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Effects of Very Low Nicotine Content Cigarettes on Smoking across Vulnerable Populations

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Abstract

There has been long-standing interest in a reduced-nicotine product standard for combusted tobacco, which is within the regulatory purview of the Food and Drug Administration (FDA). In weighing whether to establish this standard, it is important to consider potential responses among people who are at elevated risk for tobacco-related health harms. In this narrative review, we summarize studies of very low nicotine content (VLNC) cigarettes conducted between 2010–2021 in groups that the FDA has identified as vulnerable populations. Studies conducted to date in adults with mental health conditions, adults with opioid use disorder, socioeconomically-disadvantaged adults, and youth or young adults indicate that immediate switching to VLNC cigarettes decreases smoking, with minimal or no unintended negative consequences. Few studies have investigated the effects of VLNC cigarettes in racial or ethnic minorities, people who smoke menthol cigarettes, and pregnant women, but initial findings suggest that responses of these individuals are similar to responses observed in other vulnerable populations. We are not aware of studies that have investigated VLNC cigarettes in military/veteran populations, sexual or gender minority individuals, or people living in underserved rural environments. Future research directions include understanding how to promote cessation in the context of a reduced-nicotine standard, and how to correct VLNC misperceptions in vulnerable populations. Nevertheless, the evidence to date indicates that a reduced-nicotine standard is likely to have the same beneficial effects on smoking reductions as it does in less vulnerable populations, which should provide some confidence in pursuing this regulatory approach.

Keywords

cigarettes; tobacco; dependence; comorbidity; nicotine reduction; socioeconomic disadvantage; mental health; substance use; youth; menthol

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1. Introduction

The 2009 Family Smoking Prevention and Tobacco Control Act authorized the US Food and Drug Administration (FDA) to set product standards for the levels of nicotine and other constituents of tobacco products, as appropriate for the protection of public health (Congress, 2009). When setting product standards, the FDA must consider empirical evidence concerning potential effects on tobacco use among both users and nonusers of tobacco (Congress, 2009). Because nicotine is the main addictive component of tobacco (USDHHS, 1998), there has been long-standing interest in establishing a reduced-nicotine product standard for combusted tobacco (Benowitz & Henningfield, 1994; Gottlieb & Zeller, 2017). Empirical evidence from randomized controlled trials (RCTs) in participants sampled from the general population supports this idea, as switching to very low nicotine content (VLNC) research cigarettes, i.e., cigarettes with 0.4 mg nicotine/g tobacco, reduces smoking and tobacco toxicant exposure among current users, with minimal mood disruption (reviewed in Berman & Glasser, 2019).

In weighing whether to move forward with a reduced-nicotine standard, it is important to consider responses to VLNC cigarettes among people at elevated risk for tobacco-related health harms due to their high rates of smoking and low rates of cessation. The FDA has identified the following groups as vulnerable populations: people with mental health conditions, substance use disorders, or socioeconomic disadvantage, youth, racial and ethnic minorities, sexual and gender minorities, individuals living in underserved rural environments, pregnant women or women of reproductive age, and veterans and those involved in the military (<https://www.fda.gov/tobacco-products/research/research-priorities>). By decreasing tobacco dependence among these vulnerable populations, a reduced-nicotine standard has the potential to increase the likelihood of smoking cessation. However, a reduced-nicotine tobacco standard could also lead to unintended negative consequences, such as compensatory increases in smoke inhalation, increases in psychiatric symptoms, or increases in other substance use in efforts to substitute for reduced cigarette reinforcement. In this narrative review, we summarize the knowledge base concerning the effects of VLNC cigarettes in vulnerable populations, and identify knowledge gaps. Studies were identified through searches in MEDLINE using the terms “nicotine reduction” or “very low nicotine content” or “reduced nicotine” and “cigarettes” along with terms describing the vulnerable populations (e.g., “mental health”, “psychiatric”, “depression”, “alcohol”).

2. Adults with Mental Health Conditions

Table 1 summarizes studies discussed throughout this review. All identified studies were conducted in the US. Much of the empirical research on VLNC cigarettes in vulnerable populations has been conducted with adults with mental health conditions. To our knowledge, the first study was a within-subjects laboratory study that compared the effects of VLNC cigarettes combined with 42 mg transdermal nicotine replacement (NRT) in 30 smokers with schizophrenia compared to 26 smokers without a mental health condition (Tidey et al., 2013). Using a within-subjects design, participants were exposed to VLNC cigarettes with NRT, VLNC cigarettes with placebo patches, NRT alone, or placebo patches alone, for 5-hr periods. After the exposure period, participants completed assessments of

cigarette craving, withdrawal, and cognitive functioning, and had a 90-min period in which they were able to smoke their usual-brand cigarettes *ad libitum*. Study results indicated that VLNC cigarettes, combined with NRT or placebo patches, reduced craving, withdrawal symptoms, and usual brand smoking in both groups of participants, without increasing psychiatric symptoms or compensatory smoking (Tidey et al., 2013; 2016). In both groups, cognitive function impairments were observed in the VLNC plus placebo patches condition, which were reversed when VLNC cigarettes were combined with active NRT (AhnAllen et al., 2015). Next, a multisite laboratory trial in three vulnerable populations, including men and women with depression or anxiety disorders, men and women receiving methadone or buprenorphine maintenance treatment for opioid use disorder, and women with socioeconomic disadvantage, used a within-subjects design to investigate the acute effects of cigarettes varying in nicotine content (0.4, 2.3, 5.2, and 15.8 mg nicotine/g tobacco) on cigarette craving, withdrawal symptoms, and cigarette reinforcement (Higgins et al., 2017). Results indicated that all doses reduced craving and withdrawal, although the duration of these effects were longer at higher doses. Cigarette preference and positive subjective ratings decreased as a function of reducing nicotine content. Depression versus anxiety diagnosis and symptom severity did not influence VLNC effects (Gaalema et al., 2019). These findings demonstrate that VLNC cigarettes can suppress cigarette craving and withdrawal, while having lower addiction potential than higher-nicotine cigarettes.

These promising findings were bolstered by findings from longer randomized trials. Tidey et al. (2017) conducted a secondary analysis of a multisite RCT of research cigarettes varying in nicotine content (Donny et al., 2015) to compare the effects of VLNC or normal nicotine content (NNC) cigarettes in 109 participants with elevated depressive symptoms and 608 participants with lower depressive symptoms (Tidey et al., 2017). Following a baseline period, participants visited the laboratory weekly to complete behavioral, physiological and subjective measures and to receive research or usual brand cigarettes. At week 6, participants in the VLNC condition had lower smoking rates, nicotine dependence, and cigarette craving levels than those in the NNC condition, regardless of depressive symptom status (Tidey et al., 2017). Furthermore, participants with elevated depressive symptoms at baseline who had been randomized to the VLNC condition had lower depressive symptoms at week 6 than those in the NNC condition (Tidey et al., 2017). Although few participants assigned to VLNC cigarettes were completely adherent with using only VLNC cigarettes during the trial (Nardone et al., 2016) effects on depressive symptoms did not change appreciably when adherence was considered (Tidey et al., 2017).

Two RCTs have investigated the effects of VLNC cigarettes in people with mental health conditions. In the first study, 58 people with schizophrenia or bipolar disorder completed a baseline period and were then randomized to a 6-week VLNC or NNC condition (Tidey et al., 2019). In weekly laboratory visits, participants completed behavioral, physiological and subjective measures and received a renewed supply of research cigarettes. At week 6, participants in the VLNC condition smoked fewer cigarettes per day and had lower breath carbon monoxide (CO) and cigarette craving levels than those in the NNC condition. There was no compensatory smoking of VLNC cigarettes (Denlinger-Apte et al., 2020). While there was no indication of increased psychiatric symptoms among those in the VLNC cigarette condition, non-adherent use of usual brand cigarettes or alternative nicotine

products, may have minimized effects of nicotine reduction on psychiatric symptoms (Reed et al., 2022). Finally, a multisite RCT of cigarettes varying in nicotine content (0.4, 2.4 or 15.8 mg/g) with a 12-week intervention period was conducted in three vulnerable populations, including men and women with depression or anxiety disorders, men and women receiving methadone or buprenorphine maintenance treatment for opioid use disorder, and women with socioeconomic disadvantage (Higgins et al., 2020). Participants completed behavioral, subjective and physiological assessments, and received free research cigarettes at weekly visits. At week 12, participants who had been randomized to 0.4 or 2.4 mg/g VLNC cigarettes smoked fewer cigarettes per day and had lower cigarette dependence, breath CO, and nicotine exposure levels than those in the NNC condition (Higgins et al., 2020). Depressive symptoms were increased in the VLNC condition but remained within the minimal range (Higgins et al., 2020). These studies indicate that a reduced-nicotine standard has the potential to reduce smoking and tobacco toxicant exposure in people with mental health conditions, with minimal mood disruption.

3. Adults with Opioid Use Disorder (OUD)

OUD is associated with very high rates of tobacco use and extremely low cessation rates (Miller & Sigmon, 2015). An acute laboratory study compared the effects of cigarettes varying in nicotine content (0.4, 2.3, 5.2, and 15.8 mg nicotine/g tobacco) on cigarette craving, withdrawal symptoms, and cigarette reinforcement in three vulnerable populations including 60 individuals receiving methadone or buprenorphine maintenance treatment for OUD (Higgins et al., 2017). Results indicated that cigarette reinforcement decreased as a function of reducing nicotine content (Higgins et al., 2017), and participants with OUD did not experience more severe cigarette craving or withdrawal than the other two populations (Streck et al., 2020). A subsequent study examined the effects of cigarettes varying in nicotine content (0.4, 2.4 or 15.8 mg/g) over a 12-week period in three vulnerable populations, including 260 people receiving methadone or buprenorphine treatment for OUD (Higgins et al., 2020). Participants received free research cigarettes throughout the trial and visited the laboratory weekly to complete behavioral, subjective and physiological assessments. Findings indicated that participants with OUD who were randomized to 0.4 or 2.4 mg/g VLNC cigarettes smoked fewer cigarettes and had lower breath CO levels at week 12 than those in the 15.8 mg/g condition (Higgins et al., 2020). Participants with OUD were less sensitive than the other two vulnerable populations to effects of nicotine reduction on nicotine and toxicant exposure, potentially due to lower VLNC adherence (Higgins et al., 2020). These findings suggest that a reduced-nicotine standard has the potential to reduce smoking in people receiving medication treatment for OUD, but these individuals may benefit from nicotine replacement if a reduced-nicotine standard is mandated.

4. Adults who use Alcohol or Cannabis

As use of alcohol and cannabis is elevated among people who smoke (Moeller et al., 2018), understanding the effects of a reduced-nicotine standard on substance use is an important consideration. To our knowledge, the first study to investigate the effects of VLNC cigarettes in adult cannabis users was a secondary analysis of a large multisite RCT (Donny et al, 2015, described above) conducted by Pacek et al. (2016). The secondary

analysis in 207 cannabis users and 510 non-users found that, at the end of the 6-week intervention, participants in the VLNC condition smoked fewer cigarettes and had lower nicotine exposure and dependence than those in the NNC condition, notwithstanding their cannabis use status (Pacek et al., 2016). Cigarette condition did not affect the prevalence of cannabis use or the proportion of days on which cannabis was used (Pacek et al., 2016). A secondary analysis of the laboratory study by Higgins et al. (2017) found that cannabis use did not moderate the effects of nicotine dose on cigarette reinforcement, although cannabis users rated cigarette satisfaction and craving reduction higher than non-users across doses (Parker et al., 2018).

A secondary analysis of the Donny et al. (2015) trial was undertaken to investigate whether alcohol use affected VLNC response. This analysis found that smoking was reduced at week 6 among 403 alcohol drinkers who had been randomized to the VLNC condition, with no indication of compensatory increases in drinking (Dermody et al., 2016). These investigators subsequently performed a secondary analysis of a 20-week trial in which the nicotine content of cigarettes was reduced either immediately or gradually (Hatsukami et al. 2018), to examine the potential moderating effects of alcohol use (Dermody et al., 2021). At baseline, alcohol users reported drinking 0.93 standard drinks per day and 1.64% binge drinking days (defined as consuming 4 drinks for women or 5 drinks for men within 2 hours). Baseline drinking did not moderate the effects of VLNC cigarettes on smoking at week 20, although nicotine exposure was reduced to a greater extent among nondrinkers. Among the 415 alcohol drinkers, the VLNC condition was associated with reduced daily alcohol use during weeks 17–20, and reduced binge drinking during weeks 9–17. Overall, these findings suggest that a nicotine reduction policy could reduce smoking regardless of alcohol use, and may also reduce alcohol use (Dermody et al., 2021).

5. Socioeconomically-Disadvantaged Adults

Socioeconomic disadvantage (low SES) is a significant predictor of smoking initiation, smoking persistence, and smoking-related health consequences (United States Department of Health and Human Services, 2014). Women of reproductive age are a particular priority, due to the potential for smoking to impact both the adult individual and their offspring *in utero* and during childhood (Higgins & Chilcoat, 2009). The first investigation recruited 53 low-SES women of reproductive age for an acute laboratory study comparing the effects of cigarettes varying in nicotine content (0.4, 2.3, 5.2, and 15.8 mg/g) on cigarette reinforcement, craving, and withdrawal symptoms (Higgins et al., 2017). Results indicated that low-SES women found VLNC cigarettes less reinforcing, although all study cigarettes reduced withdrawal and craving post-abstinence. Importantly, participants did not exhibit compensatory smoking at lower nicotine doses.

These findings were further tested in two RCTs. One trial assigned 257 low-SES women to cigarettes with 0.4, 2.4, or 15.8 mg nicotine/g tobacco for 12 weeks (Higgins et al., 2020). At week 12, participants in the two lower nicotine conditions smoked fewer cigarettes per day, and had lower nicotine exposure, dependence, and behavioral measures of reinforcement than those in the 15.8 mg/g condition. Another trial randomized 245 low-SES men and women to NNC cigarettes or cigarettes that were gradually reduced in nicotine

content over an 18-week period (RNC) (Krebs et al., 2021). At week 18, participants could choose between making a quit attempt with behavioral counseling and NRT, continuing on the study cigarettes, or returning to their usual brand. Findings indicated lower CPD and nicotine exposure, but also higher attrition and lower study cigarette adherence, in the RNC condition compared to the NNC condition. In the treatment choice phase, RNC participants were more likely to make a quit attempt, and were more likely to quit if they were biochemically-compliant with VLNC cigarette use. Finally, a secondary analysis of an RCT by Hatsukami et al. (2018) assessed the effects of immediate versus gradual nicotine reduction among 505 adults with lower educational attainment (Carroll et al., 2021). The immediate reduction approach yielded greater reductions in smoking and nicotine and toxicant exposure in low-SES adults who smoke. These results suggest that nicotine reduction may assist with transitions toward smoking reduction and cessation for low-SES adults, and that an immediate nicotine reduction approach may be both safe and effective in achieving smoking reductions.

6. Youth and Young Adults

Considerably less is known about the effects of nicotine reduction in adolescents and young adults compared to effects in adults. As youth tend to have shorter smoking histories and lighter and/or more intermittent smoking patterns than adults, youth may respond to VLNC cigarettes differently from more established smokers. If young smokers respond more positively to reduced-nicotine cigarettes, this could lead to unintended negative consequences of a reduced-nicotine standard.

The first study to test the effects of cigarette nicotine reduction in adolescents was a laboratory study that compared the effects of cigarettes with 15.8, 5.2, 1.3 or 0.4 mg/g of tobacco in 50 adolescents who smoked daily (Cassidy et al., 2018). In a within-subjects design with four sessions, participants abstained from smoking overnight and completed assessments before and after smoking one research cigarette. Cigarettes with the lowest nicotine content were rated as less satisfying than those with the highest nicotine content. All of the research cigarettes reduced withdrawal symptoms, negative affect, and craving. While reduction in withdrawal and negative affect did not differ by nicotine content, the highest-nicotine cigarette reduced abstinence-induced craving to a greater extent than the two lowest nicotine cigarettes. There was no evidence of compensatory increase in CO intake from smoking reduced-nicotine cigarettes. A similar pattern of results was reported in a laboratory study in 46 young adults, in which all nicotine doses reduced craving and withdrawal; but the higher-nicotine cigarettes resulted in greater subjective liking relative to the lower doses (Faulkner et al., 2017). A laboratory study of young adults who infrequently use tobacco also found higher positive ratings, but also higher negative ratings, for higher-nicotine cigarettes than lower-nicotine cigarettes (Sweitzer et al., 2021).

A secondary analysis of the Cassidy study described above tested the effects of nicotine reduction on cigarette demand, using a cigarette purchase task. All four research cigarettes were rated as equally reinforcing, and all were less reinforcing than participants' usual brand (Cassidy et al., 2019). This is consistent with earlier studies in adults who smoke, in that VLNC cigarettes attenuated craving and withdrawal, but were less reinforcing than

usual-brand cigarettes. Unlike adults (Higgins et al., 2017), however, adolescents did not exhibit strong dose-dependent effects of nicotine on cigarette reinforcement. Adolescents' health risk perceptions were compared after smoking 15.8 mg/g and 0.4 mg/g nicotine content cigarettes (Denlinger-Apte et al., 2019a). Although unaware of cigarette nicotine content, adolescents perceived the 0.4 mg/g nicotine cigarette to carry lower health risk than the 15.8 mg/g nicotine cigarette. Similar misperceptions about the health risks of VLNC cigarettes have been observed in adults (Byron et al., 2018; Denlinger-Apte et al., 2017).

The first nicotine reduction RCT in adolescents assigned 52 participants to either smoke VLNC (0.4 mg/g) or NNC (15.8 mg/g) cigarettes for three weeks (Cassidy et al., 2020). At week 3, the VLNC group smoked fewer cigarettes per day than those in the NNC group; nicotine exposure did not differ between groups, but had decreased significantly from baseline in both groups. Those in the VLNC group reported lower smoking satisfaction at week 2 but not at week 3. In both groups, smoking satisfaction was reduced for both VLNC and NNC cigarettes relative to satisfaction with usual brand cigarettes. There was no evidence of compensatory smoking of the VLNC cigarettes.

Three secondary analysis studies have compared effects of VLNC cigarettes in younger adults ages 18–24 versus those age 25 and older. First, Cassidy and colleagues (2019) used data from the 6-week RCT conducted by Donny and colleagues (2015) that tested the effects of cigarettes varying in nicotine content in adults who smoke daily. The younger adults showed greater dislike for and less use of the lowest nicotine content (0.4–2.4 mg/g) cigarettes than the older group after two weeks. Next, Cassidy and colleagues (2021) used data from a 20-week RCT that had compared responses to gradual versus immediate reduction in nicotine content (Hatsukami 2018). Regardless of age, immediate nicotine reduction led to greater reductions in cigarettes per day than the gradual reduction or NNC control condition. Within the immediate condition, subjective responses to the VLNC cigarettes were less positive in younger adults than in the older adults. In addition, Davis and colleagues (2019) tested age moderation effects in adults with psychiatric conditions or socioeconomic disadvantage in the laboratory study by Higgins et al. (2017). Compared with older adults, younger adults showed lower demand for reduced nicotine content cigarettes on three of five purchase task indices. There were no differences by age on the other measures. Overall, these studies suggest that responses to VLNC cigarettes are similar for younger and older adults, but where differences emerge, they are in the direction of VLNC cigarettes having lower abuse liability in younger adults. These findings counter concerns that VLNC cigarettes might be more appealing than NNC cigarettes among youth who smoke.

7. Other Priority and Vulnerable Populations

Recently, researchers have re-examined large VLNC clinical trials to examine how a low nicotine product standard may affect priority populations like Black or African Americans who smoke, women who smoke, and people with cumulative vulnerabilities. A secondary analysis of the randomized trial by Hatsukami et al. (2018) found that, regardless of race, gender, or educational attainment, people assigned to VLNC cigarettes for 20 weeks experienced significant reductions in smoking behavior and biomarkers of harm than those assigned to NNC cigarettes (Carroll et al., 2021). However, Black/African American

participants had smaller reductions in nicotine exposure than white participants, potentially attributable to lower VLNC cigarette adherence. Thus, Black/African Americans who smoke may need additional support, such as access to alternative or medicinal nicotine products, if a low nicotine product standard is implemented. Another secondary analysis created a cumulative vulnerability score that included rural status, substance use disorder, affective disorder, low educational attainment, poverty, unemployment and disability status to understand how overlapping factors may affect response to VLNC cigarettes (Higgins et al., 2021). The study found minimal evidence that having more vulnerability factors moderated the effects of VLNC cigarettes on smoking behavior and biomarkers of harm. Together, these analyses indicate that benefits of a low nicotine product standard will likely extend across several priority populations.

Another vulnerable population warranting special attention are pregnant people who smoke. Evidence suggests that pregnancy increases nicotine metabolism, which could make quitting smoking more challenging (Arger et al., 2018; Bowker et al., 2015). A nicotine reduction policy for cigarettes could be beneficial for pregnant people who may otherwise struggle to quit smoking. However, most VLNC cigarette clinical trials have excluded pregnant people who smoke due to safety concerns. A laboratory study of 10 pregnant women found that VLNC cigarettes had lower abuse liability than usual brand cigarettes (Heil et al., 2020). Additionally, participants did not engage in compensatory smoking behavior or report severe craving or withdrawal symptoms. These finds are consistent with findings in non-pregnant people who smoke, suggesting that a low nicotine product standard may benefit pregnant people too.

Finally, although not identified as a priority population by the FDA, people who smoke menthol cigarettes may require special consideration within the context of a reduced-nicotine standard for cigarettes. Several priority populations disproportionately smoke menthol cigarettes, including racial and ethnic minoritized persons, members of the LGBTQ+ community, individuals with mental health conditions and adolescents and young adults (Caraballo et al., 2011; Fallin et al., 2015; Villanti et al., 2016; Young-Wolff et al., 2015). Menthol flavoring contributes to cigarette reinforcement, and menthol smoking is associated with poorer cessation outcomes, especially among Black and African Americans who smoke. Therefore, people who smoke menthol cigarettes could be less responsive to a reduced-nicotine standard. A secondary analysis by Denlinger-Apte et al. (2019b) found that participants who received menthol VLNC cigarettes for 20 weeks experienced smaller reductions in smoking and toxicant exposure than those who smoked non-menthol VLNC cigarettes. Furthermore, those who smoked menthol VLNC cigarettes did not have increased odds of abstinence at the end of the trial, unlike participants who smoked non-menthol VLNC cigarettes. However, prior trials did not observe significant differences between participants who smoked menthol or non-menthol VLNC cigarettes (Donny et al., 2015; Benowitz et al., 2012) so more research is necessary to understand the potential impact of nicotine reduction among people who smoke menthol cigarettes.

8. Discussion

Studies in adults with mental health conditions, adults who use other substances, socioeconomically-disadvantaged adults, and youth or young adults indicate that immediate switching from usual brand to VLNC cigarettes decreases smoking rates and biomarkers of tobacco exposure, with minimal or no mood disruption, compensatory increases in smoking, or increases in other substance use. Evaluating effects of nicotine reduction on smoking cessation has not been a goal of most VLNC trials to date, and, in fact, the studies reviewed above excluded individuals with immediate quit intentions. Nevertheless, increases in abstinence have been observed in VLNC studies in vulnerable participants (Higgins et al., 2020; Krebs et al., 2021), and in studies not focused on vulnerable populations (reviewed in Piper et al., 2019). Since smoking even one cigarette per day increases risk for cardiovascular disease (Hackshaw et al., 2018), methods to promote smoking cessation among those who have reduced their cigarette intake with VLNC cigarettes are needed. One promising approach is to simultaneously promote switching to non-combusted sources of nicotine among participants using VLNC cigarettes (Smith et al., 2018). Only one of the studies reviewed above investigated the combination of VLNC cigarettes and non-combusted nicotine (Tidey et al., 2013). In this laboratory study in people with and without schizophrenia, NRT did not enhance the effects of VLNC cigarettes on usual-brand smoking, but did attenuate cognitive deficits compared to VLNC cigarettes without NRT (AhnAllen et al., 2015). Trials are underway to investigate whether co-provision of electronic cigarettes with VLNC cigarettes enhances smoking reductions compared to VLNC cigarettes alone in vulnerable populations (e.g., <https://clinicaltrials.gov/ct2/show/NCT04092387>).

Another finding that merits further investigation is that participants in VLNC trials, as well as those who have not participated in VLNC trials, often believe that VLNC cigarettes are less harmful than NNC cigarettes (Denlinger-Apte et al., 2017; Denlinger-Apte et al., 2021; Pacek et al., 2018). This misperception may be of greater concern among vulnerable populations, as some may be more likely to hold the inaccurate belief that nicotine is the primary cause of tobacco-related cancer (Snell et al., 2021). Furthermore, the belief that VLNC cigarettes have lower cancer risk was associated with reduced intention to quit smoking if the FDA were to enact a reduced-nicotine standard (Byron et al., 2018). With the FDA's recent authorization of two VLNC cigarettes as modified risk tobacco products, it is important to educate consumers that VLNC cigarettes contain similar levels of tobacco toxicants as NNC cigarettes, and that the harm reduction effects of a reduced-nicotine standard are contingent upon reducing cigarette consumption. In general population samples, nicotine misperceptions can be corrected using brief messages (Villanti et al., 2019). Developing health communications strategies for correcting misperceptions about VLNC cigarettes, electronic cigarettes, and other nicotine/tobacco products in vulnerable populations may be critical for reducing tobacco-related health harms in these individuals.

Few studies have investigated the effects of VLNC cigarettes in racial or ethnic minorities, people who smoke menthol cigarettes, people with substance use disorders other than OUD, and pregnant women, although initial findings suggest that responses of these individuals to VLNC cigarettes are similar to responses observed with other vulnerable populations.

Nevertheless, nicotine reduction may not reduce current tobacco-related health inequities unless implementation strategies that enable individuals from disadvantaged groups to quit smoking are prioritized. With regard to menthol cigarette users, one unanswered question is how a reduced-nicotine standard may interact with the FDA's proposed ban on menthol flavored cigarettes. To our knowledge, no studies have investigated the effects of VLNC cigarettes in military/veteran populations, sexual or gender minority individuals, or those living in underserved rural environments. Tobacco use has been marketed to some populations as a "free choice" aligned with their cultural values, and a reduced-nicotine standard may be viewed as an infringement on that freedom (Palmer et al., 2022). In that context, understanding how to effectively communicate the goals of nicotine reduction is particularly important.

Among youth, studies to date indicate that VLNC cigarettes are less appealing than NNC cigarettes, but most studies have focused on youth who smoke daily. Other than one study in young adults who infrequently use tobacco (Sweitzer et al., 2021), the effects of VLNC cigarettes on cigarette uptake in adolescent nonsmokers or infrequent smokers are unknown. Adolescents associate VLNC cigarettes with lower health risks, which could promote experimentation with these cigarettes or undermine motivation to quit. Effective health communications to youth will be an important component of reduced-nicotine regulatory policy.

Vulnerable populations have lower smoking cessation rates and are less likely to use recommended cessation treatments than other tobacco users (Bandi et al., 2021). By reducing the addictive potential of cigarettes sold in the US, policy simulation studies indicate that a reduced-nicotine standard for combusted tobacco products could avert millions of premature deaths (Apelberg et al., 2018; Levy et al., 2021). The empirical evidence to date indicates that a reduced-nicotine standard is likely to have the same beneficial effects on smoking reductions in vulnerable populations as it does in less vulnerable populations. While more needs to be known about how to propel those who reduce their smoking toward cessation, these findings should provide some confidence in going forward with a reduced-nicotine standard for cigarettes.

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Highlights

- A nicotine reduction strategy could reduce tobacco dependence and increase quitting
- We review nicotine reduction studies across FDA-designated vulnerable populations
- Studies show that nicotine reduction reduces smoking with few or no adverse effects

Table 1. Summaries of Studies Investigating Very Low Nicotine Content (VLNC) Cigarettes in Vulnerable Populations

Authors, year	Population (sample size)	Demographic Characteristics	Main Outcomes timeframe	Main Outcome Measures	Findings
Adults with Mental Health Conditions					
Tidey et al., 2013	Adults ages 18+ with schizophrenia spectrum disorder (n=30) and controls (n=26)	Mean age=45 % female=41 % non-white=29	Acute exposure	Craving, withdrawal, subjective effects, usual brand smoking, psychiatric symptoms	5-hour VLNC use with placebo or nicotine patches reduced craving, withdrawal symptoms, and usual brand smoke intake compared to abstinence. Cigarette satisfaction and reward were lower for VLNC than for NNC cigarettes. No effects on psychiatric symptoms among participants with schizophrenia.
AhnAllen et al., 2015; Secondary analysis of Tidey et al., 2013	Same as Tidey et al. (2013)			Assessments of attention, visual working memory, inhibitory control, processing speed	Across both the schizophrenia and control groups, inhibitory control, processing speed, and response variability were impaired in the VLNC + placebo patches condition compared to the VLNC + nicotine replacement and usual brand conditions.
Tidey et al., 2016; Secondary analysis of Tidey et al., 2013	Same as Tidey et al. (2013)			Puff topography	Across cigarette conditions, participants with schizophrenia smoked more puffs and had shorter inter-puff intervals than controls. VLNC use was associated with longer puff duration and shorter inter-puff interval, but participants smoked fewer puffs, resulting in lower smoke volume.
Higgins et al., 2017*	Adults ages 18–70 with affective disorders (n=56) or opioid use disorder (n=60); women ages 18–44 with 12 years of education (n=53)	Mean age=36 % female=71 % non-white=27	Acute exposure	Cigarette demand, cigarette choice, subjective effects, puff topography	Across groups, VLNC cigarettes were less reinforcing than NNC cigarettes. All doses reduced craving and withdrawal. No effects on topography or smoke exposure.
Gaalema et al., 2017; Secondary analysis of Higgins et al., 2017	Same as Higgins et al., 2017			Cigarette choice, craving, withdrawal, puff topography	Neither diagnosis nor symptom severity moderated the effects of nicotine reduction on cigarette choice, craving, withdrawal, or topography.
Tidey et al., 2017; Secondary analysis of Donny et al., 2015	Adults ages 18+ with clinically-significant (n=109) vs. lower (n=608) depressive symptoms	Mean age=42 % female=42 % non-white=47	6 weeks	CPD, craving, dependence, depressive symptoms	Participants assigned to cigarettes with 2.4 mg nicotine/g tobacco had lower CPD, dependence, and craving; effects were not moderated by baseline depressive symptoms. Among those with higher depressive symptoms at baseline, VLNCs reduced depressive symptoms at week 6.
Tidey et al., 2019	Adults 18–70 with schizophrenia, schizoaffective disorder, or bipolar disorder (n=58)	Mean age=43 % female=41 % non-white=41	6 weeks	CPD, craving, withdrawal, subjective responses, toxicant exposure, psychiatric symptoms	Those assigned to VLNC cigarettes had lower CPD, CO levels and craving, and reported lower cigarette satisfaction and reward than those assigned to NNC cigarettes. No effects on dependence, nicotine exposure, withdrawal, or psychiatric symptoms.
Denlinger-Apte et al., 2020; Secondary analysis of Tidey et al., 2019	Same as Tidey et al., 2019			Puff topography, CO boost	At week 6, participants in the VLNC condition smoked fewer puffs per cigarette and had shorter inter-puff intervals than those in the NNC condition. No effects on puff volume, puff duration, peak flow rate, or CO boost.

Authors, year	Population (sample size)	Demographic Characteristics	Main Outcomes timepoint	Main Outcome Measures	Findings
Reed et al., 2022; Secondary analysis of Tidey et al., 2019	Same as Tidey et al. 2019, focused on participants in the VLNC condition only (n = 30)		12 weeks	Biochemically-verified compliance with VLNC cigarettes	Few participants were completely adherent to using only VLNC cigarettes. Lower enjoyment of respiratory tract sensations predicted less adherence.
Higgins et al., 2020 *	Men and women ages 18–70 with affective disorders (n=258) or opioid dependence (n=260); women ages 18–44 with 12 years of education (n=257)	Mean age=36 % female=71 % non-white=18	12 weeks	CPD, CO, dependence, toxicant exposure, craving, withdrawal, cigarette demand, puff topography	Compared to those assigned to NNC cigarettes, those assigned to VLNC cigarettes smoked fewer CPD and had lower dependence and cigarette demand at Week 12, and reported more abstinent days and quit attempts across the trial. No effects on withdrawal and no compensatory smoking. Depression scores were higher in the VLNC condition but still within the minimal range.
Adults with Opioid Use Disorder					
Higgins et al., 2017 *	Adults ages 18–70 with affective disorders (n=56) or opioid use disorder (n=60); women ages 18–44 with 12 years of education (n=53)	Mean age=36 % female=71 % non-white=27	Acute exposure	Cigarette demand, cigarette choice subjective effects, puff topography	Across groups, VLNC cigarettes were less reinforcing than NNC cigarettes. All doses reduced craving and withdrawal. No effects on topography or smoke exposure.
Streck et al., (2020); Secondary analysis of Higgins et al., 2017	Same as Higgins et al., 2017, comparing effects in participants with OUD (n=65) vs. without OUD (n=135)			Craving, withdrawal	Effects of cigarette nicotine content on craving and withdrawal symptoms did not differ as a function of opioid dependence status.
Higgins et al., 2020 *	Men and women ages 18–70 with affective disorders (n=258) or opioid dependence (n=260); women ages 18–44 with 12 years of education (n=257)	Mean age=36 % female=71 % non-white=18	12 weeks	CPD, CO, dependence, toxicant exposure, craving, withdrawal, cigarette demand, puff topography	Compared to those assigned to NNC cigarettes, those assigned to VLNC cigarettes smoked fewer CPD and had lower dependence and cigarette demand at Week 12, and reported more abstinent days and quit attempts across the trial. No effects on withdrawal and no compensatory smoking. Participants with OUD were less sensitive to effects of VLNC cigarettes on nicotine and toxicant exposure.
Adults who use Alcohol and Cannabis					
Pacek et al., 2016; Secondary analysis of Donny et al., 2015	Adults 18+ who used cannabis (n=207) vs. non-users (n=510)	Mean age=42 % female=42 % non-white=47	6 weeks	CPD, craving, dependence, depressive symptoms	Cannabis users and non-users assigned to cigarettes with 2.4 mg nicotine/g tobacco had lower CPD, dependence, and craving than those assigned to NNC cigarettes; cannabis users had larger decrease in craving than non-users. VLNC use did not impact cannabis use behaviors.
Parker et al., 2018; Secondary analysis of Higgins et al., 2017	Same as Higgins et al., 2017, focusing on participants who did (n=63) vs. did not use cannabis (n=106)			Cigarette demand, cigarette choice subjective effects, puff topography	Cannabis use status did not moderate effects of nicotine dose on cigarette choice, demand, subjective effects, or topography. Cannabis users reported higher positive ratings across doses, and longer effects on withdrawal symptoms.
Dermody et al., 2016; Secondary analysis of Donny et al., 2015	Adults who drink alcohol (n=403)	Mean age=39 % female=42 % non-white=42	6 weeks	Alcohol intake, binge drinking, CPD, nicotine exposure, nicotine withdrawal	VLNC use was associated with lower alcohol use through reductions in nicotine exposure and CPD. No evidence of compensatory drinking or nicotine withdrawal.
Dermody et al., 2021; Secondary analysis of Hatsukami et al., 2018	Adults who drink alcohol (n=415) vs. non-drinkers (n=337)	Mean age=45 % female=45 % non-white=37	20 weeks	Alcohol intake, binge drinking, CPD, CO, nicotine exposure	Baseline alcohol use did not moderate effects of VLNC vs. NNC condition on Week 20 CPD or CO, but was associated with smaller reduction in nicotine exposure.

Authors, year	Population (sample size)	Demographic Characteristics	Main Outcomes timepoint	Main Outcome Measures	Findings
Adults with Socioeconomic Disadvantage					
Higgins et al., 2017 *	Adults ages 18–70 with affective disorders (n=56) or opioid use disorder (n=60); women ages 18–44 with 12 years of education (n=53)	Mean age=36 % female=71 % non-white=27	Acute exposure	Cigarette demand, cigarette choice subjective effects, puff topography	Among alcohol users, daily alcohol use and odds of binge drinking were reduced for the VLNC group. Across groups, VLNC cigarettes were less reinforcing than NNC cigarettes. All doses reduced craving and withdrawal. No effects on topography or smoke exposure.
Higgins et al., 2020 *	Men and women ages 18–70 with affective disorders (n=258) or opioid dependence (n=260); women ages 18–44 with 12 years of education (n=257)	Mean age=36 % female=71 % non-white=18	12 weeks	CPD, CO, dependence, toxicant exposure, craving, withdrawal, cigarette demand, puff topography	Compared to those assigned to NNC cigarettes, those assigned to VLNC cigarettes smoked fewer CPD and had lower dependence and cigarette demand at Week 12, and reported more abstinence days and quit attempts across the trial. No effects on withdrawal and no compensatory smoking. Depression scores were higher in the VLNC condition but still within the minimal range.
Krebs et al., 2021	Adults ages 18–65 with 16 years of education (n=245)	Mean age=45 % female=52 % non-white=38	18 weeks	CPD, nicotine exposure, CO attrition, choice to quit with support, continue research cigarette use, or resume usual brand use	The gradual nicotine reduction group had lower CPD, CO and nicotine exposure, but higher attrition and study cigarette nonadherence. Among trial completers, those in the nicotine reduction condition were more likely to make a quit attempt.
Carroll et al., 2021 *, Secondary analysis of Hatsukami et al., 2018	Adults 18+ with 12 years education (n=505); women (n=549); and Black participants (n=373) compared to participants without these characteristics	Mean age=45 % female=44 % non-white=39	20 weeks	CPD, CO, nicotine exposure, toxicant exposure	Regardless of education, gender, and race, measures of nicotine and toxicant exposure were lower in the immediate reduction group than in the gradual nicotine or control groups. However, effects of nicotine reduction on nicotine exposure were smaller for Black participants than for White participants.
Youth and Young Adults					
Faulkner et al., 2017	Young adults ages 18–25 who smoked 5 CPD (n=46)	Mean age=22 % female=50 % non-white=59	Acute exposure	Subjective effects, craving, withdrawal, affect, sustained attention, puff topography	All nicotine doses reduced withdrawal symptoms, craving, and negative affect; normal metabolizers had greater reductions in craving and withdrawal from VLNC cigarettes than slow metabolizers. Lower nicotine cigarettes did not improve attention and had lower positive ratings. No effects on topography.
Cassidy et al., 2018	Adolescents ages 15–19 who smoked daily (n=50)	Mean age=18 % female=50 % non-white=46	Acute exposure	Subjective effects, craving, withdrawal, affect, CO	All nicotine doses reduced withdrawal symptoms, craving, and negative affect. VLNC cigarettes were rated as less satisfying. No compensatory increase in CO at lower nicotine doses.
Cassidy et al., 2019; Secondary analysis of Cassidy et al., 2018	Same as Cassidy et al., 2018			Cigarette purchase task demand indices	Demand for usual brand cigarettes was higher than for research cigarettes at all nicotine doses, with no difference among doses.
Denlinger-Apte et al., 2019a; Secondary analysis of Cassidy et al., 2018	Same as Cassidy et al., 2018			Perceived health risks, subjective effects, CO	Participants perceived VLNC cigarettes as less harmful to health than NNC study cigarettes but not less addictive. Menthol preference did not moderate outcomes.

Authors, year	Population (sample size)	Demographic Characteristics	Main Outcomes timepoint	Main Outcome Measures	Findings
Cassidy et al., 2019; Secondary analysis of Donny et al., 2015	Younger adults ages 18–24 (n=93) vs. older adults ages 25+ (n=595) who smoked 5 CPD	% female=42 % non-white=42	6 weeks	CPD, subjective effects, puff topography, nicotine exposure	Younger adults assigned to cigarettes with 2.4 mg nicotine/g tobacco smoked fewer CPD and reported lower smoking satisfaction and reward after two weeks of use than older adults. Age differences were diminished after 6 weeks.
Davis et al., 2019; Secondary analysis of Higgins et al., 2017	Same as Higgins et al., 2017, focusing on younger adults ages 18–24 vs. older adults ages 25+			Cigarette demand, cigarette choice subjective effects, puff topography	Demand decreased as a function of dose and decreased more steeply in younger vs. older adults. No differences by age were observed on other measures.
Cassidy et al. 2020	Adolescents ages 15–19 who smoked daily (n=66)	Mean age=18.5 % female=50 % non-white=35	3 weeks	CPD, subjective effects, nicotine exposure	Participants assigned to VLNC cigarettes smoked fewer CPD at week 3 than those assigned to NNC cigarettes. Nicotine exposure and smoking satisfaction were decreased in both groups.
Cassidy et al., 2021; Secondary analysis of Hatsukami et al., 2018	Young adults ages 18–24 (n= 87) compared to older adults ages 25% (n=1163)	Mean age=34 % female=61 % non-white=34	20 weeks	CPD, nicotine exposure; subjective effects	Across age groups, CPD was lower in the immediate nicotine reduction condition and nicotine exposure was lower in the immediate and gradual nicotine conditions. Positive subjective effects were lower among young adults than older adults in the immediate reduction condition.
Sweitzer et al., 2021	Young adults ages 18–25 who smoked at least 5 cigarettes per month (n=87)	Mean age=21 % female=49 % non-white=27	30 min	CO, subjective responses, cigarette choice	CO boost was higher after smoking a VLNC cigarette than an NNC cigarette. Positive, negative, and dizziness reactions were highest in the NNC condition. Dose did not significantly affect cigarette choice.
Other Priority and Vulnerable Populations					
Denlinger-Apte et al. (2019b), Secondary analysis of Hatsukami et al., 2018	Adults 18+ who smoke menthol (n=346) vs. non-menthol cigarettes (n=406)	Mean age=45 % female=44 % non-white=39	20 weeks	CPD, CO, nicotine exposure, toxicant exposure, abstinence	Across menthol status, VLNC cigarette use led to reductions in smoking and toxicant exposure, and increases in abstinence. However, effects tended to be smaller in menthol smokers.
Heil et al., 2020	Pregnant women (n=10)	Mean age=31 % female=100 % non-white=10	Acute exposure	Cigarette demand, cigarette choice subjective effects, puff topography	Demand, choices, and positive subjective effects were lower for VLNC compared to usual brand cigarettes. VLNC cigarettes reduced craving and withdrawal with no compensatory smoking.
Carroll et al., 2021,*; Secondary analysis of Hatsukami et al., 2018	Adults 18+ with 12 years education (n=505); women (n=549); and Black participants (n=373) compared to participants without these characteristics	Mean age=45 % female=44 % non-white=39	20 weeks	CPD, CO, nicotine exposure, toxicant exposure	Regardless of education, gender, and race, measures of nicotine and toxicant exposure were lower in the immediate reduction group than in the gradual nicotine or control groups. However, effects of nicotine reduction on nicotine exposure were smaller for Black participants than for White participants.
Higgins et al., 2021; Secondary analysis of Higgins et al., 2020	Adults ages 18–70 (n=775) with vulnerabilities including rurality, affective disorder, substance use disorder, low educational attainment, poverty, unemployment, physical disability	Mean age=36 % female=71 % non-white=18	12 weeks	CPD, toxicant exposure, dependence, craving, withdrawal	Number of cumulative vulnerabilities (0–1, 2–3, 4) was positively associated with CPD but did not moderate responses to nicotine reduction.

Notes: VLNC, very low nicotine content; NNC, normal nicotine content; CO, carbon monoxide; CPD, cigarettes per day

* Study addresses more than one vulnerable group and is included in more than one section of this table.

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