dependence, Heaviness of Smoking Index) and one dimension of behavioral economic demand (Amplitude, which corresponds with the number of cigarettes purchased at "free" price). This finding suggests behavioral economic demand measures may be sensitive to changes in physiological states. Blood nicotine is a more direct measure of nicotine exposure as not all nicotine present in tobacco will be absorbed by the smoker, so assessing blood nicotine allows us to more conclusively relate nicotine content of tobacco to abuse liability of cigarettes.

Many previous studies have used traditional modeling methods relying on fitting group-level curves or by using a two-stage approach (whereby demand parameters are obtained by fitting a single curve per participant and per cigarette and using these estimates in subsequent statistical tests). Both methods present statistical limitations, most notably in how error (the difference between model predictions and observed data) is handled. Population-level (i.e., group-level) models implicitly assume independence across all data points and ignore subject dependency, whereas downstream (i.e., second stage) analyses from the two-stage approach treats estimates from the first stage as known constants with no variability. Furthermore, in some cases, the two-stage method results in non-estimable parameters for some participants given highly specific response patterns (or as some may consider unsystematic). Mixed-effects modeling, therefore, is a superior approach compared to more traditional methods as this type of modeling: 1) recognizes the inherent clustering of the data (e.g., cigarette prices are clustered within participant) and appropriately incorporates this information into the standard error of the demand estimate; 2) provides both population-level (i.e., group-level) parameter estimates and individual predictions; 3) can incorporate nonsystematic datasets that may not be estimable by themselves; and 4) integrates covariates of interest within a single model. A more thorough and in-depth discussion about the relative benefits of mixed-effects modeling for behavioral economic demand data can be found in Kaplan et al.[31] We are aware of no studies using nonlinear mixed-effects modeling to examine these research cigarettes' abuse liability in human participants. To identify nonaddictive nicotine levels in cigarettes, the current study had two goals. First, quantify differences in blood nicotine across usual-brand cigarettes and SPECTRUM cigarettes differing in nicotine level. We hypothesized blood nicotine would be highest among the usual brand and the full-strength SPECTRUM cigarettes (15.8 mg/g) and decrease dependently with nicotine level. Second, investigate the relative contributions of nicotine content in the cigarettes and blood nicotine on behavioral economic measures of abuse liability within a parametric analysis. We hypothesized nicotine content and blood nicotine would both significantly relate to behavioral economic measures of abuse liability. To efficiently study these variables with a high degree of experimental control, we incorporated a double-blinded, within-subject demand procedure where all participants sampled all nicotine levels in a randomized order across sessions and completed behavioral economic tasks. This procedure maximized our ability to detect relationships between demand and blood nicotine but was not powered to detect relationships with demographic or use severity measures. This paper advances previous research by using sophisticated behavioral economic demand modeling methods[31] and examining physiological measures of nicotine as they relate to the abuse liability of cigarettes differing in nicotine content.

Methods

Participants

We recruited a total of 122 participants from the community surrounding and including Roanoke, VA during 2017–2019. Eligibility criteria included: self-reported smoking between 5–40 cigarettes per day, breath carbon monoxide (CO) level of >10 ppm at intake, not pregnant/lactating, and no immediate plans to quit smoking cigarettes or move out of the area. Twenty-five participants were not eligible for enrollment and 61 did not complete the entire study (lost to follow-up $n = 31$; voluntary withdrawal $n = 24$; terminated $n = 6$). Thus, the final sample included 36 participants, consistent with our a priori power analysis targeting an effect size of $f = 0.175$ (halfway between a "medium" and "small" effect by convention; Cohen 1992) with 80% power and a type 1 error rate of $\alpha = 0.05$. All participants provided written informed consent and this protocol was monitored by the Virginia Tech Institutional Review Board (#16-472) and registered with clinicaltrials.gov (NCT02951143).

Procedure

Following consent, participants completed a battery of behavioral assessments. Relevant to the current paper, participants completed the Fagerström Test of Nicotine Dependence (FTND[32]), a six-item questionnaire providing an overall measure of nicotine dependence; Timeline Followback (TLFB[33]), capturing daily usage of tobacco products during the previous 30 days; Minnesota Nicotine Withdrawal Scale (MNWS[34]), a 15-item Likert questionnaire assessing withdrawal-like feelings during the previous 24 hrs; and Questionnaire on Smoking Urges-Brief (QSU[35]), a 10-item Likert questionnaire assessing current smoking urges.

Subsequent experimental sessions were double-blind, randomized with respect to order, and at least one day apart. In these sessions, participants smoked one cigarette each of usual brand or SPECTRUM investigational cigarettes (15.8 mg/g, 5.2 mg/g, 2.4 mg/g, 1.3 mg/g, and 0.4 mg/g) in the

flavor consistent with their usual brand (tobacco versus menthol). To participate in that day's experimental session, participants had to have abstained from smoking cigarettes for 8–12 hours (typically overnight), validated by a breath CO level <8 ppm. This duration of abstinence is enough to produce negligible breath CO in smokers with this level of smoking. This criterion was chosen over alternatives (e.g., 50% of baseline CO) to increase the likelihood that minimal amounts of blood nicotine would be present in the participant's system prior to cigarette exposure, thereby providing a uniform baseline from which to make comparisons. If participants failed to meet this criterion, their session was rescheduled for the next available time slot at least a day later. Thus, each of the 36 participants smoked one of each of the six cigarette types reflecting a fully crossed experimental design.

Blood Draw Sessions

Participants sat in a ventilated smoking booth with a butterfly catheter inserted intravenously for all sessions, allowing readily accessible and rapid blood draws. The session began with a 3 mL blood draw, CO sample, and series of physiological ratings, similar to the MNWS, answered on a Visual Analog Scale (VAS; 0–100). Five minutes into the session, participants took 10 guided puffs (~60 mL each) of the day's assigned cigarette, with an approximately 30-sec interpuff interval. At 10, 15, 20, 30, 45, and 60 min into the session, 3 mL of blood, CO, and physiological and subjective VAS responses were obtained (see Supplementary Table S1 for all VAS questions and Supplementary Figure S1 for a schematic of the session). At 20 min, participants completed a Cigarette Purchase Task (CPT[13,14]) for that day's cigarette as well as other measures not reported here. This paper reports on the associations between the CPT and blood nicotine obtained throughout the session, which was our predetermined primary outcomes and analyses.

The CPT was trait-based and contained typical instructions such as assuming no access to other cigarettes or nicotine products and no stockpiling (see Supplemental Materials for full instructions). Prices per cigarette included: $0.00 (free), $0.01, $0.05, $0.10, $0.25, $0.50, $1, $2, $5, $10, $25, $50, $100, $200.

Data Analysis

Demographics

We calculated bivariate correlations between demographic variables of interest, including age, education, monthly income, cigarettes smoked per day, MNWS total score, QSU total score, FTND, and individual-level demand predictions for usual brand cigarettes only.

Blood Nicotine

Blood nicotine (expressed in ng/mL) at minute 0 was subtracted from blood nicotine at minutes 10, 15, 20, 30, 45, and 60 to yield a change (Δ) in blood nicotine (negative values were truncated to 0). Using Δ blood nicotine, we calculated Area Under the Curve (AUC) via the trapezoidal rule and maximum Δ blood nicotine (C_{max}), which we then used in subsequent analyses. Linear mixed-effects models specifying a random intercept for participant were used to compare AUC and C_{max} measures across the different cigarettes.

Behavioral Economic Demand

We used the following exponentiated equation[36] to derive relevant demand measures:

$$Q = Q_0 \cdot 10^{k(e^{-\alpha \cdot Q_0 \cdot C} - 1)}$$

where Q represents consumption at each price point, Q_0 is the amount of consumption at free price, k is a weighting parameter signifying the range of consumption in logarithmic units (fixed at 2), α is the rate of change in elasticity across the entire curve, and C is the price per cigarette. The parameters Q_0 and α were fit in $\log_{10}$ space and are reported as such in the rest of this paper. Analyses were conducted using a nonlinear mixed-effects modeling approach[31,37] whereby demand parameters and session- and subject-specific parameters were estimated simultaneously using maximum likelihood estimation.[38] Random intercepts were specified for participant and cigarette type. A blocked covariance matrix was specified to account for the experimental design's crossed nature, with the first block containing a symmetric covariance matrix for participant and the second block containing a diagonal covariance matrix for cigarette type.

Unless otherwise noted, for nonlinear models, we report post hoc estimated marginal means controlling for false discovery rate via Benjamini-Hochberg adjustments to *p*-values. Results were considered significant at the $\alpha = .05$ level, and all analyses were performed in R v.3.6.1[39] using the following packages: *beezdemand*,[40] *nlme*,[41] *lme4*,[42] *geepack*, [43] *tidyverse*,[44] *tableone*,[45] *emmeans*,[46] *MESS*,[47] and *sjPlot*.[48]

Results

Participant Demographics

A total of 36 participants were included in the final analyses. Participant demographics are presented in Table 1. Supplementary Table S2 shows Pearson bivariate correlations among several of the demographic variables measured and Supplementary Table S3 shows the results of a nonlinear mixed-effects model with usual brand cigarettes and several cigarette relevant variables. Apart from Log(Q_0) and Log(α),

Table 1. Participant Demographics

	Overall (*n* = 36)
Numeric variables: median [IQR]	
Age	38.50 [33.00, 48.25]
Monthly income	550.00 [0.00, 1125.00]
Numeric variables: mean (SD)	
Education	12.42 (1.86)
FTND	6.56 (1.65)
MNWS	11.33 (9.65)
QSU-Brief	43.36 (14.16)
Cigarettes per day	18.58 (7.24)
Categorical variables: [Reference] *n* (%)	
Sex [Male]	21 (58.30)
Ethnicity [Not Hispanic]	36 (100.00)
Usual brand cigarette flavor[Tobacco]	18 (50.00)
Race	
White	27 (75.00)
African American	9 (25.00)

FTND: Fagerström test of nicotine dependence; MNWS: Minnesota Nicotine Withdrawal Scale; QSU-Brief: Questionnaire of Smoking Urges

cigarettes smoked per day and FTND score were the only variables significantly correlated ($r_{Pearson} = 0.55, p < .001$).

In an exploratory analysis, we were interested in what variables might be associated with participants not being able to complete the six blood draw sessions used in the current study. We constructed a generalized linear model (logistic regression) with demographic and substance use variables to predict the likelihood of completing all six sessions (outcome variable). The results are shown in Supplementary Table S4. Higher MNWS was associated with a lower likelihood of completing the study (Odds Ratio = 0.95; $p = .048$). Although not statistically significant, more cigarettes smoked per day was also associated with a lower likelihood of completing the study (OR = 0.92; $p = .053$).

Blood Nicotine

As a manipulation check to ensure the different nicotine content cigarettes resulted in differential levels of blood nicotine and for validation of our procedures, we first compared blood nicotine levels across the different cigarettes. A significant cigarette effect was observed for AUC ($\chi^2(5) = 465.21, p < 0.0001$; see Figure 1) and C_{max} ($\chi^2(5) = 280.4, p < 0.0001$; see Supplementary Figure S2). Both AUC and C_{max} decreased in orderly relations with nicotine level, with participant's usual brand cigarette resulting in the highest values. All pairwise comparisons were significant except between the three lowest nicotine levels (2.4 mg/g, 1.3 mg/g, and 0.4 mg/g) for both AUC and C_{max} (see Supplementary Tables S5 and S6 for estimated marginal means). Participants' changes in blood nicotine and associated AUCs can be seen in Supplementary Figures S3–S8. That the three lowest nicotine levels were not different from one another is not surprising given the small amount of nicotine in these cigarettes.

Demand Measures

Our first demand analysis compared estimates of Q_0 and α across 1) usual brand and the 15.8mg/g nicotine level cigarette (i.e., the full-strength nicotine control cigarette) and 2) the five different investigational cigarettes. Estimated marginal means are reported in Table 2 and predictions from the nonlinear mixed-effects model are shown in Figure 2. Overall, usual brand cigarettes tended to maintain the highest Q_0 and lowest α (i.e., greater valuation), suggesting these cigarettes were the most highly valued of the array. However, no statistically significant differences in Q_0 (t(2977) = 1.520, $p = .3636$) nor α (t(2977) = –1.798, $p = .1084$) were observed between usual brand and 15.8 mg/g cigarettes. Among the investigational cigarettes, the two lowest nicotine levels (1.3 mg/g and 0.4 mg/g) tended to result in the lowest levels of Q_0 and α. Only the 0.4 mg/g cigarette maintained statistically significantly higher α (lower valuation) compared to the 15.8 mg/g cigarette (t(2977) = –2.883, $p = .0159$). We did not detect any significant differences in Q_0 between the 15.8 mg/g nicotine level and any other investigational cigarettes.

Our second demand analysis aimed to determine the relative contributions of nicotine content in the cigarettes and blood nicotine AUC on behavioral economic parameters of abuse liability. To compare these variables, we constructed three models with the same random effects structure but differing in the fixed effects structure. In one model, we included logged nicotine level as a continuous covariate. In an-

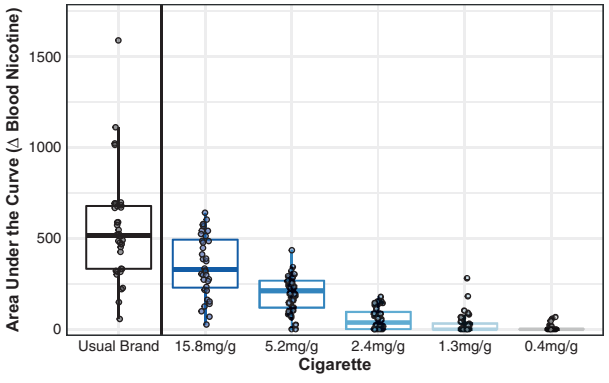

Figure 1. Area under the change in blood nicotine curve. Each dot represents a single participant. The horizontal line within the box represents the median, the length of the box represents the interquartile range, and the whiskers extend to 1.5 times the interquartile range.

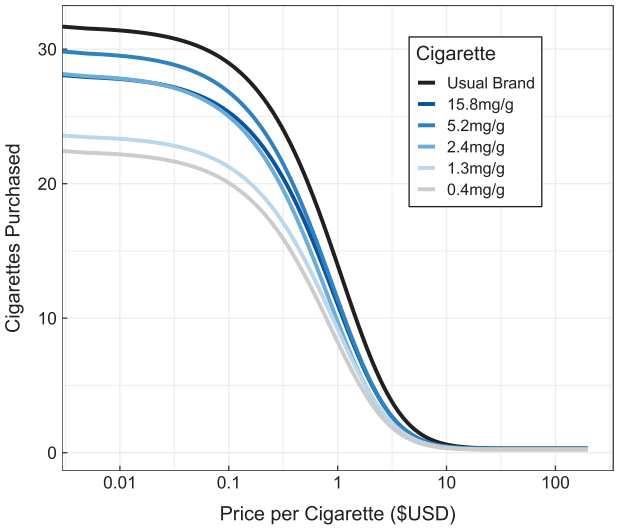

Figure 2. Predictions from the nonlinear mixed-effects model across the different cigarettes examined in the Cigarette Purchase Task.

Table 2. Estimated Marginal Means of Demand Parameters from the Nonlinear Mixed-Effects Model

Cigarette	Estimated marginal mean	Standard error	95% CI
Log(Q0)			
Usual brand	1.50	0.0583	[1.39, 1.62]
15.8 mg/g	1.45	0.0555	[1.34, 1.56]
5.2 mg/g	1.47	0.0538	[1.37, 1.58]
2.4 mg/g	1.45	0.0678	[1.32, 1.58]
1.3 mg/g	1.37	0.0975	[1.18, 1.56]
0.4 mg/g	1.35	0.0727	[1.21, 1.49]
Log(α)			
Usual brand	–2.21	0.0837	[–2.37, –2.04]
15.8 mg/g	–2.09	0.0600	[–2.21, –1.97]
5.2 mg/g	–2.10	0.0649	[–2.23, –1.98]
2.4 mg/g	–2.03	0.0629	[–2.15, –1.91]
1.3 mg/g	–2.01	0.0683	[–2.15, –1.88]
0.4 mg/g	–1.96	0.0711	[–2.10, –1.82]

Degrees of freedom = 2977.

other model, we included square root transformed AUC as a continuous covariate. In a final model, we included both variables. We conducted two separate likelihood ratio tests (LRT) comparing each of the simpler models to the more complex model with both covariates. This allows us to determine if the addition of either variable significantly improved the model fits.

The model with AUC only revealed this measure significantly predicted α ($F(2481) = 29.25$, $p < .0001$) but not Q_0 ($F(2481) = 0.35$, $p = .5518$). Each square root unit increase in AUC predicted a decrease (higher valuation) of 0.0126 units in $\log_{10}(\alpha)$. Similarly, the model with nicotine level only revealed this measure significantly predicted α ($F(2481) = 31.01$, $p < .0001$) but not Q_0 ($F(2481) = 1.12$, $p = .2902$). Each log unit increase in nicotine level predicted a decrease of 0.0751 units in $\log_{10}(\alpha)$. Neither LRT tests comparing either the addition of AUC ($LR = 2.754$, $p = .2524$) or the addition of nicotine level ($LR = 4.652$, $p = .0977$) to the simpler models were significant, suggesting high overlap in the explanatory power of these two variables in predicting change in demand elasticity. The fact that results from the LRT tests did not recommend combining AUC and nicotine level into a single model is further supported by the strong correlation between the two measures, $r_{Pearson} = 0.825$, 95% CI [0.777, 0.863], $p < .0001$.

Discussion

With the recent interest in FDA and scientific inquiry examining the potential impacts of reducing nicotine in combustible cigarettes to nonaddictive levels,[6] the current paper contributes to this body of literature in novel and important ways. First, this study represents the first investigation into the relation between cigarette nicotine level, blood nicotine, and behavioral economic measures of abuse liability. Second, our results are largely consistent with previous findings suggesting low nicotine content cigarettes correspond with low abuse liability levels. Specifically, our results suggest a nicotine content of 1.3 mg/g or lower may reduce the likelihood that first-time smokers will choose to continue smoking and may help current smokers abstain or transition to harm-reducing alternatives. The current study comprised of two primary aims.

Our first aim quantified blood nicotine across usual brand and SPECTRUM investigational cigarettes. First, we observed a strong correlation between nicotine content and blood nicotine ($r = 0.825$, $p < .0001$). Although this relation is much stronger than a previous study[49] ($r = 0.21$, $p < .001$), the previous study used cigarettes differing in ventilation and tar values. Second, contrary to our initial hypothesis we observed blood nicotine from the full-strength control (15.8 mg/g) was significantly lower than usual brand cigarettes. Even though only 10 guided puffs of each cigarette were administered (~60 mL puff volume), participants' smoking topography may have differed slightly between the usual brand and SPECTRUM cigarettes. Whereas Tidey and colleagues[50] found participants tended to engage in longer puff durations and marginally higher puff volumes compared to usual brand cigarettes, which would result in greater blood nicotine, other reports and our observations[51] suggest participants tend to dislike these cigarettes.[52] This may have contributed to somewhat lower puff volume but still within an acceptable range.

Our second aim investigated the relative contributions of nicotine content in cigarettes and blood nicotine on behavioral economic measures of abuse liability within a parametric analysis. Our hypothesis that cigarette nicotine content and blood nicotine would significantly relate to behavioral economic demand measures was partly confirmed. Whereas we found neither nicotine content nor blood nicotine predicted Q_0, we did find both variables predicted α. Furthermore, blood nicotine was significantly related to FTND dependency scores ($r_{pearson} = .38$, $p = .022$). This latter (i.e., significant relation between blood nicotine and dependency), but not the former (i.e., nonsignificant relation between blood nicotine and Q_0), finding is consistent with those from Higgins et al.[30] Specifically, those authors found nicotine intake (COT+3HC) was significantly related to heaviness of smoking and FTND, as well as Amplitude (Q_0 in the current study), but not Persistence (a combination of demand parameters largely representing price sensitivity, including α).

Several possibilities for these differences exist. One reason could be due to the disparate sample sizes (745 vs 36). We observed Q_0 associated with the two lowest nicotine content cigarettes tended to be lower than the other cigarettes, but these differences did not meet statistical significance. Another reason could be due to differences in sample demographics; whereas our inclusion criteria were relatively broad, the samples in Higgins et al.[30] included smokers with affective disorders, opioid dependence, and women of reproductive age with less than or equal to a high school degree. The reason why blood nicotine content among vulnerable populations was not significantly related to measures of Persistence is unclear but may serve as an insightful area of future research. Another reason for the discrepancy could be due to statistical differences such as the Principal Component Analysis used by Higgins et al. to derive the two main Amplitude and Persistence factors. Note that this approach differs fundamentally from the approach used here. Specifically, those authors derived demand parameters by fitting a single regression to each participant independently (first stage) and then carried forward those values into the Principal Component Analysis (second stage). On the other hand, we carried out all estimation within a single model using the nonlinear mixed-effects modeling approach. We believe this method is preferred given it 1) leverages all available data (single-stage approaches are sometimes unable to fit curves to certain participant response patterns) and 2) models the inherent correlated nature of purchase task data resulting in more accurate standard errors. The degree to which the different sample sizes and statistical techniques contributed to the discrepant findings is unknown, however, α has been theorized to be most sensitive to differences in abuse liability[53] and our mixed-effects modeling approach here reflected this.

We found only the lowest nicotine level (0.4 mg/g) statistically significantly differed from the full-strength control (15.8 mg/g) in measures of α; we did not find differences in the intermediate nicotine levels, although the 1.3 mg/g cigarette tended to display abuse liability measures closer to the 0.4 mg/g levels than higher nicotine levels. Whereas this trend is similar to previous research, comparisons should be viewed cautiously given differences in statistical techniques between the current paper and previous studies. For example, Higgins et al.[22] found consumption at free price (which was not derived in their study) for the two lowest nicotine content cigarettes (0.4, 1.3 mg/g) was significantly lower compared to their control cigarette (15.8 mg/g). They failed to detect any

significant differences in α ($p = 0.05$), although mean α for the 0.4 and 1.3 mg/g cigarettes were higher compared to 5.2 and 15.8 mg/g cigarettes. From a data analytic standpoint, our study differs from Higgins et al. in that they fit curves at the individual level, constrained Q_0 to participant's reported consumption at free price, winsorized α >1, and excluded participants from the α analysis if they reported all zero consumption, whereas we made no modifications to our data. Smith et al.[24] found significant increases in α for the two lowest nicotine content cigarettes (1.3, 0.4 mg/g compared to 15.8 mg/g) only after participants were required to abstain for 24 hours, but not at Week 6 of their study protocol. They also found significant reductions in Q_0 for the three lowest nicotine content cigarettes under these same conditions. However, Smith et al. excluded over 100 participants from their derived demand analysis due to various exclusion criteria, whereas we did not exclude any data.

In terms of potential policy implications, our findings suggest the 0.4 mg/g level may be the ideal target level to effectively minimize the abuse liability of combustible cigarettes, but that 1.3 mg/g may also be effective. These levels are consistent with other reduced-nicotine research.[5,24] Recall, participants in our study smoked only one of each of the different types of cigarettes, constituting relatively acute exposure. This acute exposure resulted in low relative reinforcing efficacy among the two lowest nicotine content cigarettes by virtue of participants reducing their reported consumption more rapidly in face of increasing costs. The relatively low reinforcement obtained from these cigarettes may be effective in reducing cigarette uptake among first-time (naïve) smokers because adequate levels of reinforcement are not obtained to support continued smoking.

Several strengths of the current paper are worth noting. First, we used sophisticated modeling techniques[31] to quantify behavioral economic demand measures of cigarette abuse liability. This nonlinear mixed-effects modeling approach allowed us to estimate behavioral economic demand parameters and associated errors with greater accuracy than previous approaches. Second, we directly related physiological measures of blood nicotine with these behavioral economic measures of abuse liability, all within a full statistical model. Finally, we completed these aims using a fully within-subject experimental preparation allowing each participant to serve as their own control.

Notwithstanding the numerous strengths of the current study, several limitations suggest avenues for future research. First, participants were provided a relatively brief and controlled (10 puff) exposure to the cigarettes, and responses on the behavioral economic purchase task were most likely influenced by a combination of nicotine obtained from the cigarettes and how subjectively pleasing they were. Future research could provide extended access to better isolate the effects of nicotine compared to subjective perceptions. In addition, implications for public policy should be tempered by the fact that we controlled puff administration in this study in a manner not directly applicable to a public health setting. Although in unrestricted scenarios, smokers may increase puffs or puff volume to achieve greater nicotine intake, our research questions necessitated the controlled delivery of puffs. Second, we collected blood at only six timepoints throughout the session and only one timepoint during the ascending limb of the pharmacokinetic nicotine curve, which is quite rapid for smoked tobacco. As a result, we could not fit more complex nonlinear functions to these curves and relied on area under the curve, which is a measure of nicotine exposure collapsed over the entire one-hour session. Third, the CPT was hypothetical, and we used a trait-based vignette to better assess typical consumption patterns rather than a state-based vignette that would better model momentary purchasing intentions. Although the CPT was hypothetical, previous research suggests good correspondence between hypothetical and experiential purchase tasks.[54] Additionally, participants in the current study directly experienced the product described in the purchase task. The use of the trait-based (e.g., imagine a typical day in which you smoke) versus a state-based vignette (e.g., imagine you could smoke right now) was unlikely to alter the pattern of demand results we observed here given that participants were explicitly told to imagine the cigarette they were purchasing was the one they had experienced during that session. A final limitation is the relatively small sample size compared to previous behavioral economic studies examining reduced-nicotine cigarettes. The current within-subjects design study was powered to detect statistical differences in abuse liability measures and was not necessarily powered to detect relations with demographic and/or smoking-related variables.

In summary, our results largely conform to previous findings suggesting a very low nicotine content cigarette maintains low abuse liability relative to cigarettes containing greater amounts of nicotine. Specifically, we found the two lowest nicotine content cigarettes tested resulted in the lowest reinforcement obtained as measured by participants reporting greater reductions in cigarettes purchased as the price of these cigarettes increased. These results suggest a nicotine content of 1.3 mg/g or lower may not confer the amount of reinforcement from nicotine needed to maintain smoking behavior over the long term among individuals without a prior nicotine history (i.e., first-time smokers). The low reinforcement value of these cigarettes may also help current smokers more easily abstain or transition to harm-reducing alternatives.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

Declaration of Interest

B.A.K., E. M. C., C.T.F., and M.N.K. have no conflicts of interest to report. Although the following activities/relationships do not create a conflict of interest pertaining to this manuscript, in the interest of full disclosure, W. K. B. is a principal of HealthSim, LLC, BEAM Diagnostics, Inc., and Notifius, LLC; a scientific advisory board member of Sober Grid, Inc. and DxRx, Inc.; and a consultant for ProPhase, LLC and Teva Branded Pharmaceutical Products R&D, Inc.

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Data Availability

Data are available by reasonable request to the corresponding author.

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