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Smoking abstinence and cessation-related outcomes one month after an immediate versus gradual reduction in nicotine content of cigarettes

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Abstract

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Appendix A. Supplementary data

Supplementary material to this article can be found online at https://doi.org/10.1016/j.ypmed.2022.107175.

The United States Food and Drug Administration has the authority to reduce the nicotine content in cigarettes to minimal or non-addictive levels and could do so immediately or gradually over time. A large clinical trial compared the two approaches. This secondary analysis assesses abstinence and cessation-related outcomes one month after the trial concluded, when participants no longer had access to very low nicotine content (VLNC) research cigarettes. Smokers not interested in quitting (N = 1250) were recruited for the parent trial from 2014 to 2016 across 10 sites throughout the US and randomized to a 20-week study period during which they immediately switched to VLNC cigarettes, gradually transitioned to VLNC cigarettes with five monthly dose reductions, or smoked normal nicotine research cigarettes (control). At the one-month follow-up, both immediate and gradual reduction resulted in greater mean cigarette-free days (4.7 and 4.6 respectively) than the control group (3.2, both $p < .05$). Immediate reduction resulted in fewer mean cigarettes per day (CPD = 10.3) and lower Fagerström Test for Cigarette Dependence (FTCD = 3.7) than the gradual (CPD = 11.7, $p = .001$; FTCD = 3.8, $p = .039$) and control (CPD = 13.5, $p < .001$; FTCD = 4.0, $p < .001$) groups. Compared to controls, gradual reduction resulted in reduced CPD ($p = .012$) but not FTCD ($p = .13$). Differences in CO-verified 7-day point-prevalence abstinence were not significant. Findings demonstrate that switching to VLNC cigarettes resulted in reduced smoking and nicotine dependence severity that was sustained for at least a month after the VLNC trial period in smokers who were not interested in cessation. The greatest harm reduction endpoints were observed in those who immediately transitioned to VLNC cigarettes.

Keywords

Cigarette smoking; Nicotine reduction; Very low nicotine content cigarettes; Tobacco regulatory science; Harm reduction; Smoking cessation

1. Introduction

The Food and Drug Administration (FDA) has the authority to reduce the nicotine content in cigarettes to a minimally addictive level in the United States and could do so on a specific date (i.e., immediately) or gradually over time (Food and Drug Administration, 2018). In an effort to determine the more optimal approach in implementing a nicotine product standard on cigarettes, a large NIH/FDA-funded randomized clinical trial was conducted comparing a gradual nicotine reduction versus an immediate nicotine reduction approach during a 20-week study period among smokers who were not immediately interested in cessation (Hatsukami et al., 2018). The results showed that, although smokers found gradual reduction more acceptable, participants assigned to the immediate reduction group experienced greater reduction in biomarkers of harm, cigarettes per day (CPD), and nicotine dependence, as well as more days of abstinence than smokers who gradually reduced or those with no reduction (controls). In contrast, the gradual reduction and control groups did not significantly differ on these outcomes during the study period (Hatsukami et al., 2018), demonstrating the benefit of immediate reduction while smokers were still using study cigarettes. This trial conducted a follow-up four weeks after the study period when participants no longer had access to the study cigarettes that they were assigned to smoke during the study period. The follow-up data provide an opportunity to examine the potential sustained effects of

being exposed to reduced nicotine content cigarettes on cessation-related outcomes and the differences between gradually reducing nicotine versus an immediate and prolonged use of VLNC cigarettes among smokers who were not interested in quitting at baseline.

Smoking cessation after a period of exposure to immediate versus gradual nicotine reduction could provide evidence for an optimal approach to a nicotine product standard that would decrease dependence and increase quitting. Further, the FDA recently authorized the marketing of VLNC cigarettes as a modified risk tobacco product (Food and Drug Administration, 2021) and thus US smokers may soon have the option to transition to VLNC cigarettes in a market where normal nicotine cigarettes are also available. One prior large trial found participants who abruptly switched to VLNC cigarettes versus normal nicotine cigarettes over six weeks achieved greater reductions in CPD (mean difference = −3.6, $p < .001$) and were more likely to report that they did not "currently smoke cigarettes" at a 30-day follow-up (10.9% vs 2.0%; $p = .02$; (Donny et al., 2015)). Another large multi-site trial of smokers with psychiatric conditions or socioeconomic advantage found 12 weeks of VLNC cigarettes did not significantly affect the proportion of participants who achieved 24-h abstinence or attempted to quit during a 30-day follow-up (Higgins et al., 2020). A third trial assigned participants to gradually transition to VLNC cigarettes versus smoke normal nicotine research cigarettes over eight months and offered participants the option to either continue smoking their assigned research cigarettes, return to their usual brand, or quit smoking during a follow-up phase (Krebs et al., 2021). Participants assigned to VLNC cigarettes were more likely to choose to quit than those assigned to normal nicotine cigarettes (31% vs 21%, $p < .001$), but the difference in the proportion who achieved abstinence at a 12-week follow-up was not significant (9% vs 3%, $p = .07$).

To our knowledge, no prior research has examined abstinence, cigarette smoking, or dependence outcomes after an immediate versus gradual transition to VLNC cigarettes. The present secondary analysis examined smoking abstinence and cessation-related outcomes during a one-month follow-up period after participants completed an immediate switch to VLNC cigarettes, a gradual transition to VLNC cigarettes, or smoked normal nicotine study cigarettes over five months.

2. Methodology

The full study methodology is described in detail elsewhere (Hatsukami et al., 2018). Briefly, data for this secondary analysis are from a randomized, parallel, double-blind trial conducted at 10 sites throughout the United States. Each site obtained approval to conduct the study from their institutional review board. Individuals were eligible if they were of legal age to purchase cigarettes, smoked ≥5 CPD, provided biochemical verification of smoking (breath carbon monoxide (CO) of ≥8 ppm or urinary cotinine level of ≥1000 ng/mL), and provided breath alcohol level of <0.02% at screening. Individuals were excluded if they intended to quit smoking in the next 30 days, self-reported use of tobacco products other than cigarettes on ≥10 of the past 30 days, had prior exposure to reduced nicotine content study cigarettes, demonstrated serious psychiatric or medical disease or had a recent (within three months) change in symptoms or medications, submitted positive urine toxicology

screening results for illicit drugs other than cannabis or were breastfeeding, pregnant, or planning to become pregnant.

Participants were recruited between 2014 and 2016, with the final follow-up occurring in 2017 (Hatsukami et al., 2018). Eligible participants (N = 1250) underwent a two week baseline period of smoking their usual brand cigarettes before they were assigned (in a 2:2:1 ratio) to one of the following groups for 20 weeks: (1) immediately switch to VLNC cigarettes (0.4 mg of nicotine per gram of tobacco; n = 503), (2) gradually transition to research cigarettes with progressively lower nicotine every four weeks: 15.5, 11.7, 5.2, 2.4, and 0.4 mg of nicotine per gram of tobacco (n = 498), or (3) smoke usual nicotine content research cigarettes (15.5 mg of nicotine per gram of tobacco; control group, n = 249). Of note, commercially available usual brand cigarettes typically range from 15 to 18 mg of nicotine per gram of tobacco (Kozlowski et al., 1998). Participants attended weekly study visits during the first four weeks and then biweekly visits for the next 16 weeks during the 20-week study period. At the conclusion of the study period, participants were advised to set a quit date and provided with a "Clearing the Air" self-help manual (National Cancer Institute, 2008) and a list of local smoking cessation resources. Participants received no research cigarettes after week 20 and were invited to complete a final follow-up study visit at week 24.

Outcomes.

This secondary analysis reports outcomes during the follow-up period, between the conclusion of the study period (week 20; after which research cigarettes were no longer available to participants) and the week 24 follow-up visit. Self-reported 7-day point-prevalence abstinence was biochemically verified with breath CO of <6 ppm at the 24-week follow-up. Using timeline follow-back, participants reported the number of CPD during the follow-up period. The number of days of cigarette abstinence (i.e., cigarette-free days) was determined from participants' self-reported CPD by counting a day with zero CPD as a cigarette-free day. Participants were not asked whether a smoke-free day was associated with an intention to quit. Additionally, participants reported intention to quit with the Contemplation Ladder (0 = no thought of quitting to 10 = taking action to quit (Biener and Abrams, 1991)) and cigarette dependence with the Fagerström Test for Cigarette Dependence (FTCD; 0 = least to 7 = most dependent (Fagerstrom, 2012)) at week 24. The full FTCD includes an item to assess CPD. However, we report CPD as a separate outcome and thus use a modified version of the FTCD without the CPD item to avoid redundancy.

2.1. Analysis—Continuous outcomes were analyzed using linear regression, binary outcomes were analyzed using logistic regression, and the number of abstinence days, which were treated as count data, were analyzed using quasi-Poisson regression with the scale parameter being estimated using deviance to handle over-dispersion, and the logarithm of total number of days as the offset term in the regression. Analysis of non-abstinence outcomes (CPD, dependence, and Contemplation Ladder) were conducted among the subset of participants who did not achieve CO-verified 7-day point-prevalence abstinence at week 24. Group (immediate reduction, gradual reduction, or control) was the primary variable in the regression models, with the baseline level of the outcome variable, when available,

being adjusted as a covariate. Analyses testing adherence to study cigarettes (percent of total CPD that were study cigarettes at week 20) as a predictor of abstinence outcomes are limited to the 981 participants who provided data on cigarettes per day at the end of the study period (i.e., week 20). Adherence to study cigarettes was self-reported and the use of VLNC cigarettes was verified with urinary total nicotine equivalents (TNE). Linear mixed modeling was used to examine change in CPD over time during follow-up among the 953 participants who provided CPD data at follow-up (i.e., weeks 20 to 24). We assessed change in cigarette-free days over time during follow-up using generalized estimating equation (GEE) modeling on the daily abstinence data. SAS 9.4 was used for all analyses if not otherwise specified.

Missing data for 7-day point-prevalence abstinence and number of cigarette-free days were treated as smoking in primary analyses. In sensitivity analyses, missing data for 7-day point prevalence abstinence were imputed by multiple imputation using the discriminant function method (Brand, 1999). In a sensitivity analysis for the missing number of cigarette-free days, which is zero-inflated count data, a two-step procedure was adopted: in the first step, based on the imputed complete binary continuous abstinence variable (yes/no), zero was imputed for people who achieved continuous abstinence; in the second step, the missing number of days of abstinence was imputed by the Markov Chain Monte Carlo (MCMC) method for people who did not achieve continuous abstinence. Missing data for continuous variables were imputed by multiple imputation using the MCMC method in our primary analyses. Twenty data sets were created. The same auxiliary variables (baseline age, gender, race, ethnicity, education, marital status, employment, menthol status, FTCD, CPD, urinary TNE, and serum cotinine) were used in the multiple imputation as in the main outcome paper (Hatsukami et al., 2018). For the count data, we also performed multiple imputation with hurdle negative binomial model by using the R package ‘countimp’ (Kleinke and Reinecke, 2019) as a sensitivity analysis.

3. Results

Most participants (61.8%) identified as White, 30.4% as Black, and 7.8% as some other race, and 5.3% identified as Hispanic. Most (59.6%) had more than a high school education, 32.6% had a high school education, and 7.8% had less than high school. At baseline, participants were a mean 45.1 (SD = 1 3.4) years old, smoked a mean 17.1 CPD (SD = 8.2), and reported a mean dependence score of 5.3 (SD = 2.1) on the FTCD including the CPD item. Detailed participant characteristics by condition are reported elsewhere (Hatsukami et al., 2018). In total, 32.0% to 37.2% of participants in the immediate, 19.5% to 22.5% in the gradual and 15.7% to 16.7% in the control groups were missing data on one or more of the five reported outcomes at the 24-week follow-up (Table S1 in the Supplement). Missing data at follow-up is largely consistent with the proportion of missing data in each condition at the end of the study period (i.e., week 20; (Hatsukami et al., 2018)), indicating most participant who were missing at follow-up dropped out during the study period.

3.1. Point-prevalence abstinence and cigarette-free days at follow-up

Few participants (≤10%) achieved CO-verified 7-day point-prevalence abstinence at the week-24 follow-up (Table 1). Though groups did not significantly differ, there was numerically more abstinence in both reduction groups with a trend indicating greater odds of point-prevalence abstinence in the gradual versus the control group. Most (61.3%) who achieved point-prevalence abstinence at follow-up quit smoking cigarettes during follow-up, after VLNC cigarettes were discontinued. Both the gradual and immediate reduction groups resulted in a greater number of cigarette-free days compared to controls, suggesting that switching to VLNC cigarettes resulted in a mean increase of 1.4 to 1.5 cigarette-free days at follow-up (Table 1). The proportion of participants in each group who reported a cigarette-free day was highest at the beginning of the follow-up period and consistently declined over time in all three groups (Fig. S1) such that the odds of abstinence on any given day decreased by 5% per week during follow-up (OR = 0.95, 95% CI = 0.91, 0.98). The group by time interaction for cigarette-free days was not significant ($p = .35$).

After controlling for study group, adherence to study cigarettes during the study period was associated with 7-day point-prevalence abstinence (OR = 1.04, 95% CI = 1.01, 1.07) and cigarette-free days (RR = 1.03, 95% CI = 1.02, 1.04) during the follow up period. Thus, a 1% increase in adherence to study cigarettes was associated with a 4% increase in the odds of point prevalence abstinence and a 2% increase in the rate of cigarette-free days during follow-up. Study group by adherence interactions were not significant for point-prevalence abstinence ($p = .59$) or cigarette-free days ($p = .20$) during follow-up.

In a series of sensitivity analyses, we compared point-prevalence abstinence and cigarette-free days between groups when missing data were handled with multiple imputation instead of treated as continued smoking (Table S2). In contrast to our primary findings, significantly more participants achieved 7-day point-prevalence abstinence in the immediate (OR = 2.2, 95% CI = 1.2, 4.0) and gradual (OR = 1.9, 95% CI = 1.02, 3.4) conditions compared to the control condition, but differences between immediate versus gradual groups remained non-significant (OR = 1.2, 95% CI = 0.8, 1.8). Findings from sensitivity analyses of cigarette-free days were similar to the primary findings reported above.

3.2. Cigarettes per day, cigarette dependence, and intention to quit smoking at follow-up

During follow-up, participants in the immediate group smoked fewer CPD than the gradual or control groups, and the gradual group smoked fewer CPD than the control group (Table 2). Across all three groups, smoking was lowest at the beginning of the follow-up period with a small gradual increase in CPD at a mean increase of approximately 0.2 cigarettes per 10 days during follow-up ($\beta = 0.018$; 95% CI = 0.005, 0.032). The condition by time interaction was not significant for CPD ($p = .51$). Dependence at follow-up was measured at week 24 only. Differences between groups were small but significant: the immediate reduction group maintained lower levels of dependence than the gradual reduction and control groups, but differences between the gradual reduction and control groups were not significant. Differences between the groups' intention to quit on the Contemplation Ladder were not significant at follow-up.

4. Discussion

This secondary analysis examined the sustained effects of exposure to an immediate or gradual transition to VLNC cigarettes at a one-month follow-up in the largest trial of VLNC cigarettes to date (Hatsukami et al., 2018). To the best of our knowledge, this analysis is the first to compare the impact of immediate versus gradual reductions on smoking at follow-up, after VLNC cigarettes were discontinued. Immediate reduction resulted in more cigarette-free days than the control group as well as fewer CPD and lower nicotine dependence than the gradual reduction and control groups. Gradual reduction resulted in more cigarette-free days and fewer CPD than the control group.

Both immediate and gradual groups had more cigarette-free days than controls during follow-up. The benefit to immediate reduction compared to controls at follow-up is consistent with findings during the study period (Hatsukami et al., 2018) and further demonstrates the sustained gains from immediately switching to VLNC cigarettes. The benefits from immediate reduction are also consistent with a likely mechanism of action; that is, more exposure to the least reinforcing (VLNC) cigarettes should be associated with faster and greater extinction to expected reinforcement from cigarettes. Contrary to the study period (Hatsukami et al., 2018), gradual reduction participants also had more cigarette-free days than controls during follow-up, indicating that some of the effect of gradual reduction on abstinence could be delayed but ultimately similar to immediate reduction. The proportion of participants who were cigarette-free on each day during follow-up gradually diminished over time, which suggests difficulties maintaining abstinence in a marketplace where normal nicotine cigarettes are available and demonstrates the need for research examining longer term cessation outcomes after exposure to VLNC cigarettes.

Point-prevalence abstinence was qualitatively greater (but not statistically significant) for immediate and gradual reduction groups compared to controls when missing data were imputed as smoking, but effects for both groups were statistically significant in the multiply imputed sample. Of note, only 7%, 3%, and 2% of participants in the immediate, gradual, and control conditions, respectively, were abstinent at the end of the study period (week 20; (Hatsukami et al., 2018)). Thus, most participants who achieved cessation in the gradual condition appeared to have quit smoking during follow-up. Point-prevalence abstinence at follow-up in both reduction groups (immediate = 9%; gradual = 10%) was similar to abstinence at follow-up in a prior large multi-site 6-week trial of an immediate switch to VLNC cigarettes (11%) in a similar population of smokers with no initial quitting intentions (Donny et al., 2015). We also found that greater adherence to assigned study cigarettes during the study period was associated with greater abstinence at follow-up, which is consistent with a prior analysis of smokers who switched to VLNC cigarettes, but intended to quit at baseline (Dermody et al., 2015). However, we found no interaction between group and adherence, which suggests that compliance, and not necessarily use of VLNC cigarettes per se, was associated with increased abstinence. Nonetheless, our findings suggest greater abstinence among both reduction groups than the control group at follow-up, which is noteworthy given the importance of cessation for harm reduction from VLNC cigarettes (World Health Organization, 2015).

We found a small, graded effect in which CPD was lowest in the immediate reduction group, followed by the gradual group, and highest in the control group. Similarly, there was a small effect in which dependence was lower in the immediate reduction group compared to both the gradual and control groups. The benefit to immediate reduction at follow-up is consistent with findings at the end of the study period, when participants were still smoking VLNC cigarettes (Hatsukami et al., 2018). Thus, some of the gains from immediate reduction appear to have been sustained one month after study cigarettes were discontinued. Further, reductions in CPD were relatively stable throughout the follow-up period, which further supports the potential for sustained improvements resulting from exposure to nicotine reduction. Benefits in both immediate and gradual groups suggest that use of VLNC cigarettes could help to reduce smoking, even in a market where normal nicotine cigarettes are available, but the effects are likely to be modest. Importantly, it remains unclear whether smokers would choose to use VLNC cigarettes outside of a research setting in a market where both VLNC and normal nicotine cigarettes are available.

4.1. Limitations

Limitations include a substantial amount of missing data, largely due to dropout during the study period (Hatsukami et al., 2018). There was disproportionately more missing data in the immediate than gradual or control groups, which reflects findings from the parent trial that participants found immediate reduction less acceptable than gradual reduction (Hatsukami et al., 2018). Thus, follow-up findings could have been influenced by attrition bias. In addition, follow-up was limited to one month after study cigarettes were discontinued and therefore long-term effects remain unclear. Participants received free study cigarettes and were encouraged to use them as part of the research protocol, which limits the generalizability of our findings. Some effects were small and, thus, the clinical implications regarding the extent to which exposure to VLNC cigarettes affects abstinence-relevant outcomes is unclear. However, small effects can have a large population-level impact if a reduced nicotine standard for cigarettes is implemented. Finally, this trial recruited only individuals who were unmotivated to quit, and, thus, future research is needed to identify the influence of immediate versus gradual reduction among smokers who are interested in smoking cessation. Notably, procedures designed to facilitate extinction while switching to VLNC cigarettes (immediate or gradual) among cessation-motivated smokers should be examined.

5. Conclusions

Both immediate and gradual reduction of nicotine in cigarettes during an experimental period of VLNC cigarette use was associated with more cigarette-free days, reduced smoking, and reduced nicotine dependence compared to a control group at a one-month follow-up, when smokers no longer had access to study cigarettes. Immediate reduction resulted in small but significant improvements over gradual reduction. Findings demonstrate sustained effects from a period of nicotine reduction, with the greatest benefits from immediate reduction and provide further support for a reduced nicotine standard for cigarettes. These findings also support the need for future research examining long term

cessation outcomes among smokers who switch to VLNC cigarettes as a smoking cessation tool.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

EMK, XL, JJ, MA PMC, JDR, LGS, ECD, and DKH have nothing to disclose. DJD has served as a paid expert witness in litigation against tobacco companies. JM has provided consulting and marketing research services to GlaxoSmithKline Consumer Healthcare on smoking cessation behavioral support programs. AAS has received grant support through the Pfizer GRAND grant funding program. RV has received compensation for consulting or scientific advisory board service to Canopy Health Innovations Inc., MyMD Pharmaceuticals, Mira Therapeutics Inc., Syqe Medical Ltd., Radicle Science LLC, and WebMD. NLB serves as a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications, and has been a paid expert witness in litigation against tobacco companies.

References

Biener L, Abrams DB, 1991. The Contemplation Ladder: validation of a measure of readiness to consider smoking cessation. Health Psychol. 10, 360–365. [PubMed: 1935872]

Brand J, 1999. Development, Implementation and Evaluation of Multiple Imputation Strategies for the Statistical Analysis of Incomplete Data Sets.

Dermody SS, Donny EC, Hertsgaard LA, Hatsukami DK, 2015. Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation. Tob. Control 24, 536–539. [PubMed: 25192771]

Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG-, Al'absi M-, Carmella SG, Cinciripini PM, et al. , 2015. Randomized trial of reduced-nicotine standards for cigarettes. N. Engl. J. Med 373, 1340–1349. [PubMed: 26422724]

Fagerstrom KO, 2012. Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. Nicotine Tob. Res 14, 75–78. [PubMed: 22025545]

Food and Drug Administration, 2018. Tobacco Product Standard for Nicotine Level of Combusted Cigarettes: 83 FR 11818. https://www.govinfo.gov/app/details/FR-2018-03-16/2018-05345.

Food and Drug Administration, 2021. FDA Authorizes Marketing of Tobacco Products that Help Reduce Exposure to and Consumption of Nicotine for Smokers Who Use Them, https://www.fda.gov/news-events/fda-newsroom/press-announcements.

Hatsukami DK, Luo X, Jensen JA, Al'absi M, Allen SS, Carmella SG, Chen M, Cinciripini PM, Denlinger-Apte R, et al. , 2018. Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial. JAMA 320, 880–891. [PubMed: 30193275]

Higgins ST, Tidey JW, Sigmon SC, Heil SH, Gaalema DE, Lee D, Hughes JR, Villanti AC, Bunn JY, et al. , 2020. Changes in cigarette consumption with reduced nicotine content cigarettes among smokers with psychiatric conditions or socioeconomic disadvantage: 3 randomized clinical trials. JAMA Netw. Open 3, e2019311. [PubMed: 33079196]

Kleinke K, Reinecke J, 2019. Countimp version 2: a multiple imputation package for incomplete count data. Technical Report.

Kozlowski LT, Mehta NY, Sweeney CT, Schwartz SS, Vogler GP, Jarvis MJ, West RJ, 1998. Filter ventilation and nicotine content of tobacco in cigarettes from Canada, the United Kingdom, and the United States. Tob. Control 7, 369–375. [PubMed: 10093170]

Krebs NM, Zhu J, Wasserman E, Kuprewicz R, Martinez DJ, Veldheer S, Livelsberger C, Modesto J, Reinhart L, et al. , 2021. Switching to progressively reduced nicotine content cigarettes in smokers with low socioeconomic status: a double-blind randomized clinical trial. Nicotine Tob. Res 23, 992–1001. [PubMed: 33249498]

National Cancer Institute, 2008. Clearing The Air: Quit Smoking Today. https://www.cancer.gov/publications/patient-education/clearing-the-air (accessed 6.16.2022).

World Health Organization, 2015. Advisory Note: Global Nicotine Reduction Strategy: WHO Study Group on Tobacco Product Regulation. World Health Organization, Geneva, https://apps.who.int/iris/handle/10665/189651.

Table 1

Abstinence during a 4-week follow-up after immediate or gradual nicotine reduction or smoking normal nicotine cigarettes (control).

	Control group (*n* = 249)	**Gradual reduction group (*n* = 498)**	**Immediate reduction group (*n* = 503)**
7-day point-prevalence abstinence, n (%)	15 (6.0)	50 (10.0)	46 (9.2)
Odds ratio (95% CI)	*Reference*	*1.7 (0.96, 3.2)*	*1.6 (0.9, 2.9)*
	–	*Reference*	*0.9 (0.6, 1.4)*
Cigarette-free days, mean (SD) [a]	3.2 (7.7)	4.6 (9.3)	4.7 (9.3)
Rate Ratio [b] *(95% CI)*	*Reference*	***1.4 (1.04, 1.9)***	***1.5 (1.1, 2.0)***
	–	*Reference*	*1.0 (0.8, 1.3)*

Note:

[a]Median days of abstinence = 0 for all three groups.

[b]Rate ratio, and not mean difference, is reported because data were analyzed using a quasi-Poisson model. 7-day point-prevalence abstinence was CO-verified. Days of abstinence were self-reported. Significant (p < .05) findings are bolded. Missing data were treated as smoking. See Table S2 for findings when missing data are handled with multiple imputation.

Table 2

Cigarettes per day, cigarette dependence, and intention to quit among participants who continued to smoke after immediate nicotine reduction, gradual nicotine reduction, or smoking normal nicotine cigarettes (control).

	Control group (*n* = 234)	Gradual reduction group (*n* = 448)	Immediate reduction group (*n* = 457)
Cigarettes per day, mean (95% CI)	13.5 (12.2, 14.8)	11.7 (10.9, 12.6)	10.3 (9.3, 11.3)
β (95% CI)	*Reference*	***−1.5 (−2.7, −0.3)***	***−3.2 (−4.5, −1.9)***
	–	*Reference*	***−1.7 (−2.8, −0.7)***
Dependence (FTCD) score, mean (95% CI)	4.0 (3.7, 4.2)	3.8 (3.6, 4.0)	3.7 (3.4, 3.9)
β (95% CI)	*Reference*	*−0.2 (−0.5, 0.1)*	***−0.5 (−0.7, −0.2)***
	–	*Reference*	***−0.3 (−0.5, −0.01)***
Contemplation Ladder score, mean (95% CI)	5.5 (5.1, 5.8)	5.5 (5.2, 5.8)	5.7 (5.4, 6.0)
β (95% CI)	*Reference*	*0.1 (−0.3, 0.5)*	*0.4 (−0.1, 0.8)*
	–	*Reference*	*0.3 (−0.1, 0.7)*

Note: FTCD=Fagerström test for cigarette dependence without the cigarettes per day item (scale: 0 = least to 7 = most dependent). Contemplation Ladder (scale: 0 = no thought of quitting to 10 = taking action to quit). Analyses are limited to the 1139 participants who did not achieve CO-verified 7-day point-prevalence abstinence at the week 24 follow-up. Significant ($p < .05$) findings are bolded. Missing data are handled with multiple imputation.