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Addiction Potential of Cigarettes With Reduced Nicotine Content in Populations With Psychiatric Disorders and Other Vulnerabilities to Tobacco Addiction

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IMPORTANCE A national policy is under consideration to reduce the nicotine content of cigarettes to lower nicotine addiction potential in the United States.

OBJECTIVE To examine how smokers with psychiatric disorders and other vulnerabilities to tobacco addiction respond to cigarettes with reduced nicotine content.

DESIGN, SETTING, AND PARTICIPANTS A multisite, double-blind, within-participant assessment of acute response to research cigarettes with nicotine content ranging from levels below a hypothesized addiction threshold to those representative of commercial cigarettes (0.4, 2.3, 5.2, and 15.8 mg/g of tobacco) at 3 academic sites included 169 daily smokers from the following 3 vulnerable populations: individuals with affective disorders (n = 56) or opioid dependence (n = 60) and socioeconomically disadvantaged women (n = 53). Data were collected from March 23, 2015, through April 25, 2016.

INTERVENTIONS After a brief smoking abstinence, participants were exposed to the cigarettes with varying nicotine doses across fourteen 2- to 4-hour outpatient sessions.

MAIN OUTCOMES AND MEASURES Addiction potential of the cigarettes was assessed using concurrent choice testing, the Cigarette Purchase Task (CPT), and validated measures of subjective effects, such as the Minnesota Nicotine Withdrawal Scale.

RESULTS Among the 169 daily smokers included in the analysis (120 women [71.0%] and 49 men [29.0%]; mean [SD] age, 35.6 [11.4] years), reducing the nicotine content of cigarettes decreased the relative reinforcing effects of smoking in all 3 populations. Across populations, the 0.4-mg/g dose was chosen significantly less than the 15.8-mg/g dose in concurrent choice testing (mean [SEM] 30% [0.04%] vs 70% [0.04%]; Cohen *d* = 0.40; *P* < .001) and generated lower demand in the CPT (α = .027 [95% CI, 0.023-0.031] vs α = .019 [95% CI, 0.016-0.022]; Cohen *d* = 1.17; *P* < .001). Preference for higher over lower nicotine content cigarettes could be reversed by increasing the response cost necessary to obtain the higher dose (mean [SEM], 61% [0.02%] vs 39% [0.02%]; Cohen *d* = 0.40; *P* < .001). All doses reduced Minnesota Nicotine Withdrawal Scale total scores (range of mean decreases, 0.10-0.50; Cohen *d* range, 0.21-1.05; *P* < .001 for all), although duration of withdrawal symptoms was greater at higher doses (η^2 = 0.008; dose-by-time interaction, *P* = .002,).

CONCLUSIONS AND RELEVANCE Reducing the nicotine content of cigarettes may decrease their addiction potential in populations that are highly vulnerable to tobacco addiction. Smokers with psychiatric conditions and socioeconomic disadvantage are more addicted and less likely to quit and experience greater adverse health impacts. Policies to reduce these disparities are needed; reducing the nicotine content in cigarettes should be a policy focus.

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Supplemental content

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Cigarette smoking is a public health burden that especially harms individuals with psychiatric conditions and socioeconomic disadvantage and is a major contributor to health disparities.[1-5] Reducing this burden will require tobacco control and regulatory policies that are more effective at changing behavior in these vulnerable populations.[6]

The present study investigates how vulnerable populations of smokers may respond to a national US regulatory policy to reduce the maximal nicotine content of cigarettes and thereby lower their potential to cause addiction. The 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA) granted the US Food and Drug Administration regulatory authority over cigarettes and other tobacco products.[7] That legislation includes authority to reduce the maximal nicotine content of cigarettes if doing so benefits public health. A regulatory question fundamental to protecting public health is whether the nicotine content of cigarettes can be set below a threshold dose necessary to produce or sustain addiction. This would allow current smokers to make more rational choices about continuing to smoke while lowering addiction risk among those newly introduced to smoking.

Benowitz and Henningfield[8] introduced the idea of decreasing nicotine content more than 20 years ago, hypothesizing that the threshold nicotine dose for reinforcing effects, a primary indicator of addiction potential, was approximately 0.7 mg/g of tobacco. A series of studies[9-12] in relatively healthy smokers conducted since the passage of the FSPTCA support the position that reducing nicotine content in cigarettes to very low levels reduces addiction potential. Moreover, cigarettes with reduced nicotine content appear to produce minimal compensatory smoking (ie, adjustments in smoking amount or topography to sustain desired nicotine blood levels).[9-12] Compensatory smoking was the major limitation in prior efforts to use light cigarettes to reduce addiction potential[13] that attempted to reduce nicotine yield through filter ventilation but left the nicotine content unchanged.

Initial studies of cigarettes with reduced nicotine content were appropriately conducted with psychiatrically and socioeconomically stable, healthy smokers. However, smoking is overrepresented among those with psychiatric conditions and socioeconomic disadvantage, among other vulnerabilities.[1-6,14,15] Thus, we studied 3 adult populations that are particularly vulnerable to tobacco addiction and its adverse health impacts: individuals with affective disorders to represent smokers with mental illness, individuals with opioid dependence to represent smokers with other substance use disorders, and socioeconomically disadvantaged women to represent smokers with socioeconomic disadvantage.[1-6,14-16] Disadvantaged women of reproductive age are of special interest because of their risk for smoking during pregnancy and while parenting young children.[14] Smoking prevalence in each of these populations exceeds prevalence in the US adult population (21.0%; 95% CI, 20.4%-21.6%), with rates of 32.2% (95% CI, 30.3%-34.1%) among those with affective disorders, 92.2% (95% CI, 86.5%-97.9%) among those with opioid (heroin) dependence, and 29.5% (95% CI, 28.0%-31.0%) among disadvantaged women of reproductive age.[17]

How smokers with comorbid psychiatric conditions or lower socioeconomic status respond to cigarettes with reduced nicotine content has not been well studied. Several small studies involving these vulnerable populations suggest that cigarettes with very low nicotine content reduce abstinence-induced withdrawal without engendering compensatory smoking.[18-21] Results from a single pilot study[21] suggest that reducing the nicotine content decreases the addiction potential of smoking among individuals with psychiatric conditions or socioeconomic disadvantage, but a small sample size precluded thoroughly examining the nicotine dose or population differences. Another study[22] demonstrated that elevated depressive symptoms did not moderate response to reduced nicotine content cigarettes, although this was not in a clinically diagnosed sample. The current study is, to our knowledge, the first large, controlled study to examine the dose-dependent effects of cigarettes with reduced nicotine content on the reinforcing effects, subjective effects, and smoking topography in vulnerable populations.

Key Points

Question Would a national policy of reducing the nicotine content of cigarettes alter the addiction potential of smoking among adults with psychiatric disorders or other vulnerabilities to tobacco addiction?

Findings In this multisite, double-blind, within-participant assessment of 169 adult smokers, the addiction potential of smoking was reduced by lowering the nicotine content of cigarettes to very low levels.

Meaning A national tobacco regulatory policy that reduces the maximal nicotine content of cigarettes to low levels may help reduce smoking in populations that are highly vulnerable to tobacco addiction.

Methods

Study Sample

Participating adult daily smokers included 56 with affective disorders, 60 with opioid dependence, and 53 socioeconomically disadvantaged women (**Table 1**). Inclusion and exclusion criteria are described in eMethods in the Supplement. The institutional review boards at the University of Vermont, Burlington; Brown University, Providence, Rhode Island; and Johns Hopkins University School of Medicine, Baltimore, Maryland, approved the study. All participants provided written informed consent.

Procedure

Data were collected from March 23, 2015, through April 25, 2016. Participants completed fourteen 2- to 4-hour experimental sessions in a within-participant design (eMethods in the Supplement provides additional details). Participants abstained from smoking for 6 to 8 hours before the sessions. Sessions were organized into 3 phases.

In phase 1 (sessions 1-5), participants sampled the research cigarettes under double-blind conditions. Participants were oriented to the research protocol in session 1 using

Table 1. Participant Characteristics

Characteristic	All (N = 169)	Participant Group[a]		
		Affective Disorders (n = 56)	Opioid Dependent (n = 60)	Disadvantaged Women (n = 53)
Age, mean (SD)	35.6 (11.4)	35.0 (12.4)	41.0 (11.2)	30.0 (7.0)
Female	120 (71.0)	31 (55.4)	36 (60.0)	53 (100)
Participant race or ethnicity classification				
White	123 (72.8)	40 (71.4)	42 (70.0)	41 (77.4)
Native American or Alaskan Native	0	0	0	0
Asian	1 (0.6)	1 (1.8)	0	0
Black or African American	23 (13.6)	3 (5.4)	12 (20.0)	8 (15.1)
Native Hawaiian or Pacific Islander	1 (0.6)	0	1 (1.7)	0
Other or >1 race	15 (8.9)	8 (14.3)	5 (8.3)	2 (3.8)
Latino	6 (3.6)	4 (7.1)	0	2 (3.8)
Educational attainment				
Eighth grade or less	4 (2.4)	1 (1.8)	2 (3.3)	1 (1.9)
Some high school	23 (13.6)	4 (7.1)	10 (16.7)	9 (17.0)
High school graduate or equivalent	58 (34.3)	16 (28.6)	22 (36.7)	20 (37.7)
Some college	64 (37.9)	20 (35.7)	21 (35.0)	23 (43.4)
2-y Associate's degree	10 (5.9)	5 (8.9)	5 (8.3)	0
College graduate or 4-y bachelor's degree	6 (3.6)	6 (10.7)	0	0
Graduate or professional degree	4 (2.4)	4 (7.1)	0	0
Marital status				
Married	27 (16.0)	8 (14.3)	5 (8.3)	14 (26.4)
Never married	103 (60.9)	37 (66.1)	32 (53.3)	34 (64.2)
Divorced or separated	35 (20.7)	10 (17.9)	21 (35.0)	4 (7.5)
Widowed	4 (2.4)	1 (1.8)	2 (3.3)	1 (1.9)
Cigarettes smoked, mean (SD), No./d	15.8 (7.5)	16.3 (9.5)	16.5 (6.1)	14.5 (6.3)
Primary smoker of mentholated cigarettes	59 (34.9)	20 (35.7)	23 (38.3)	16 (30.2)
Breath CO level, mean (SD), ppm	22.4 (11.9)	22.0 (12.4)	23.3 (12.4)	21.7 (10.9)
Age started smoking regularly, mean (SD), y	16.3 (4.3)	16.2 (3.1)	16.2 (5.5)	16.4 (3.7)
Fagerström Test for Nicotine Dependence, mean (SD) score[b]	5.0 (2.2)	5.0 (2.3)	5.3 (1.8)	4.6 (2.3)

Abbreviation: CO, carbon monoxide.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Scores range from 0 to 10, with higher scores indicating greater dependence.

their usual-brand cigarette. In sessions 2 to 5, participants smoked 1 research cigarette per session. The research cigarettes were identical in appearance but varied in nicotine content (15.8, 5.2, 2.4, and 0.4 mg/g; Spectrum cigarettes, 22nd Century Group, Inc). The highest dose served as a control for nicotine levels typical of commercial cigarettes, whereas the lowest dose represents a dose below the hypothesized 0.7-mg/g threshold dose for addiction. Participants were instructed to smoke the research cigarettes as usual but used a plastic cigarette holder connected to a device that recorded smoking topography.[23] After smoking the assigned cigarette each session, participants completed the Cigarette Purchase Task (CPT), which is a behavioral economic simulation task that models (1) cigarette smoking rate when unconstrained by cost, (2) maximal amount of money that an individual is willing to spend on daily smoking, (3) the price at which the smoking rate begins decreasing proportionate to increasing price, (4) the price at which an individual would quit smoking rather than incur the cost, and (5) overall sensitivity of smoking rate to price.[24-26] In addition, the modified Cigarette Evaluation Questionnaire (mCEQ),[27] Minnesota Nicotine Withdrawal Questionnaire (MNWQ),[28] Questionnaire of Smoking Urges-Brief Scale (QSU-Brief),[29] and Fagerström Test for Nicotine Dependence[30] were administered.

Phase 2 (sessions 6-11) directly tested the relative reinforcing effects of the different doses in the cigarettes by allowing participants to choose which cigarette they preferred to smoke.[31,32] Each of the 6 possible cigarette dose-pair combinations was tested once in separate sessions. In these 3-hour sessions, a participant sat alone in a comfortable, ventilated room with reading materials (eFigure 1 in the Supplement). When they wished to smoke, they used a computer mouse to click on 1 of 2 icons on a screen representing the 2 cigarettes available that session. After 10 clicks on the icon, they could take 2 puffs of the associated cigarette.[31] Participants were free to choose either option as often as they wished or to abstain.

Last, phase 3 (sessions 12-14) used the same arrangement as in phase 2 but compared only the lowest and highest doses (0.4 and 15.8 mg/g). This phase assessed whether preference could be reliably shifted away from the high dose. Puffs from the low

dose were always available by clicking that option 10 times, but the number of clicks necessary to earn puffs from the highest dose started at 10 and increased each time it was chosen to 160, 320, 640, 1280, 2400, 3600, 4800, 6000, 7200, and 8400 clicks.[33] Participants were informed of the different response requirements in advance. Participants completed the CPT for the 0.4- and 15.8-mg/g doses after the concurrent choice sessions in phase 3 to assess relative demand for the 2 cigarettes outside the concurrent choice test arrangement.

Statistical Methods

Analyses of phase 1 results examined differences between the research cigarettes on the CPT and mCEQ and smoking topography by using repeated-measures analysis of variance, with nicotine dose as the within-participant factor. The MNWS, QSU-Brief, and breath levels of carbon monoxide (CO) boost were examined similarly with time as another within-participant factor. To measure CO boost, presmoking CO values were subtracted from postsmoking CO values. Analyses also included a fixed effect for session. Time-by-dose interactions were included to test whether the CO boost or subjective effects before and after smoking differed by dose; when not significant, interaction effects were dropped from the models.

Because the research cigarettes were presented in random order using a Latin square, sequence was included in the model as a random effect. An additional random effect was included to account for the 3 study sites and a fixed effect to examine population differences. Significant time, dose, or interaction effects were followed by post hoc testing using Bonferroni corrections. Differences in preference among all possible dose pairs (phase 2) were similarly examined using repeated-measures analysis of variance, with each pairwise combination as the within-participant factor. Significant dose-pair effects were followed with post hoc testing. Differences among participants in preference for the highest- vs lowest-dose cigarettes (phase 3) were examined using a repeated-measures analysis of variance, with session as the repeating factor and population as the between-subjects factor. Effect sizes were computed using the Cohen *d* for pairwise comparisons and η^2 value for interaction effects. Exploratory analyses examining possible moderating effects of sex and cigarette mentholation status were conducted with 2 primary outcome measures (concurrent choice and mCEQ). To describe aggregate-level cigarette demand on the CPT, we fit a demand curve[34] to mean reported consumption at each price across participants and doses. An extra sum-of-squares *F* test evaluated whether demand inelasticity differed significantly across doses; this test was also used to compare aggregate dose curves across populations and sessions.

To quantify participant-level CPT demand elasticity, a demand curve was fit to individual consumption at each price for each dose. When fitting demand curves, we constrained demand intensity to the participants' reported consumption at $0.00 to leave elasticity as the only fitted parameter. Elasticity values greater than 1.00 were winsorized to 1.00 before statistical analysis (22 of 845 cases). All other demand indices were empirically quantified from observed values. Maximal expenditure, maximal price, breakpoint, and α values were $\log_{10}$ transformed to correct for skewness. We reviewed CPT results and found systematic patterns[35] in 92.7% of demand curves; no data were excluded from analyses. In cases in which participants reported zero consumption across all prices, curve fitting was not possible; thus, elasticity was not analyzed and other demand indices were quantified as 0.

Data were complete for all but the MNWS, QSU-Brief, and smoking topography measures. Missing data for topography measures amounted to 3% or less, whereas missing data for the other measures was limited to at most 2 missing observations per session. All analyses were completed using maximum likelihood estimation procedures. Significance for all tests was $P < .05$. Post hoc testing was based on unpaired *t* tests (between participants) or paired *t* tests (within participant). All were 2-tailed, with *P* values for post hoc tests subject to Bonferroni correction.

Results

Direct Testing

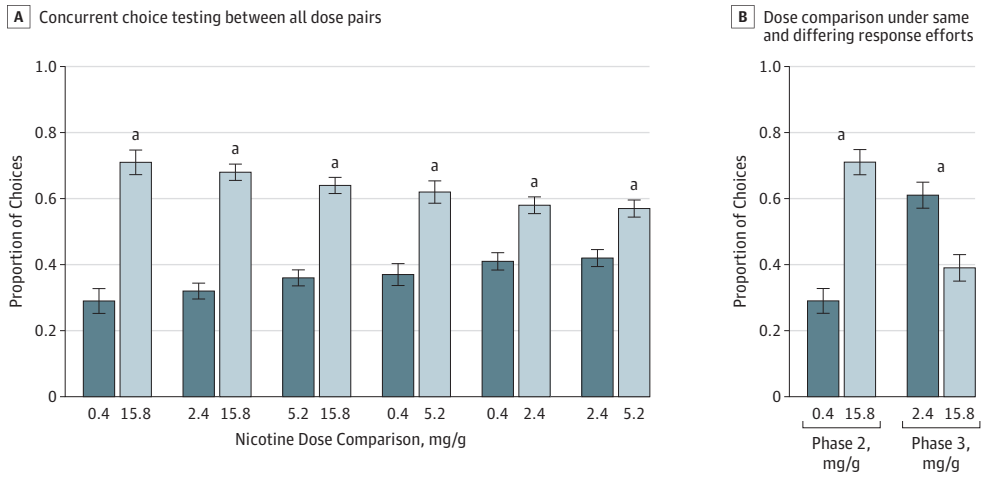
One hundred sixty-nine daily smokers (120 women [71.0%] and 49 men [29.0%]; mean [SD] age, 35.6 [11.4] years) were included in the analyses. In concurrent choice testing with the cigarettes available at an equal response effort, participants chose those with higher compared with lower nicotine content across each of the 6 dose pairs, a finding consistent with cigarettes with reduced nicotine content having lower addiction potential ($t_{159}>2.96$; $P < .008$) (**Figure 1**A). The only difference between populations ($F_{2,154} = 3.27$; $P = .04$) in that regard was at the 0.4- vs 2.4-mg/g dose pair, at which smokers with affective disorders chose the higher dose more frequently ($t_{154} = 3.46$; $P < .001$), whereas disadvantaged women ($t_{154} = 1.92$; $P = .06$) and participants with opioid dependence ($t_{154} = 0.11$; $P = .91$) did not exhibit a significant preference between those 2 doses (eFigure 2 in the Supplement).

When concurrent choice testing in phase 3 involved a greater effort to obtain the cigarette with the highest vs lowest nicotine content cigarette (15.8 vs 0.4 mg/g), preference was reversed from that when those same doses were available at equal response effort (Figure 1B). Participants more frequently chose to smoke the cigarette with the 0.4-mg/g dose than the cigarette with the 15.8-mg/g dose ($t_{160} = 4.73$; $P < .001$), with no differences across sessions ($F_{2,293} = 0.03$; $P = .78$) or populations ($F_{2,160} = 0.41$; $P = .67$). We found no significant interactions of dose and sex or cigarette mentholation status with choice between dose pairs ($F_{5,831} \leq 1.86$; $P \geq .05$).

Simulation

Mean estimated rate of cigarette smoking in the CPT decreased as a function of increasing price across the 4 doses in a manner described by an exponential demand equation (**Figure 2**A). The estimated rate of smoking decreased as a function of decreasing nicotine dose ($F_{3,75} = 5.40$; $P = .002$). No population differences were found except at the 2.4-mg/g dose ($F_{2,57} = 14.00$; $P < .001$), at which smoking rate was greater among those with opioid dependence than among smokers with affective disorders ($F_{1,38} = 20.00$; $P < .001$) and disadvantaged women ($F_{1,38} = 21.00$; $P < .001$) (eFigure 3A in the Supplement).

Figure 1. Concurrent Choice Testing



A, Mean proportion of choices allocated to all possible 2-dose comparisons across the 4 nicotine dose cigarettes (0.4, 2.4, 5.2, and 15.8 mg/g of tobacco) across six 3-hour 2-dose concurrent choice sessions. Data points represent mean proportions of choices allocated to the different nicotine dose cigarettes and across participants and populations; error bars, SEM. Dose pairs are ordered to show those with largest to least preference differences going from left to right. B, The mean proportion of choices allocated to the 15.8-mg/g dose when it was available at the same response effort (fixed-ratio of 10 responses) as the 0.4-mg/g dose (phase 2; left) and when it was available at different response effort (progressive ratio starting at 10 responses that incremented upward to a maximum of 8400 responses) compared with the 4-mg/g dose (fixed-ratio 10) (phase 3; right). Phase 2 and phase 3 are described in the Procedure subsection of the Methods section. Data points represent means across participants and sessions (phase 3); error bars, SEM.

[a] Statistically significant difference at $P < .05$ after Bonferroni correction.

Significant effects of nicotine dose were also observed across 4 of the 5 CPT indices, including the number of cigarettes that participants estimated smoking per day if cigarettes were free of cost (demand intensity) (Figure 2B), how much they were willing to spend daily on smoking (maximum expenditure) (Figure 2C), price at which the smoking rate began to decrease proportionate to increasing price (maximum price) (Figure 2D), and of particular relevance to addiction potential, the price at which participants indicated they would quit smoking rather than incur the cost (breakpoint) (Figure 2E) ($F_{3,484} \geq 5.38$; $P \leq .001$). Overall sensitivity to price did not increase significantly as nicotine dose decreased ($F_{3,437} = 2.62$; $P = .05$) (Figure 2F). The only effect of population ($F_{2,97} = 5.02$; $P = .008$) across these 5 indices was with cigarettes smoked per day if free of cost (demand intensity) (eFigure 3B in the Supplement), with greater smoking among those with opioid dependence compared with disadvantaged women ($t_{163} = 3.02$; $P = .009$). We found no significant interactions between nicotine dose and population ($F_{6,484} \leq 0.98$; $P > .05$). A small proportion of participants reported zero demand across all prices that varied by dose for 0.04 mg/g (19 of 166 [11.4%]), 2.3 mg/g (10 of 164 [6.1%]), 5.2 mg/g (5 of 165 [3.1%]), and 15.8 mg/g (4 of 166 [2.4%]) ($F_{3,492} = 8.12$; $P < .001$).

The CPT assessments were also completed at the end of phase 3 sessions. Demand remained higher for the 15.8- vs 0.4-mg/g dose ($F_{1,38} = 7.45$; $P = .01$) (eFigure 4 in the Supplement), suggesting that the preference reversal observed in the concurrent choice tests resulted from the greater effort required to obtain the high dose and not a generalized change in the relative reinforcing value of the 2 doses. We found no significant differences across sessions or populations.

Participant Ratings and Compensatory Smoking Measures

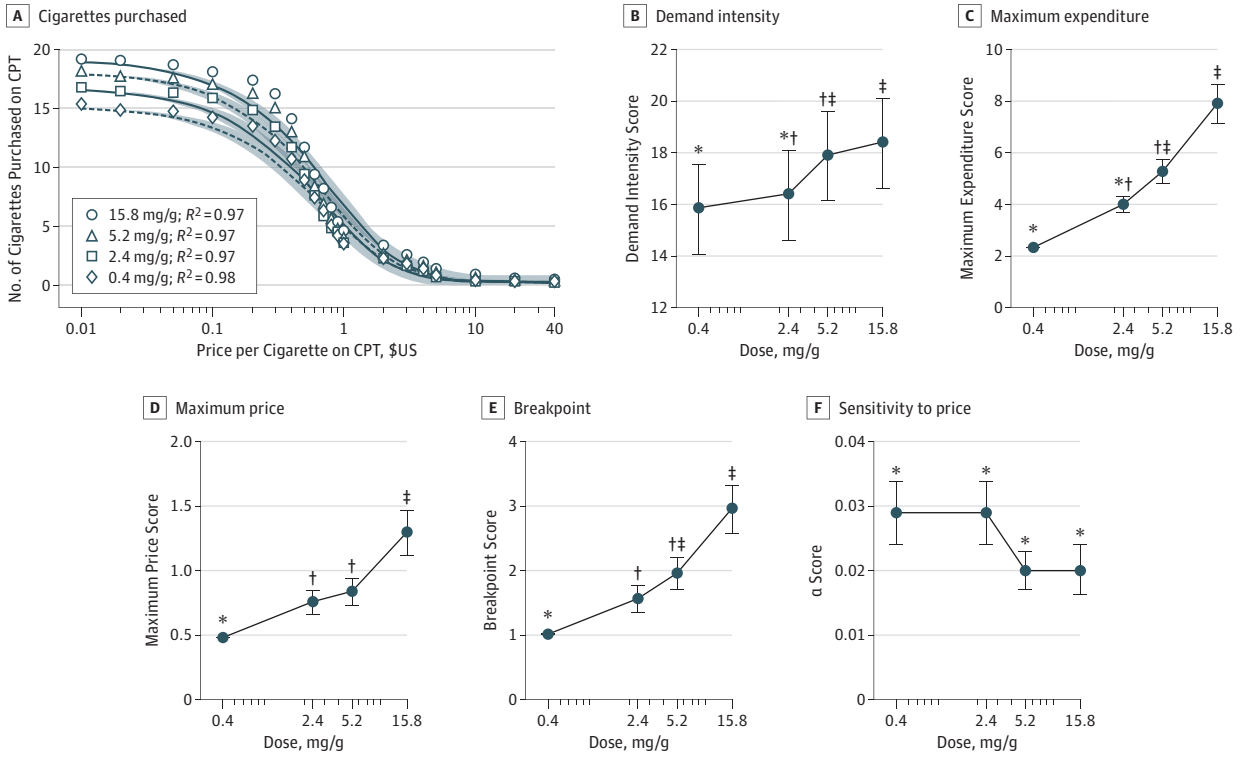
In tests of subjective effects, positive ratings of smoking on the mCEQ decreased as a function of reducing nicotine content, a finding consistent with reduced addiction potential ($F_{3,501} \geq 7.08$; $P < .001$) (**Table 2**); there were no significant interactions between dose and sex or cigarette mentholation status ($F_{3,495} \leq 2.33$; Ps $\geq .05$). Each of the doses significantly reduced nicotine withdrawal symptoms and craving on the MNWS ($t_{2016} > 2.67$; $P < .001$), although duration of effects was greater at higher doses (**Table 3**) (dose-by-time interaction; $F_{12,2014} = 2.64$; $P = .002$). Results of the QSU-Brief are found in eTable 1 in the Supplement. Only 1 significant difference between populations was found for the MNWS total score (main effect; $F_{2,166} = 7.54$; $P = .001$), with symptoms among disadvantaged women significantly lower than among individuals with opioid dependence ($t_{166} = -2.42$; $P = .02$) or affective disorders ($t_{95} = -3.81$; $P < .001$).

No significant changes were noted across doses in smoking topography (eFigure 5 in the Supplement) or breath CO exposure levels (eTable 2 in the Supplement) indicative of compensatory smoking. The results suggest that participants may smoke the reduced nicotine content cigarettes less intensely. These effects were consistent across populations.

Discussion

Overall, our results indicate that reducing the nicotine content of cigarettes reduces the relative reinforcing effects of smoking and thus addiction potential in populations with psychiatric conditions and other vulnerabilities to tobacco

Figure 2. Results From the Cigarette Purchase Task (CPT) Simulating Estimated Demand for Each of the Different Nicotine Content Cigarettes at Escalating Prices



A, Overall demand (estimated consumption levels across prices ranging from $0 to $40 per cigarette). Data points represent means across participants; shaded areas, 95% CI in the best lines. B-F, Data points represent means across participants; error bars, SEM. Demand intensity indicates estimated consumption at $0 price (range, 0-100, with higher scores indicating greater consumption when cigarettes are free); maximal expenditure, estimated maximal expenditure participants were willing to incur for smoking in 1 day (range, 0-1600, with higher scores indicating greater expenditure); maximal price, estimated price at which demand begins to decrease proportional to price increases (range, 0-40, with higher scores indicating a greater cigarette unit price associated with unit elasticity for cigarettes); breakpoint, estimated price at which participants would quit smoking rather than incur its costs (range, 0-60, with higher scores indicating a greater cigarette unit price associated with discontinuation of smoking); and α, estimated overall sensitivity of demand to price increases (range, 1.096^{-20} to 1, with higher scores indicating greater sensitivity to cigarette unit price increases). Data points not sharing a symbol differ significantly ($P < .05$) after Bonferroni correction.

Table 2. mCEQ Subscale Scores Across Research Cigarettes

	Nicotine Level of Research Cigarettes by Subscale Score, Mean (SEM)[a]			
mCEQ Subscale	0.4 mg/g	2.4 mg/g	5.2 mg/g	15.8 mg/g
Smoking satisfaction	3.2 (0.1)*	3.6 (0.1)†	3.9 (0.1)†	4.6 (0.1)‡
Psychological reward	2.7 (0.1)*	2.8 (0.1)*†	3.1 (0.1)†	3.4 (0.1)‡
Aversion	1.5 (0.1)*	1.5 (0.1)*	1.5 (0.1)*	1.7 (0.1)†
Enjoyment of respiratory tract sensations	2.9 (0.1)*	3.1 (0.1)*	3.6 (0.3)†	4.1 (0.1)‡
Craving reduction	3.4 (0.1)*	3.7 (0.1)*†	4.0 (0.3)†	4.6 (0.1)‡

Abbreviation: mCEQ, modified Cigarette Evaluation Questionnaire.

[a] Data points not sharing a symbol differ significantly ($P < .05$) after Bonferroni correction.

addiction. Although this association was graded with no clear threshold effect, the 0.4-mg/g dose most consistently and robustly differed from the 15.8-mg/g control dose, a finding supporting a prior hypothesis about reducing nicotine content below 0.7 mg/g.[8] A thresholdlike effect was reported previously in a trial examining chronic exposure among more medically and socially stable smokers who maintained lower rates of smoking at doses of 2.4 mg/g or less compared with higher doses.[12] Whether a similar pattern emerges during extended exposure in more vulnerable populations should be examined in future studies.

Reductions in reinforcing effects were achieved in the present study without causing untoward withdrawal, craving, or compensatory smoking. The consistency of effects noted across the 3 vulnerable populations underscores the generality of these results, especially regarding the control that nicotine content exerts over smoker preferences, despite considerable individual differences. Overall, the present findings are consistent with the lower smoking rates, decreased nicotine dependence severity, increased quit attempts, and lower intensity of demand observed in clinical trials of cigarettes with reduced nicotine content among more stable smokers.[9-12,36]

Table 3. Time Course of Effects of the Varying Dose Research Cigarettes on MNWS Desire to Smoke and Total Scores

MNWS Score	Nicotine Level of Research Cigarettes by Score, Mean (SEM)[a]			
	0.4 mg/g	2.4 mg/g	5.2 mg/g	15.8 mg/g
Desire to smoke				
Presmoking baseline	3.0 (0.1)*[1]	3.0 (0.1)*[1]	3.0 (0.1)*[1]	3.1 (0.1)*[1]
At 15 min	2.2 (0.1)*[2]	2.1 (0.1)*†[2]	1.9 (0.1)†[2]	1.5 (0.1)‡[2]
At 30 min	2.4 (0.1)*[2,3]	2.4 (0.1)*[3]	2.3 (0.1)*†[3]	2.0 (0.1)†[3]
At 45 min	2.6 (0.1)*[3]	2.7 (0.1)*[4]	2.7 (0.1)*[4]	2.4 (0.1)*[4]
At 60 min	2.9 (0.1)*[1]	2.9 (0.1)*[1,4]	2.8 (0.1)*[1,4]	2.7 (0.1)*[4]
Total				
Presmoking baseline	1.1 (0.1)*[1]	1.0 (0.0)*[1]	1.1 (0.1)*[1]	1.1 (0.1)*[1]
At 15 min	0.7 (0.1)*[2]	0.7 (0.1)*[2]	0.7 (0.1)*[2]	0.6 (0.1)*[2]
At 30 min	0.8 (0.1)*[2]	0.8 (0.1)*[3]	0.9 (0.1)*[3]	0.7 (0.1)*[2]
At 45 min	1.0 (0.1)*[1]	0.9 (0.1)*[1]	1.0 (0.1)*[4]	0.8 (0.1)*[4]
At 60 min	1.1 (0.1)*†[1]	1.0 (0.1)*†[1]	1.1 (0.1)*[1,4]	0.9 (0.1)†[4]

Abbreviation: MNWS, Minnesota Nicotine Withdrawal Scale.

[a] Within each assessment time, data points not sharing a symbol differ significantly ($P < .05$) after Bonferroni correction. Within each dose, data points not sharing a number differ significantly ($P < .05$) after Bonferroni correction.

The ability of increased response cost to shift preference to the 0.4- vs 15.8-mg/g dose (Figure 1B) suggests that cigarettes with very low nicotine content can serve as economic substitutes for cigarettes with commercial-level nicotine content when the cost to obtain the higher-dose products is greater. This observation is consistent with unit-price models of drug abuse wherein reinforcing value corresponds to the ratio of drug dose and cost.[37,38] This observation has considerable tobacco regulatory implications. For example, allowing cigarettes with very low nicotine content to be sold in common retail outlets while restricting the sale of cigarettes with higher nicotine content to less plentiful or more regulated stores would be predicted to shift preference toward the former. This same concept may also extend to regulatory efforts to shift preference from combusted to less harmful noncombusted tobacco products.

Over time, smokers with comorbid psychiatric conditions and socioeconomic disadvantage have become a larger proportion of smokers in developed countries, in part because they are more addicted and thus less likely to try to quit or to succeed if they try.[1-6,14,15] Smoking in these populations is an important contributor to health disparities.[2,3] Thus, it is important that tobacco control and regulatory policies are developed that are effective among populations with comorbid psychiatric conditions and socioeconomic disadvantage.

Limitations

The present study assessed acute response in a laboratory setting, leaving unanswered whether results can be generalized to vulnerable populations with chronic use of cigarettes with reduced nicotine content in naturalistic settings. That question can only be answered by field trials in vulnerable populations, which are under way. The acute laboratory model was an appropriately safe setting to begin examining cigarettes with reduced nicotine content in medically and socially unstable populations. The laboratory models used in the present study are well-validated methods for assessing the addiction potential of drugs in naturalistic settings.[39,40] Results from prior studies of acute response to cigarettes with reduced nicotine content in laboratory settings in the general population of smokers used similar methods,[32,41] and results align closely with those seen during chronic exposure in naturalistic settings.[12]

Conclusions

Our results suggest that a national regulatory policy reducing the nicotine content of cigarettes may reduce the addiction potential of cigarettes and that those effects would extend to populations that are highly vulnerable to tobacco addiction. In addition, the results suggest how regulatory policies could potentially shift preferences from more- to less-harmful tobacco products. Studies of extended exposure to reduced nicotine content cigarettes and studies in populations with other psychiatric conditions are warranted.

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