Examining The Effect Of Very Low Nicotine Content Cigarettes On Weight Among Smokers With Psychiatric Conditions Or Socioeconomic Disadvantage

EXAMINING THE EFFECT OF VERY LOW NICOTINE CONTENT CIGARETTES ON WEIGHT AMONG SMOKERS WITH PSYCHIATRIC CONDITIONS OR SOCIOECONOMIC DISADVANTAGE

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Abstract

Introduction: There is a pharmacological effect of nicotine on weight, such that reductions in nicotine exposure lead to weight gain. Weight gain may be an unintended consequence of a nicotine reduction policy. To our knowledge, two studies have examined the relationship between very low nicotine content cigarettes (VLNCs) and weight, both in general-population smokers. As would be expected, only smokers adherent to VLNCs gained weight. The aim of this study is to examine associations between VLNCs and weight among vulnerable populations.

Methods: This is a secondary analysis of a double-blind, randomized controlled trial evaluating the effects of VLNCs among individuals from three vulnerable populations: smokers with affective disorders, opioid use disorder (OUD), and disadvantaged women. Participants were assigned to smoke one of three research cigarettes (15.8, 2.4, or 0.4-mg/g) over 12 weeks in lieu of their usual brand cigarettes. Biomarker levels did not differ considerably by cigarette dose among smokers with OUD, suggesting this population was less adherent. Thus, the present analyses examined associations between VLNCs and weight across all three populations but also grouped smokers with affective disorders and disadvantaged women together and examined smokers with OUD separately. Linear mixed models were used to examine differences in weight change and also a subjective measure, "increased appetite/hunger/weight gain," over time by cigarette dose.

Results: Among all populations, there was no effect of dose on weight gain. There was a graded effect of dose on "increased appetite/hunger/weight gain" ratings during the 12-week study, with the 0.4-mg/g condition having the highest average rating, then the 2.4-mg/g condition, followed by the 15.8-mg/g condition, although only the comparison between the 0.4-mg/g and 15.8-mg/g cigarette conditions was statistically significant (1.95 vs. 1.73; $p = .01$). Analyses limited to participants with affective disorders and disadvantaged women demonstrated a graded effect of dose on weight gain during the 12-week study, with the 0.4-mg/g condition having the highest average weight gain, then the 2.4-mg/g condition, followed by the 15.8-mg/g condition, although only the comparison between the 0.4-mg/g and 15.8-mg/g cigarette conditions was statistically significant (3.10 vs. 1.69 lbs; $p = .01$). This same graded pattern was evident once again in analyses of "increased appetite/hunger/weight gain" ratings in these two populations, with statistical significance between the lowest and highest doses (2.00 vs. 1.76; $p = .02$). Among smokers with OUD, there was no effect of cigarette dose or time on weight or subjective "increased appetite/hunger/weight gain."

Discussion: Consistent with prior observations in the general population of smokers, smokers with affective disorders and disadvantaged women gained weight when smoking VLNCs. However, the amount of weight gained does not meet a commonly accepted definition of clinically significant weight change (i.e., > 5% baseline weight). Subjective appetite/weight gain also increased, but remained at an overall low level. These findings are reassuring and suggest few, if any, adverse consequences of implementing a nicotine reduction policy with regard to weight.

Table of Contents

List of Tables

List of Figures

Introduction

Cigarette smoking is the leading cause of preventable death in the United States (US DHHS, 2020). Nearly 1 in 5 deaths is attributed to cigarette smoking which equates to about 480,000 deaths each year. Smokers are also at greater risk for heart disease, stroke, and lung cancer than nonsmokers. Quitting smoking reduces risk for smoking-related disease, and while two-thirds of cigarettes smokers report a desire to quit, one of the main reasons smokers continue to smoke is nicotine, the highly addictive chemical component of cigarettes and other tobacco products (US DHHS, 1988).

In 2009, the Family Smoking Prevention and Tobacco Control Act granted the FDA the ability to reduce, without completely eliminating, nicotine levels in cigarettes on the U.S. market (U.S. Congress, 2009). This legislation was based on a proposed hypothesis that reducing the nicotine content of cigarettes below a reinforcing threshold will reduce smoking prevalence by making it 1) less likely that new users of cigarettes will transition to chronic use and 2) easier for current smokers to stay abstinent should they attempt to quit (Benowitz and Henningfield, 1994). More recently, the FDA has issued an Advanced Notice of Proposed Rulemaking to elicit commentary on a proposed tobacco product standard to set a maximum nicotine level for cigarettes (FDA, 2018).

The Benefits of a Nicotine Reduction Policy

General Population

Several studies have been conducted with smokers in the general population to test the reinforcing threshold hypothesis (e.g., Benowitz et al., 2012; Benowitz et al., 2015; Hatsukami et al., 2013; Hatsukami et al., 2018). A large scale, double-blind, randomized controlled trial testing this hypothesis was published in the New England

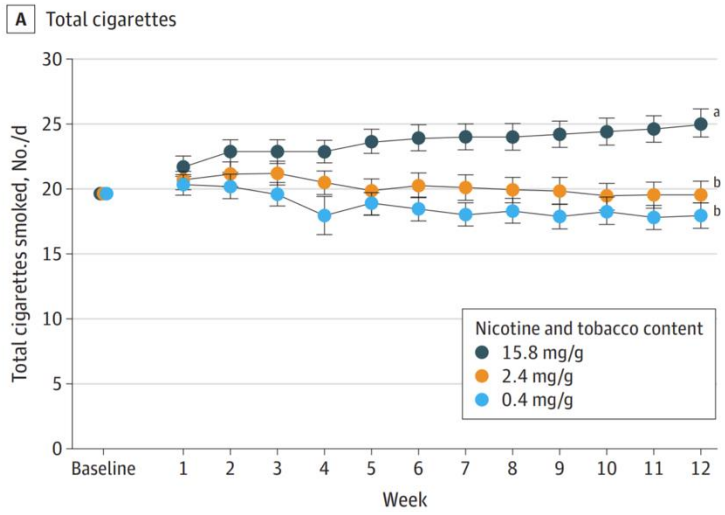
Journal of Medicine and investigated the effects of cigarettes of varying nicotine content on cigarettes smoked per day (CPD) and nicotine dependence (Donny et al., 2015). The results demonstrated that participants randomized to smoke very low nicotine content (VLNC) cigarettes (i.e., 2.4-, 1.3-, or 0.4-mg of nicotine/g of tobacco) smoked fewer cigarettes and had lower levels of nicotine dependence at the end of the six-week trial than participants randomized to smoke normal nicotine content (NNC) cigarettes (i.e., 15.8-mg/g) or participant usual brand. Additionally, examination of cessation-related outcomes demonstrated that smokers assigned to the 0.4-mg/g condition made more quit attempts than those assigned to smoke 15.8-mg/g cigarettes. These outcomes are consistent with results of other trials where VLNC cigarettes have been associated with lower abuse liability and lower consumption of CPD in general-population smokers (see review by Berman and Glasser, 2019).

Vulnerable Populations

Beyond the general population, research has also examined effects of VLNC cigarettes in populations with psychiatric disorders and socioeconomic disadvantage. These vulnerable populations are of special interest because they have a disproportionate prevalence of smoking compared to the U.S. adult population, with rates of 32% among those with affective disorders, 92% among those with opioid use disorder (OUD), and 30% among socioeconomically disadvantaged women of reproductive age compared to 21% in the general population (Higgins et al., 2017). In addition to having higher rates of smoking, research also suggests these groups have greater addiction severity and less success quitting smoking (Chilcoat, 2009; Higgins & Chilcoat, 2009; Cooper et al., 2016; Richter et al., 2001; Weinberger et al., 2017). These disparities in smoking rate,

dependence, and cessation underscore the need to understand how these subpopulations respond to VLNC cigarettes since adoption of a nicotine product standard will disproportionately impact these vulnerable populations. Two controlled trials in smokers with serious mental illness (i.e., schizophrenia, schizoaffective disorder, bipolar disorder) examined acute (Tidey et al., 2013; Tidey, Cassidy, and Miller, 2016) and extended exposure (Tidey et al., 2019) to VLNC cigarettes and found reductions in cigarette use without compensatory smoking behaviors. Additionally, our group conducted a study of the acute effects of VLNC cigarettes among populations with affective disorders, opioid use disorder, and socioeconomic disadvantage and found VLNC cigarettes decreased the addiction potential of smoking without evidence of compensation (Higgins et al., 2017). Most recently, our group expanded on the study of acute effects with a 12-week randomized controlled trial that analyzed the effects of extended exposure to VLNC cigarettes on smoking rates and dependence severity in these same three populations (Higgins et al., 2020). At the end of this trial's 12-week study period, smokers randomized to the VLNC conditions (i.e., 2.4- and 0.4-mg/g) smoked fewer CPD compared to smokers randomized to use NNC

Figure 1. Total CPD by cigarette dose condition in Higgins et al. (2020)



Note. Data points are arithmetic means collapsed across participants and populations; error bars indicate SEM. Data not sharing a superscript letter differed significantly in post hoc testing and in slope of linear trends.

cigarettes (Figure 1). Moreover, smokers assigned to the VLNC cigarettes were less dependent than those in the NNC cigarette condition. Finally, participants assigned VLNC cigarettes reported more days of cigarette abstinence and more quit attempts compared to those randomized to NNC cigarettes.

Data from these trials support Benowitz and Henningfield's (1994) hypothesis that reductions of cigarette nicotine content below a reinforcing threshold will decrease nicotine-seeking behavior in both the general population and vulnerable populations of smokers. The abstinence-related outcomes are particularly encouraging, especially considering that all of these studies excluded smokers interested in quitting, and provide further evidence that a nicotine reduction policy would benefit public health.

The Potential Negative Consequences of a Nicotine Reduction Policy

While it appears a nicotine reduction policy would bring about substantial health benefits, it is also possible that there could be unintended adverse consequences of a tobacco product standard for cigarettes. The FDA has conveyed the importance of evaluating adverse effects of a product standard so that any final policy may anticipate and address these issues (Gottlieb & Zeller, 2017). For example, researchers have examined whether VLNC cigarettes induce compensatory use of other substances and found that transitioning to VLNC cigarettes did not result in alterations in the use of alcohol or cannabis (Dermody et al., 2016; Pacek et al., 2016), which is reassuring. Researchers have also examined potential misperceptions about VLNC cigarettes and shown that many smokers view these products as less harmful than NNC cigarettes in terms of potential disease risk (Mercincavage et al., 2017; Byron, Jeong, Abrams, & Brewer, 2018), which has potential to lead smokers to be less motivated to quit or less

likely to switch to non-carcinogenic nicotine products. As a result, any potential nicotine reduction policy will need to be accompanied by educational efforts to accurately convey the potential adverse health effects of chronic use of VLNC cigarettes for smokers and smoking-naïve populations.

Another potential unintended consequence of reducing nicotine content in cigarettes is weight gain. As described in upcoming sections, there is an extensive literature linking smoking, and exposure to nicotine specifically, to weight changes, including evidence that decreases in nicotine exposure due to cessation or reduced content in cigarettes leads to weight gain. This is a concern because like smoking, obesity and overweight increase risk for many of the leading causes of death in the US, including heart disease, cancer, stroke, Alzheimer's disease, and diabetes (Johnson et al., 2014). Thus, it is important to understand whether implementation of a nicotine reduction policy will put smokers at risk for weight gain following exposure to VLNC cigarettes and if so, how much weight. Before describing the work I have conducted to begin to address these questions, I will review the literature on smoking, nicotine exposure, and weight.

Smoking, Nicotine Exposure, and Weight

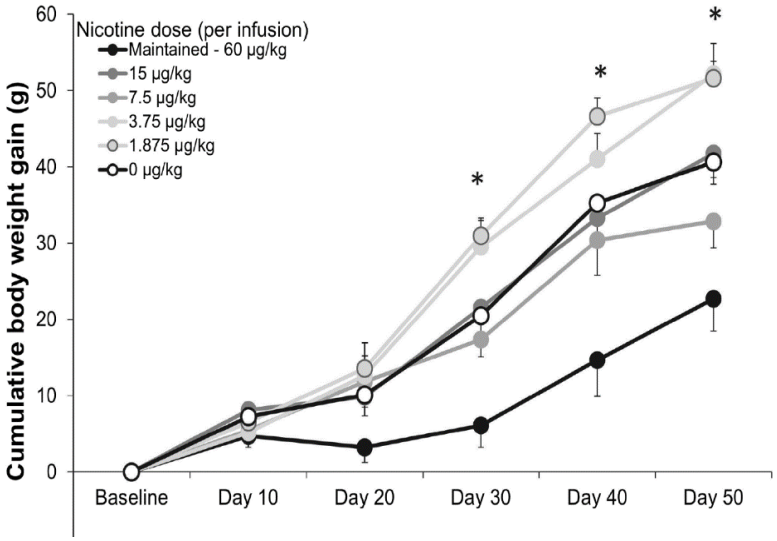
Observational Studies of Smoking and Weight

The association between cigarette smoking and weight has been reported for decades. For example, in one of the earliest and most comprehensive reviews of this literature, the authors identified 70 studies examining the impact of smoking on weight (Klesges et al., 1989). Of the 29 cross-sectional studies, 24 (83%) reported that smokers weighed less than non-smokers. Of the 41 prospective studies, 31 (76%) presented

evidence that smokers who abstain gain more weight than non-smokers and people who start smoking lose weight in relation to non-smokers.

The mechanisms underlying the association between cigarette smoking and weight are likely complex and multi-faceted. For instance, one factor may be a behavioral mechanism in which smoking serves as an alternative to eating, resulting in decreased caloric intake (Audrain-McGovern and Benowitz, 2011). Then during a period of smoking abstinence, smokers may use eating as a substitute for the familiar 'hand to mouth' behavior of smoking, leading to increased caloric intake (Bush, Lovejoy, Deprey, & Carpenter, 2016). However, there is also support from experimental studies that provide clear evidence of a pharmacological mechanism whereby nicotine is a key element in the relationship between cigarette smoking and weight.

Figure 2. Effects of nicotine dose reduction on weight gain in Rupprecht, Smith, Donny, & Sved (2016)



Note. Weight gain in rats where dose was reduced from 60µg/kg/infusions. Reductions in nicotine dose resulted in significant increases in weight gain compared to constant self-administration of 60µg/kg/infusions. * indicates 60µg/kg/infusions different from 3.75 and 1.875µg/kg/infusions.

Experimental Studies of Smoking and Weight

Pre-clinical Experimental Studies. Evidence from experimental pre-clinical studies, which also date back several decades, helped establish that changes in nicotine

exposure specifically, as opposed to some other constituent of a cigarette, result in weight changes. An early literature review of animal research identified 15 studies from as early as 1959 (Winders and Grunberg, 1989) and in 14 of the studies, acute and chronic nicotine administration suppressed weight gain. Eight of these studies also discontinued nicotine administration and five reported this led to significant weight gain. Researchers administered the nicotine in the studies in this review, but results from animal self-administration studies have resulted in similar findings. For example, in one study, rats who could self-administer nicotine gained less weight compared to rats self-administering saline and rats who were no longer given the opportunity to self-administer nicotine gained more weight than rats previously administering saline (Bunney, Burroughs, Hernandez, & LeSage, 2016). As another example, when the dose of nicotine available to self-administer was reduced among rats, weight increased more for rats that subsequently had lower doses of nicotine available to self-administer (Figure 2; Rupprecht, Smith, Donny, & Sved, 2016).

Pre-clinical research has also examined the relationship between nicotine and weight at the neurochemical and molecular levels. For instance, research has examined the relationship between nicotine and dopamine. Nicotine excites cells in the brain reward system which results in the release of dopamine, a neurotransmitter (Reinholz et al., 2008). Some researchers have suggested that chronic nicotine exposure from cigarette smoking leads to overstimulation of dopaminergic signaling and subsequent smoking cessation would lead to reductions in this signaling. In an animal model of nicotine use, researchers demonstrated nicotine exposure increases dopamine in the nucleus accumbens, which is part of the reward system, and administration of an antagonist to

precipitate withdrawal after chronic decreases extracellular dopamine (Rada, Jensen, and Hoebel, 2001). This is important in regards to weight because dopamine is involved in the regulation of food intake and associated with food reward, such that ingestion of highly palatable foods stimulates dopamine release in reward pathways (Erlanson-Albertsson, 2005; Volkow, Wang, and Baler, 2011). Thus, in an effort to maintain dopamine levels after quitting, former smokers may increase eating behavior or food intake, which could lead to weight gain.

Several nicotinic acetylcholine receptor (nAChR) subtypes have been linked to the regulation of weight by nicotine, including the α3β4 subtype. Mice treated with nicotine or cytisine, a full agonist of the α3β4 nAChRs with weaker effects for other nAChRs subtypes, decrease their food intake and experience less weight gain in a dose-dependent manner (Mineur et al., 2011). This may be because activation of α3β4 nAChRs is known to stimulate the pro-opiomelanocortin neurons (POMC) in the arcuate nucleus, which play an integral role in appetite, food intake, and regulation of weight (Krude et al., 2003; Williams and Schwartz, 2005). In an experiment where POMC knockout mice were treated with varying doses of nicotine or cytisine, they showed no differences in food intake as compared to saline treatment, whereas control mice treated with cytisine did, with higher doses associated with larger decreases. This finding suggests POMC neurons are involved in the critical mechanisms underlying food intake and appetite regulation which are influenced by nicotine exposure (Mineur et al., 2011). Overall, there is strong, consistent evidence from the pre-clinical literature that nicotine plays a significant role in the relationship between cigarette smoking and weight.

Clinical Experimental Studies.

Smoking, Nicotine Replacement Therapy and Weight. Like pre-clinical studies of nicotine self-administration, trials of nicotine replacement therapy (NRT) have often included weight measures, allowing isolation of the effect of nicotine on weight in humans. For example, a meta-analysis of 62 randomized controlled trials was conducted to analyze weight gain among smokers who achieved abstinence by comparing weight changes among those who quit without treatment and those who quit using NRT or other treatments (Aubin, Farley, Lycett, Lahmek, & Aveyard, 2012). Based on the extensive literature summarized in earlier paragraphs that indicates it is the absence of nicotine specifically that leads to post-cessation weight gain, it would be expected that untreated quitters would gain more weight than quitters treated with NRT. However, average weight gain among untreated quitters and quitters treated with NRT in this meta-analysis was comparable. For example, at 3 months, untreated quitters had gained an average (95%CI) of 6.3 (5.3 to 7.2) lbs while quitters treated with NRT gained 5.0 (3.7 to 6.4) (Aubin, Farley, Lycett, Lahmek, & Aveyard, 2012).

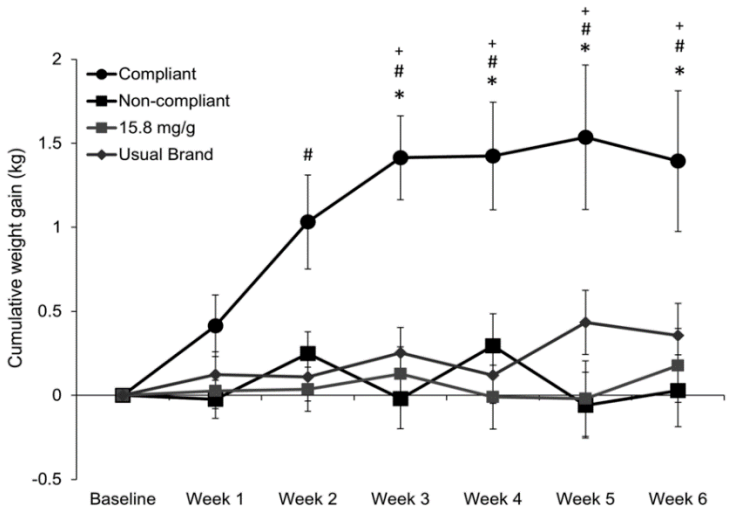
One potential explanation for this surprising lack of differences is nonadherence to NRT. Research examining NRT use has found that smokers frequently use less NRT than recommended and cease treatment earlier than recommended (see review by Ferguson, Shiffman, & Gitchell, 2011), with one recent systematic review of NRT randomized controlled trials reporting an average NRT adherence of only 61% (Mersha, Eftekhari, Bovill, Tollosa, & Gould, 2021). In recognition of this, the authors of one study in the Aubin meta-analysis (Garvey et al., 2000) later reanalyzed their data to examine weight gain as a function of NRT adherence (Ferguson, Shiffman, Rohay,

Gitchell, & Garvey, 2011). Prior to considering adherence, they reported that the amount of weight gained at one month did not differ between abstinent smokers assigned to use nicotine gum and those randomized to placebo gum (2.4 lbs vs. 3.5 lbs, respectively). However, when adherence was considered, there was a significant adherence and treatment interaction such that participants assigned to nicotine gum who were adherent (i.e. ≥ 9 pieces/day on average) gained less weight than non-adherent users (1.3 lbs vs. 3.5 lbs). These results underscore the importance of considering adherence when studying the relationship between smoking, nicotine, and weight.

VLNC Cigarettes and Weight. The evidence highlighting a pharmacological effect of nicotine on weight in animal and human studies suggests that use of VLNC cigarettes may lead to weight gain for current smokers. To my knowledge, only two studies have examined this possibility to date, both in general-population smokers. The first was a study examining smoking behaviors and biomarkers of tobacco smoke exposure in which the nicotine content of cigarettes was gradually tapered during a 26-week period to a very low level (RNC condition) and compared to participants who continued to smoke their usual brand cigarettes (control) (Benowitz et al., 2012). In addition to reporting on smoking behavior outcomes, investigators briefly reported weight outcomes. The study found that weight did not change among control or among RNC participants. However, once again underscoring the importance of considering adherence, RNC participants who self-reported adherence to their assigned cigarettes gained an average weight 4.4 lbs over 26 weeks (Benowitz et al., 2012).

The second study examined the effect of an abrupt switch to VLNC cigarettes on weight gain. In this secondary analysis using data that assessed the effects of six weeks of exposure to VLNC cigarettes among general-population smokers (Donny et al., 2015), investigators focused on weight gain associated with the varying nicotine levels in cigarette conditions participants were assigned to during the trial (Rupprecht et al., 2017). Surprisingly once again, results comparing mean changes in weight in each of the conditions failed to show differences in weight gain between participants assigned to smoke VLNC cigarettes and participants assigned to NNC cigarettes or participant usual brand. However, given evidence that participants assigned to smoke VLNC cigarettes used other nicotine-containing tobacco products (Nardone et al., 2016), which would be expected to block weight gain, Rupprecht and colleagues (2017) conducted a subgroup analysis of the relationship between biomarkers of nicotine exposure and weight gain by identifying participants assigned to use the 0.4-mg/g cigarette and biochemically verified as adherent. Results from this model indicated adherent participants assigned to smoke the 0.4-mg/g dose gained more weight (an estimated 3.1 lbs based on Figure 3) than non-

Figure 3. Weight gain over time in compliant and non-compliant individuals in the 0.4-mg/g cigarette conditions of Rupprecht et al. (2017)



Note. *p<1.01 comparing compliant and non-compliant groups. #p<0.01 comparing compliant and 15.8-mg/g groups. +p<0.01 comparing compliant and usual brand groups.

adherent 0.4-mg/g, 15.8-mg/g, and usual brand groups in weeks 3, 4, 5, and 6 of the study (Figure 3; Rupprecht et al., 2017).

Evaluation of VLNC Cigarettes and Weight Gain in Vulnerable Populations

While these studies in general-population smokers are a first step towards understanding the possible effect of a nicotine reduction policy on smokers' weight, further research is needed to understand weight outcomes in vulnerable populations after exposure to VLNC cigarettes, including those with psychiatric conditions or socioeconomic disadvantage. In addition to these vulnerable populations having higher rates of smoking, addiction severity, and less success in cessation compared to the general population (Chilcoat, 2009; Higgins & Chilcoat, 2009; Cooper et al., 2016; Richter et al., 2001), these groups also face greater risk for overweight and obesity. For example, depression increases the odds (OR: 1.58) of developing obesity (Luppino et al., 2010). A study of patients receiving methadone to treat OUD found that 42% of the sample met criteria for overweight, obesity, or morbid obesity at the time of treatment entry and this rate increased to 76%, 82%, and 88% at one, two, and three years post-intake, respectively (Sweeney et al., 2018). Finally, the prevalence of obesity among women with a high school degree or less is 17% higher than the rate among women with a college degree (45% vs. 28%; Ogden et al., 2017). Weight gain that results from implementation of a nicotine product standard that reduces the nicotine content of commercial cigarettes could have the unintended consequence of increasing health risks associated with overweight and obesity.

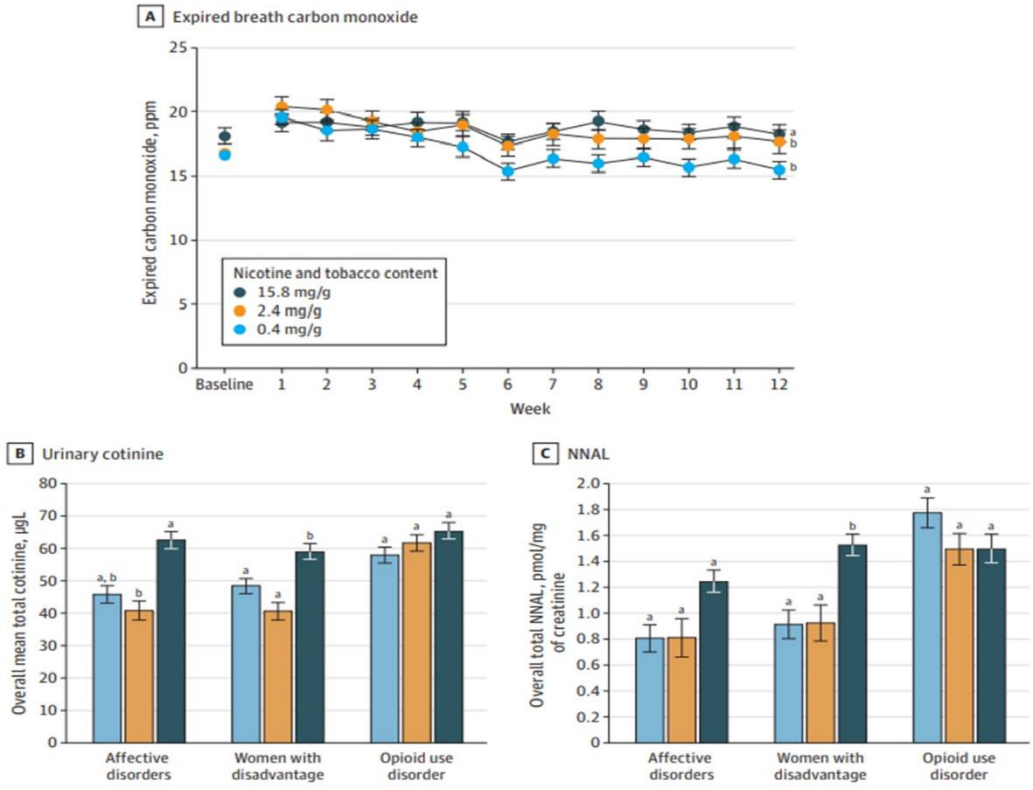
Thus, the goal of the present study is to extend the current literature examining weight gain related to VLNC cigarette exposure to smokers with affective disorders,

OUD, and women of socioeconomic disadvantage in three important ways. First, using data from Higgins et al. (2020), I explore whether smoking VLNC cigarettes is associated with weight gain. To my knowledge, this is the first study of weight gain related to VLNC exposure in these vulnerable populations. Second, this study extends previous work examining VLNC cigarettes and associated weight gain by analyzing data from a longer period of exposure to VLNC cigarettes after an abrupt switch. While Rupprecht et al. (2017) provided data through six weeks of VLNC exposure, this study examines the effect over 12 weeks of exposure. Third, in addition to analyzing the objective measure of participant weight as in previous studies, this study also includes an analysis of a subjective measure. More specifically, I look at participant responses to one of the items on the Minnesota Tobacco Withdrawal Scale (MTWS), a commonly used measure of nicotine withdrawal which asks about subjective "increased appetite, hunger, or weight gain."

> *Hypothesis 1*: Participants randomly assigned to smoke the 0.4-mg/g and 2.4-mg/g VLNC cigarettes will gain more weight and report higher "increased appetite/hunger/weight gain" ratings during the 12-week study period compared to participants assigned to the 15.8 mg/g NNC cigarettes.

I should note here that the results of some of the biomarker analyses in the Higgins et al. (2020) study suggest a potential complication for the first analysis. As noted in the primary outcomes paper and as expected, breath carbon monoxide (CO), a

Figure 4. CO, urinary cotinine, and NNAL levels by population in Higgins et al. (2020)



Note. A, Data points are arithmetic means across participants and populations; error bars represent SEM. Doses not sharing a letter differ in linear trends across the 12-week study period. B and C, Data points are geometric means across participants and time at each dose; error bars represent SEM. Data points not sharing a letter differed significantly in post-hoc testing.

biochemical marker of combustible cigarette use, varied by dose but not by population, with steeper decreases among those assigned to VLNC vs. NNC cigarettes (Figure 4, top panel). However, urinary cotinine and NNAL levels, both biomarkers specific to nicotine use, only varied by dose among smokers with affective disorder and women with disadvantage and not among smokers with OUD (Figure 4, bottom panels). The reductions in breath CO biochemically confirm the self-reported reductions to combustible CPD across populations, but the fact that cotinine and NNAL did not differ

by dose among smokers with OUD suggest these participants used more noncombustible forms of nicotine, such as e-cigarettes, smokeless tobacco, and NRT. Thus, it is possible that noncombustible nicotine use in this group increased nicotine to a level that counteracted the weight gain that would be predicted based on self-reported adherence to VLNC cigarettes and a reduction in CPD. Therefore, in addition to examining the relationship between VLNC cigarette use and weight gain across the study sample as a whole, I conduct two subgroup analyses, one that looks at this relationship in smokers with affective disorders and women of socioeconomic disadvantage together and another in smokers of OUD alone.

Hypothesis 2a: Smokers with affective disorders and women with socioeconomic disadvantage assigned to smoke VLNC cigarettes will gain more weight and report higher "increased appetite/hunger/weight gain" ratings during the study period compared to participants in these populations assigned to the NNC cigarettes.

Hypothesis 2b: Smokers with OUD assigned to smoke VLNC cigarettes will not gain more weight nor report higher "increased appetite/hunger/weight gain" rating than those assigned to smoke NNC cigarettes during the study period.

Methods

Participants

Study data were collected from 775 participants enrolled in three parallel, 12-week, randomized, double-blind trials investigating the effects of VLNC cigarettes on primary outcomes of smoking rate, toxin exposure, and dependence severity. Each trial included daily smokers from three vulnerable populations: individuals with affective

disorders (n=258), individuals with OUD (n=260), and socioeconomic disadvantaged women (n=257).

Participants were recruited at three sites (University of Vermont [all populations], John Hopkins University [women of disadvantage and smokers with OUD], and Brown University [smokers with affective disorders]) through Facebook ads, newspaper ads, community bulletin boards, and word-of-mouth referrals. The local Institutional Review Board at each site approved the study. The three trials shared several inclusion criteria, namely: at least 18 years of age; at least 5 CPD for the past year; expired breath CO sample greater than 8 ppm; no psychiatric conditions with potential to interfere with study results or completion; without serious illness or negative health change in past 90 days; not pregnant or nursing; no use of tobacco or nicotine products other than cigarettes on more than 9 days in past 30; sufficiently literate to complete study tasks; and report current use of contraception, history of surgical sterilization, or being post-menopause among women. Shared exclusion criteria across trials included prior regular use of VLNC cigarettes, plans to quit smoking in next 30 days, cessation attempt in past 30 days where abstinence exceeded 3 days, exclusive use of roll-your-own cigarettes, positive urine toxicology results for drugs other than cannabis, breath alcohol level greater than 0.01, and recent suicide ideation or attempt.

For the two trials focused on psychiatric conditions, inclusion criteria included meeting diagnostic criteria for an affective disorder or for OUD with stable enrollment in opioid maintenance treatment. Population-specific exclusion criteria included over 70 years of age in trials of smokers with psychiatric conditions, and over 44 years of age in the trial of disadvantaged women; and co-morbid substance use disorder in trials

examining affective disorders and disadvantaged women. Participants were paid up to $2,601 for participation.

Procedures Relevant to the Proposed Analyses

Individuals were invited to complete a screening assessment to determine eligibility for the trial. At screening, participants provided demographic information and tobacco use and exposure history, including characteristics like age, race, sex, CPD, and menthol preference. Eligible participants were randomly assigned to one of three research cigarettes varying in nicotine content (mg of nicotine/g of tobacco; 0.4-mg/g, 2.4-mg/g, or 15.8-mg/g) and completed a two-visit, one-week baseline period. During first baseline visit, participants were provided a free supply of usual brand cigarettes for use during the subsequent week to establish baseline smoking rate. The supply was 150% of self-reported smoking rate to accommodate potential increases in smoking rate. Participants used an interactive-voice-response (IVR) system daily throughout the study to report prior day cigarette consumption, other tobacco or nicotine product use, and nicotine withdrawal symptoms.

At the second baseline visit, participants received their first supply of study cigarettes and blood samples were drawn to determine baseline nicotine metabolite ratio (NMR) in plasma. They then reported to the clinic weekly for the next 12 weeks where they returned unused study cigarettes and were resupplied. At each weekly visit, research staff dispensed twice the number of cigarettes used during the one-week baseline to accommodate potential smoking rate increases or missed visits. Participants were instructed to only use the study cigarettes, counseled on managing adherence difficulties, queried about plans to quit smoking, and offered support if interested in quitting.

At each weekly study visit, participants were also asked to remove their shoes and outerwear before stepping on to the scale. Participants were told to plant both feet firmly and evenly on the scale surface and to stand upright. Research staff recorded participant weight to the nearest 0.1 kg. The self-report MTWS was completed every other week during the study intervention. The MTWS consisted of fifteen items rated on a scale of 0-4 where 0 = none, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe (Hughes, 2020; Hughes & Hatsukami, 1986). Current literature supports the reliability of the MTWS in measuring withdrawal and craving severity among smokers (e.g. Etter & Hughes, 2006; Hughes, 2007; Piper, 2015; West, Ussher, Evans, & Rashid, 2006). Participants were instructed to respond based on how they have felt or what they have noticed since their last study visit. This study will focus on participant ratings for the item "increased appetite, hunger, or weight gain."

Data Analysis Plan

Weight changes were calculated as participant weight, in pounds, at each visit minus their baseline weight, defined as the average of the three weight measurements taken prior to receiving their assigned study cigarettes (one at screening and one at each of the two baseline visits). To inspect for outliers, weight data were graphed and visually examined for major shifts in weight trajectory. Transformations were considered, but unnecessary as weight change was normally distributed.

To test Hypothesis 1, a linear mixed model was used to examine differences in weight gain over time with a random intercept to account for between-subject weight differences. In addition to cigarette dose, study week, and an interaction term for cigarette dose and study week, the model also included fixed effects for study site, baseline

weight, age, menthol, sex, population, race, NMR, and time of year at enrollment. As participant weight was measured at baseline and weekly during the study period, and weight was considered as a continuous variable, a growth curve was used to examine the trajectory of changes over the 12 weeks of the trial. Time of year at study enrollment was included as a fixed effect since certain times of the year are associated with weight gain (e.g., Diaz-Zavala et al., 2017). This was included as a covariate by mapping the calendar year onto a circle and converting dates into angles which are represented by sine and cosine values (Le et al., 2003). The sine and cosine variables must be interpreted together to understand the effect of time of year at enrollment. To examine the effect of time of year at enrollment, the difference in the -2 Log Likelihood Estimates between the models with and without these two variables, which is distributed as a chi-squared statistic with 2 *df,* was examined. Additionally, during the study, a shortage of two doses of research cigarettes (2.4mg/g non-menthol and 15.8 mg/g cigarettes, both menthol and non-menthol) resulted in revision of the randomization sequence. This revision resulted in an over-assignment to the 0.4 mg/g menthol cigarette until the cigarettes in short supply became available again. To accommodate any potential influence of this revision on outcomes, menthol cigarette use was included as a fixed effect in all models.

Another linear mixed model was used to examine differences in participant response to the MTWS "increased appetite/hunger/weight gain" item over time with a random intercept to account for between-subject differences. The model included fixed effects for study site, the baseline value of MTWS "increased appetite/hunger/weight gain," age, menthol, sex, population, race, NMR, time of year at enrollment, cigarette dose, study week, and an interaction term for cigarette dose and study week.

Subgroup analyses to test Hypotheses 2a and 2b included two linear mixed models to determine differences in weight gain over time. The first model focused on smokers with affective disorders and women of socioeconomic disadvantage combined and the second on smokers with OUD. Both models looked at weight gain over time with a random intercept to account for between-subject differences. Models included fixed effects for study site, baseline weight, age, menthol, sex, race, NMR, time of year at enrollment, cigarette dose, study week, and an interaction term for cigarette dose and study week. Growth curves were used to examine the trajectory of changes over the 12 weeks of the trial.

In addition, two linear mixed models were conducted to examine differences in participant response to the MTWS "increased appetite/hunger/weight gain" item. As for weight, the first model focused on smokers with affective disorders and women of socioeconomic disadvantage combined and the second on smokers with OUD. Both models examined differences in response to the MTWS "increased appetite/hunger/weight gain" item over time with a random intercept to account for between-subject differences. The model included fixed effects for study site, baseline MTWS appetite/hunger/weight, menthol, sex, age, race, NMR, time of year at enrollment, cigarette dose, study week, and an interaction term for cigarette dose and study week.

In all models, the interaction term for cigarette dose and study week was nonsignificant, thus it was removed and models were re-run. When there was a statistically significant effect of cigarette dose ($p < .05$), post-hoc tests were conducted to explore the nature of significant findings. All pairwise comparisons were conducted using

Bonferroni multiple comparison adjustment. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Participant Characteristics

Participant demographics among the whole sample and by population are shown in Table 1. Overall, the mean (± SD) age of the sample was 35.59 (± 11.05), 71.10% identified as women, 82.14% were white, and 73.55% had a high school degree or some college. Regarding smoking characteristics, the mean CPD was 17.79 (± 9.18), 45.29% smoked mentholated cigarettes, and 73.06% had a normal NMR (≥ 0.31). Participants weighed 190.63 (± 51.58) lbs on average at baseline, with 46.0% of the sample meeting the definition of obese (BMI: 31.04 [± 8.27]). MTWS "increased appetite/hunger/weight gain" rating was 1.67 (± 1.05) at baseline.

Weight across Populations

In the full sample, there were no significant differences in weight gain between participants assigned to the VLNC cigarette conditions and those assigned to NNC cigarettes (Table 1, upper panel). There was a significant main effect of study week on weight ($F(1, 6612) = 10.90$, $p = .001$), with participants across cigarette dose conditions gaining an average (± SE) of 2.26 (±0.33) lbs at week 12 of the study period (Figure 5).

There was a significant main effect of dose in subjective reports of "increased appetite/hunger/weight gain" ($F(2, 676) = 4.81$; $p = .01$; Table 2, lower panel). Post hoc testing indicated smokers randomly assigned to the 0.4-mg/g VLNC cigarettes reported higher "increased appetite/hunger/weight gain" ratings compared to those assigned to the 15.8-mg/g NNC cigarettes during the study period, with average ratings of 1.95 (±0.08)

and 1.73 (±0.08), respectively (p = .01; Figure 6). This effect is independent of the three significant covariates in the model, namely 1) baseline rating of "increased appetite/hunger/weight gain", 2) sex, and 3) population (Table 2, lower panel). Regarding the first significant covariate, participants reporting higher "increased appetite/hunger/weight gain" ratings at baseline tended to have higher ratings during the study (p < .001). Regarding the second, females had a higher average "increased appetite/hunger/weight gain" rating compared to males during the study period with mean ratings of 1.94 (±0.07) and 1.78 (±0.09), respectively (p = .04). Third, smokers with affective disorders reported higher average "increased appetite/hunger/weight gain" ratings compared to smokers with OUD during the study period with mean (± SE) ratings of 2.00 (± 0.08) and 1.78 (± 0.09), respectively (p = .04). The effect of study week on ratings of "increased appetite/hunger/weight gain" across populations was not significant.

Table 1. Demographics

Characteristic	Overall (N=775)	Disadvantaged Women (n=257)	Opioid Use Disorder (n=260)	Affective Disorders (n=258)
Nicotine Dose (n, %)				
0.4-mg/g	286 (36.90)	93 (36.19)	92 (35.38)	101 (39.15)
2.4-mg/g	235 (30.32)	81 (31.52)	81 (31.15)	73 (28.29)
15.8-mg/g	254 (32.77)	83 (32.30)	87 (33.46)	84 (32.56)
Age, y	35.59 ± 11.05	31.00 ± 6.97	38.44 ± 10.42	37.29 ± 13.35
Baseline Weight, lbs	190.63 ± 51.58	193.53 ± 56.47	189.91 ± 46.28	188.46 ± 51.65
Baseline "Increased Appetite/Hunger/Weight Gain" Rating	1.67 ± 1.05	1.44 ± 0.92	1.52 ± 0.94	2.05 ± 1.19
Baseline BMI	31.04 ± 8.27	32.52 ± 9.15	30.59 ± 7.22	30.01 ± 8.15
Women (n, %)	551 (71.10)	257 (100.0)	143 (55.00)	151 (58.53)
Race/Ethnicity (n, %)				
Non-Latino				
White	630 (82.14)	204 (80.00)	211 (82.75)	215 (83.66)
Black	68 (8.87)	33 (12.94)	22 (8.63)	13 (5.06)
Latino	23 (3.00)	3 (1.18)	6 (2.35)	14 (5.45)
Non-Latino Other or > 1 Race	46 (6.00)	15 (5.88)	16 (6.27)	15 (5.84)
Education (n, %)				
< High School	102 (13.16)	36 (14.01)	49 (18.85)	17 (6.59)
High School Grad/Equivalent or Some College	570 (73.55)	220 (85.99)	188 (72.31)	162 (62.79)
Associate's Degree	38 (4.90)	0 (0.00)	12 (4.62)	25 (9.69)
College Degree or Higher	65 (8.39)	0 (0.00)	11 (4.23)	54 (20.93)
Marital Status (n, %)				
Married	112 (14.45)	51 (19.84)	27 (10.38)	34 (13.18)
Never Married	461 (59.48)	146 (56.81)	163 (62.69)	152 (58.91)
Divorced, Widowed, Separated	202 (26.06)	60 (23.35)	70 (26.92)	72 (27.91)
Primary Smoker of Mentholated Cigs (n, %)	351 (45.29)	121 (47.08)	118 (45.38)	112 (43.41)
Cigarettes Per Day, No.	17.79 ± 9.18	15.23 ± 7.40	22.33 ± 9.83	15.78 ± 8.39
Normal Nicotine Metabolite Ratio (≥ .31; n, %)	526 (73.06)	160 (66.39)	173 (77.23)	193 (75.69)
Breath Carbon Monoxide Level, ppm	18.02 ± 9.85	16.16 ± 8.12	19.47 ± 9.77	18.41 ± 11.16
FTND Score (range, 0-10)	5.56 ± 2.35	4.84 ± 2.21	6.61 ± 2.03	5.23 ± 2.43
Used Other Tobacco Products, Last 30 Days (n, %)	117 (17.67)	43 (18.78)	23 (11.33)	51 (22.17)

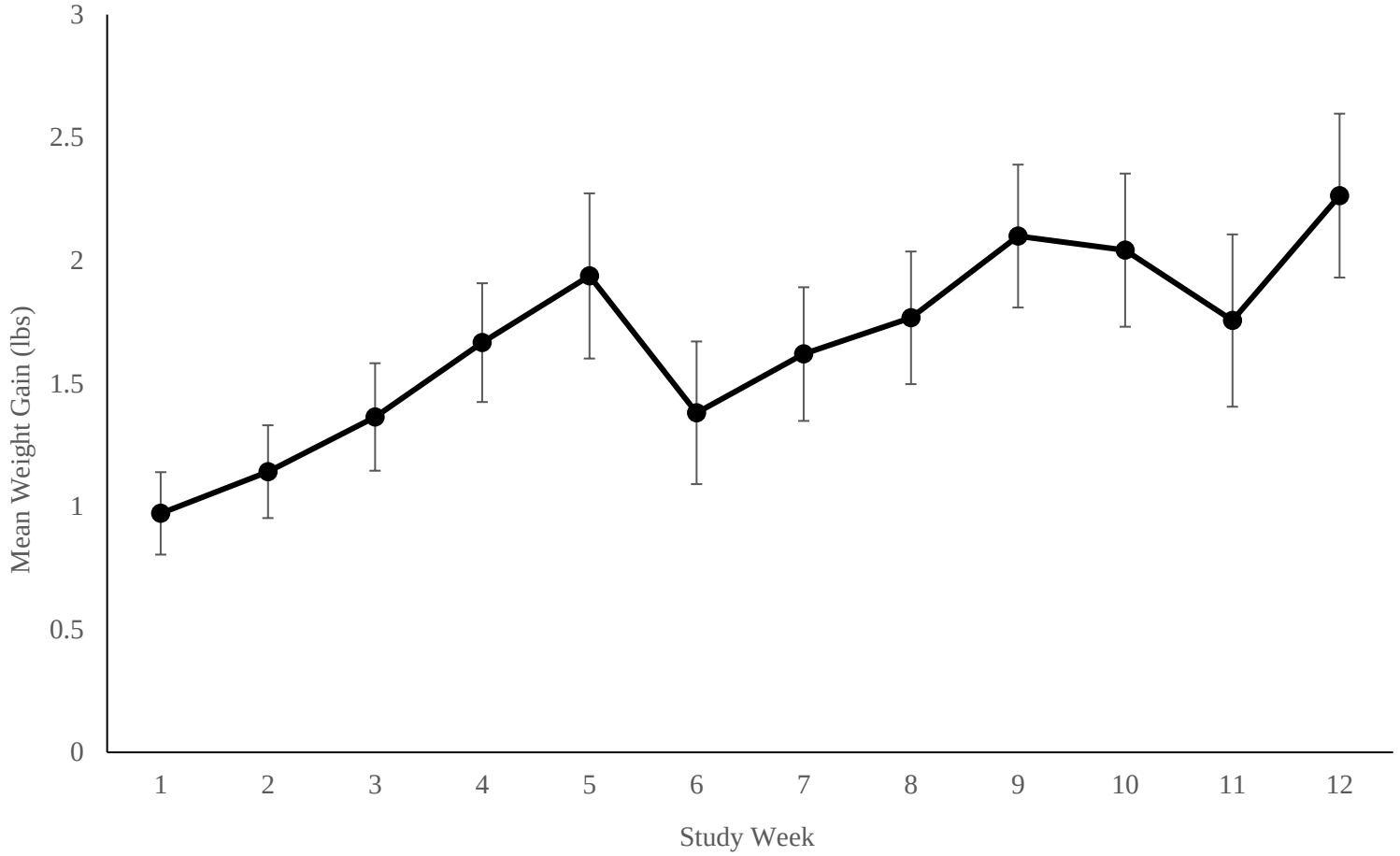
Note. Values are means ± SD unless otherwise noted. OUD, opioid use disorder; FTND, Fagerström Test for Nicotine Dependence.

Table 2. Models of Weight Change and Subjective "Increased Appetite/Hunger/Weight Gain" Ratings across All Populations

	Num DF	Den DF	F Value	Pr > F
Weight Change				
Nicotine Dose	2	675	2.30	.10
Week	1	6612	10.90	.001*
Baseline Weight	1	675	1.24	.27
Site	2	675	0.10	.91
Menthol	1	675	0.51	.48
Sex	1	675	0.37	.54
Race/Ethnicity	3	675	1.39	.24
Age	1	675	2.77	.10
Nicotine Metabolite Ratio	1	675	1.80	.18
Population	2	675	0.58	.56
Time of Year at Enrollment[a]	2	-	-	.90
MTWS "Increased Appetite/Hunger/Weight Gain"				
Nicotine Dose	2	676	4.81	.01*
Week	1	2978	1.71	.19
Baseline "Increased Appetite/Hunger/Weight Gain"	1	676	173.26	<.001*
Site	2	676	0.11	.89
Menthol	1	676	0.69	.41
Sex	1	676	4.26	.04*
Race/Ethnicity	3	676	1.15	.33
Age	1	676	0.38	.54
Nicotine Metabolite Ratio	1	676	0.13	.72
Population	2	676	3.42	.03*
Time of Year at Enrollment[a]	2	-	-	.99

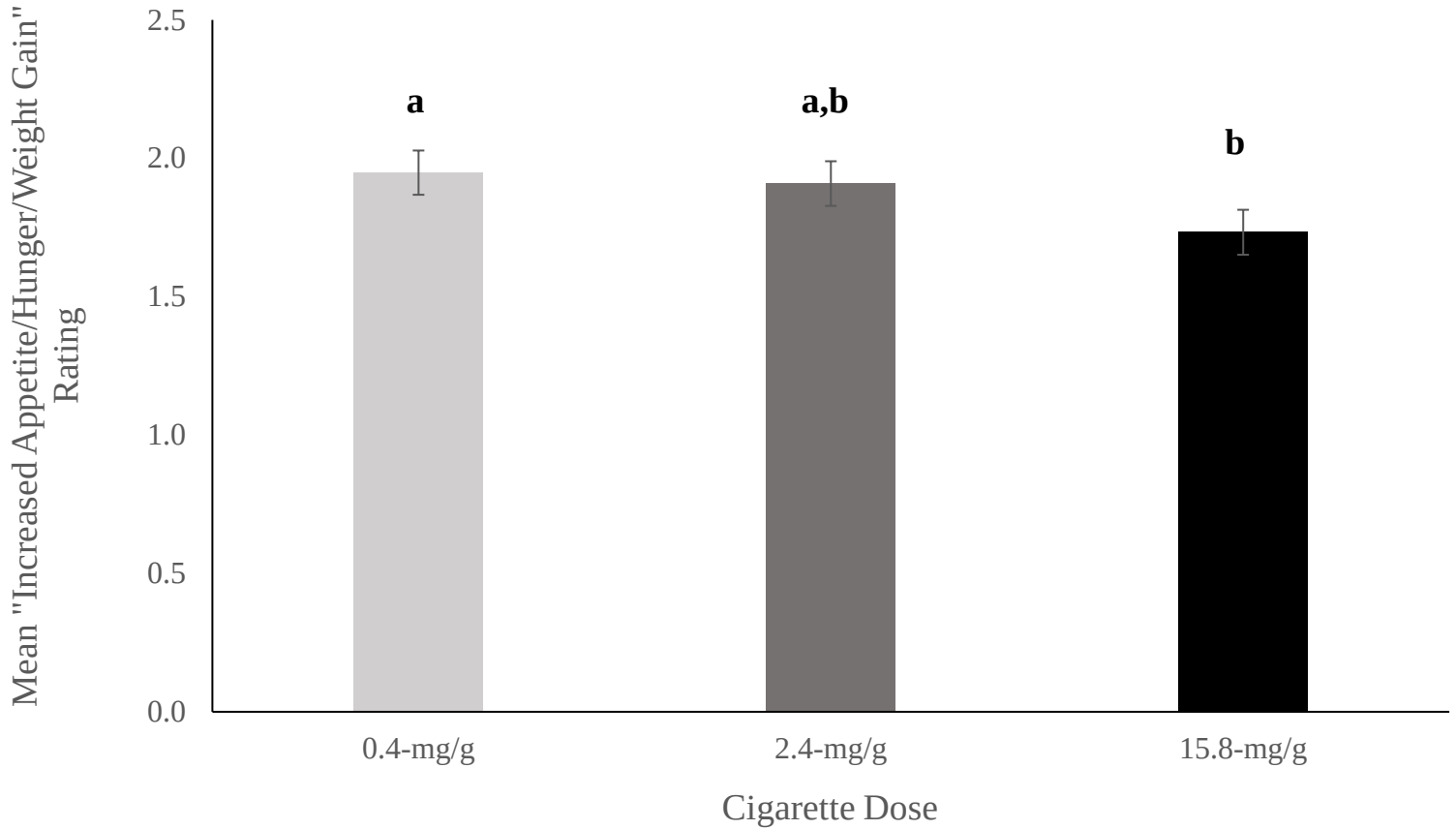
Note. [a]Time of year at enrollment variable is the difference in -2 Log Likelihood estimates, which is distributed as a chi-squared statistic with 2 df. Thus, there is no F-statistic to report. * denotes $p < .05$. MTWS, Minnesota Tobacco Withdrawal Scale.

Figure 5. Mean Cumulative Weight Gain over the Study Period across All Populations



Note. Error bars are SE. Significant effect of study week on cumulative weight gain (p = .001).

Figure 6. Mean Minnesota Tobacco Withdrawal Scale "Increased Appetite/Hunger/Weight Gain" Ratings by Cigarette Dose across All Populations



Note. Error bars are SE. Responses to items on the Minnesota Tobacco Withdrawal Scale range from 0-4, but are restricted here to show differences by doses. Data points not sharing a letter are significantly different (p = .01).

Weight among Smokers with Affective Disorders and Disadvantaged Women

There was a significant main effect of dose on weight change among smokers with affective disorders and disadvantaged women ($F(2, 461) = 4.40$, $p = .01$; Table 3, upper panel). Examination of the mean estimates by dose condition shows a graded effect, such that participants in these populations assigned to the VLNC cigarette conditions gained more weight compared to those assigned to the NNC condition, although post-hoc testing only indicated a statistically significant difference between participants in the 0.4-mg/g and 15.8-mg/g conditions, with average weight gains of 3.10 (±0.52) lbs and 1.69 (±0.54) lbs, respectively ($p = .01$; Figure 7). Similar to the model looking at all populations together, there was also a significant effect of study week on weight ($F(1, 4498) = 13.87$; $p < .001$), with participants across cigarette dose conditions having a cumulative weight gain of 2.57 (±0.40) lbs at week 12 of the study period.

Differences in subjective "increased appetite/hunger/weight gain" ratings among smokers with affective disorders and disadvantaged women mirrored the dose difference found in weight gain ($F(2, 462) = 3.76$, $p = .02$; Table 3, lower panel). Mean estimates show a graded effect, with those using VLNC cigarettes reporting higher average "increased appetite/hunger/weight gain" ratings than smokers using NNC cigarettes during the study period and post-hoc testing again indicating a statistically significant difference between those assigned to the 0.4-mg/g and 15.8-mg/g conditions (average ratings of 2.00 (±0.10) and 1.76 (±0.10), $p = .02$; Figure 8). This dose effect is independent of the baseline rating of "increased appetite/hunger/weight gain", which was the only significant covariate ($p < .001$; Table 3, lower panel). As in the full sample,

participants reporting higher “increased appetite/hunger/weight gain” ratings at baseline tended to have higher “increased appetite/hunger/weight gain” ratings during the study. The effect of study week on ratings of “increased appetite/hunger/weight gain” among smokers with affective disorders or disadvantaged women was not significant.

Weight among Smokers with Opioid Use Disorder

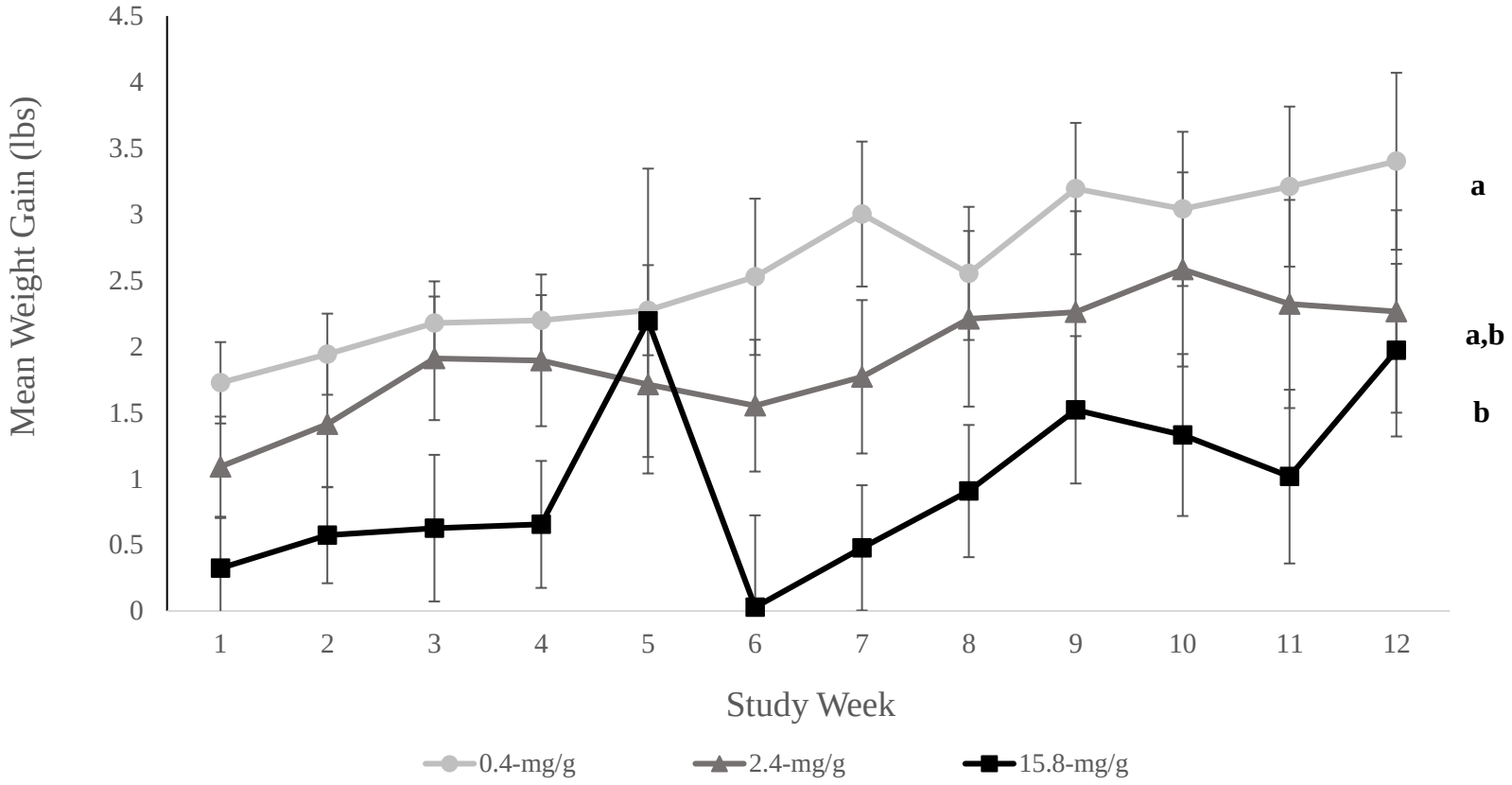
There was no main effect of dose on weight change among smokers with OUD (Table 4, upper panel), nor were any of the covariates in this model significant, including study week. Findings for subjective “increased appetite/hunger/weight gain” ratings for smokers with OUD parallel the weight results in this population, with no main effect of dose on “increased appetite/hunger/weight gain” ratings (Table 4, lower panel). However, the model once again revealed baseline “increased appetite/hunger/weight gain” ratings as a significant covariate ($p < .001$) as well as age, with younger smokers with OUD reporting higher “increased appetite/hunger/weight gain” ratings compared to older smokers with OUD during the study period ($p = .02$). There was no effect of study week on ratings of “increased appetite/hunger/weight gain” among smokers with OUD.

Table 3. Models of Weight Change and Subjective "Increased Appetite/Hunger/Weight Gain" Ratings among Smokers with Affective Disorders and Disadvantaged Women

	Num DF	Den DF	F Value	Pr > F
Weight Change				
Dose	2	461	4.40	.01*
Week	1	4498	13.87	<.001*
Baseline Weight	1	461	1.34	.25
Site	2	461	0.59	.56
Menthol	1	461	0.98	.32
Sex	1	461	0.00	.95
Race/Ethnicity	3	461	0.85	.47
Age	1	461	0.65	.42
Nicotine Metabolite Ratio	1	461	0.95	.33
Time of Year at Enrollment[a]	2	-	-	.54
MTWS "Increased Appetite/Hunger/Weight Gain"				
Dose	2	462	3.76	.02*
Week	1	2029	0.46	.50
Baseline "Increased Appetite/Hunger/Weight Gain"	1	462	134.38	<.001*
Site	2	462	2.48	.09
Menthol	1	462	0.82	.37
Sex	1	462	2.70	.10
Race/Ethnicity	3	462	0.24	.87
Age	1	462	0.44	.51
Nicotine Metabolite Ratio	1	462	1.78	.18
Time of Year at Enrollment[a]	2	-	-	.99

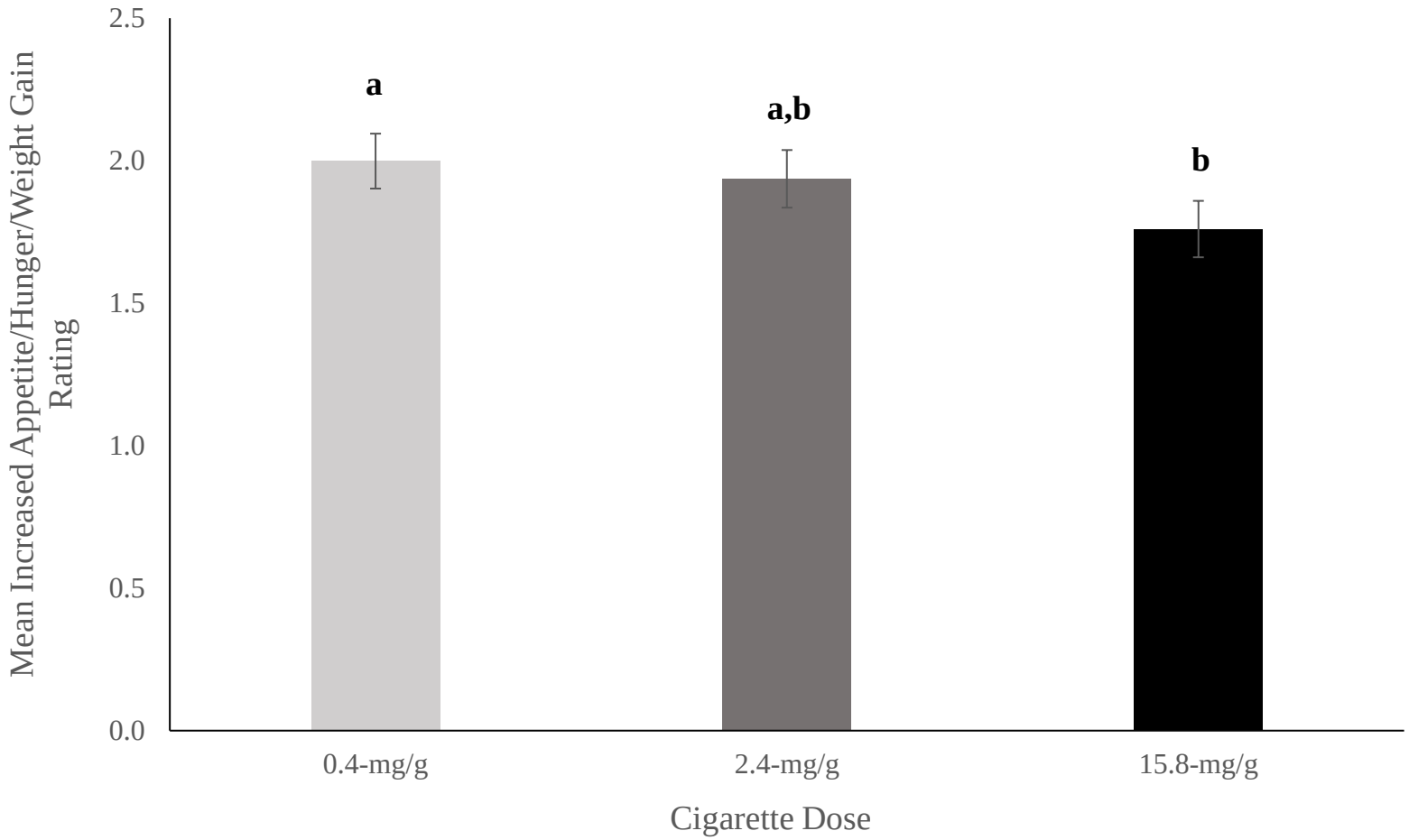
Note. [a]Time of year at enrollment variable is the difference in the -2 Log Likelihood estimates, which is distributed as a chi-squared statistic with 2 df. Thus, there is no F-statistic to report. * denotes $p < .05$. MTWS , Minnesota Tobacco Withdrawal Scale,.

Figure 7. Mean Cumulative Weight Gain by Dose among Smokers with Affective Disorders and Disadvantaged Women



Note. Error bars are SE. Doses not sharing a letter are significantly different (p = .01). Peak in weight gain at week 5 for the 15.8-mg/g is due to one participant who had a 150 lb weight gain at this time point, which is presumed to be an error in the recorded data.

Figure 8. Mean Minnesota Tobacco Withdrawal Scale "Increased Appetite/Hunger/Weight Gain" by Cigarette Dose among Smokers with Affective Disorders and Disadvantaged Women



Note. Error bars are SE. Responses to items on the Minnesota Tobacco Withdrawal Scale range from 0-4, but are restricted here to show differences by doses. Data points not sharing a letter are significantly different (p = .02).

Table 4. Models of Weight Change and Subjective "Increased Appetite/Hunger/Weight Gain" Ratings among Smokers with Opioid Use Disorder

	Num DF	Den DF	F Value	Pr > F
Weight Change				
Dose	2	204	1.46	.23
Week	1	2113	0.18	.67
Baseline Weight	1	204	0.86	.35
Site	2	204	1.45	.23
Menthol	1	204	0.16	.69
Sex	1	204	0.62	.43
Race	3	204	0.34	.79
Age	1	204	2.36	.13
Nicotine Metabolite Ratio	1	204	0.61	.44
Time of Year at Enrollment[a]	2	-	-	.94
MTWS Increased Appetite/Hunger/Weight Gain				
Dose	2	204	0.68	.51
Week	1	948	2.41	.12
Baseline "Increased Appetite/Hunger/Weight Gain"	1	204	39.58	<.001*
Site	2	204	1.88	.17
Menthol	1	204	0.29	.59
Sex	1	204	0.25	.61
Race	3	204	1.73	.16
Age	1	204	5.45	.02*
Nicotine Metabolite Ratio	1	204	1.90	.17
Time of Year at Enrollment[a]	2	-	-	.98

Note. [a]Time of year at enrollment variable is the difference in the -2 Log Likelihood estimates, which is distributed as a chi-squared statistic with 2 df. Thus, there is not an F-statistic to report. * denotes p <.05. Minnesota Tobacco Withdrawal Scale, MTWS.

Discussion

The present study examined the effect of VLNC cigarette use on weight changes, both objective and subjective measures, among smokers with psychiatric conditions or socioeconomic disadvantage. Regarding Hypothesis 1, which focused on these outcomes in the total sample, there were no significant differences in weight gain by cigarette dose condition. Although the relationship between nicotine and weight gain in the literature is very reliable, this result was not wholly unexpected given the initial null results of Rupprecht et al. (2017) using data from a large sample of general-population smokers and the biomarker data reported in the primary outcomes paper for the present sample of vulnerable population smokers (Higgins et al., 2020). There were, however, significant differences in subjective reports of "increased appetite/hunger/weight gain" by dose in the total sample. To my knowledge, this is the first time the effect of VLNC cigarettes on a subjective measure of appetite, hunger, or weight has been examined. Both dose and population were significant such that smokers assigned to use 0.4-mg/g cigarettes reported higher "increased appetite/hunger/weight gain" ratings than smokers using the 15.8-mg/g cigarette and smokers with affective disorders reported higher "increased appetite/hunger/weight gain" ratings during the study period than smokers with OUD. Thus, Hypothesis 1 is partially supported.

The results of Rupprecht et al. (2017) underscored the importance of adherence as a critical component of the relationship between VLNC cigarette use and weight gain in general-population smokers and the same was observed in these analyses using data from vulnerable populations, the focus of Hypothesis 2. It is important to note I found a graded effect of dose on weight gain and subjective "increased appetite/hunger/weight

gain" ratings among smokers with affective disorders and disadvantaged women, the two populations whose biomarker data in the primary outcomes paper suggested better adherence to their assigned study cigarettes. Means of weight gain by dose show these smokers assigned to the 0.4-mg/g cigarette gained the most weight, then smokers assigned to the 2.4-mg/g cigarette gained slightly less than this group but more weight than those in the 15.8-mg/g condition (3.10 vs. 2.38 vs. 1.69 lbs, respectively). This pattern was the same for subjective "increased appetite/hunger/weight gain" ratings (2.00 vs. 1.94 vs. 1.76, respectively). However, the difference between the 2.4-mg/g VLNC cigarette and the NNC cigarette condition for both and subjective measures did not reach statistical significance. In contrast, among smokers with OUD, whose biomarker data suggested they were less adherent to the study cigarettes relative to the other populations, there were no differences in weight gain or subjective "increased appetite/hunger/weight gain" ratings by cigarette dose. Thus, Hypotheses 2a and 2b are partially supported by these analyses.

As noted in the Introduction, the present study provided an opportunity to extend previous work examining VLNC cigarettes and associated weight gain by analyzing data from a longer period of exposure to VLNC cigarettes after an abrupt switch. Rupprecht et al. (2017) reported that smokers who were adherent to the 0.4-mg/g dose had a cumulative weight gain of 3.1 lbs in the last week of the six week study, very similar to the cumulative weight gain of 3.40 lbs seen in smokers with affective disorders and disadvantaged women assigned to the 0.4-mg/g cigarette at week 12 in this study. Much of this weight gain occurred quickly in both studies, with participants gaining around 2 lbs in the first two weeks. Participants in Rupprecht et al. (2017) then gained another

pound in the third week before plateauing for the remaining three weeks of the study period while in the present study, an additional pound was gained more slowly over the next ten weeks and it is unclear whether weight gain has leveled off.

Although weight gain in both studies was statistically significant, it is important to also consider these findings in terms of its clinical significance. A common definition of clinically significant weight change is a change >5% of a patient's baseline weight (Stevens et al., 2006; Williams, Bray, and Ryan; 2015). On average, smokers with affective disorders and disadvantaged women assigned to the 0.4-mg/g cigarette condition weighed 190.42 lbs at baseline and had a cumulative weight gain of 3.40 lbs at week 12, or 1.8% of their baseline weight. This is consistent with Rupprecht et al. (2017), where the total sample weighed 189.16 lbs and smokers who were adherent to the 0.4-mg/g dose gained approximately 3.1 lbs, or an estimated 1.6% of their baseline weight. Thus, the observed weight gain is not considered clinically significant in either study. It is possible that weight gain continues in vulnerable populations, but at the pace observed, would need to continue for a long period to reach clinical significance. These observations should be reassuring to the FDA as it continues to consider the benefits and risks of implementing a national nicotine reduction policy.

While there was a statistically significant difference in "increased appetite/hunger/weight gain" ratings by cigarette dose in my model examining all the populations together, subgroup analyses suggest this effect was driven by differences by cigarette dose among smokers with affective disorders and disadvantaged women as no difference was found among smokers with OUD. However, among smokers with affective disorders and disadvantaged women, the mean "increased

appetite/hunger/weight gain" ratings for those assigned to the 0.4-mg/g and 15.8-mg/g cigarettes were 2.00 and 1.76, on a scale where 2 = mild. Although these values are statistically different, the fact that both are generally mild in severity may suggest that there is also not a lot of clinical significance in this dose difference.

That said, policymakers may still want to consider how smokers might react to small increases in weight and subjective appetite, hunger, and weight gain prior implementing a nicotine reduction policy. Evidence from the smoking cessation literature demonstrates that concerns about post-cessation weight gain can be a barrier to quitting and a reason for relapse (Clark et al., 2006; Tuovinen et al., 2018). Should smokers associate VLNC cigarettes with weight gain, even if it is a modest weight gain, or perceive increases in appetite or hunger when switching to VLNC cigarettes, they may be less likely to use these products. Consequently, although the actual changes are small and seem unlikely to increase adverse health risk, implementation of a nicotine reduction policy may need to be accompanied by efforts to assuage concerns about weight gain and to address subjective increases in appetite, hunger, and weight gain among smokers to lower these potential barriers to use of these products.

Overall, this study extends the current literature examining weight gain related to VLNC cigarette exposure for smokers with affective disorders, OUD, and women of socioeconomic disadvantage. In addition to providing the first analysis of the effect of VLNC cigarettes on weight in these vulnerable populations, this study also provides data examining a longer period of VLNC exposure and contributes some initial data on a subjective measure of increased appetite/hunger/weight gain. The present study has some limitations that merit mention. First, the study participants were paid volunteers not

selected to be representative of the U.S. population, which could limit generalizability. Additionally, the subjective measure used in this study groups appetite, hunger, and weight gain together and participants may have completed this item considering one, two, or all three of these factors in their responses. Thus, it is difficult to draw conclusions about which factors the subjective differences apply to. Finally, the results of current study do not speak to the mechanism(s) by which nicotine reduction increases weight. As discussed in the Introduction, pre-clinical research has provided evidence that nicotine influences neural pathways integral to regulation of appetite, food intake, and weight change. However, the specific process and down-stream effects by which reductions in nicotine cause increases in weight are unclear. It could be that reductions in nicotine result in changes to peripheral hormones which increase an individual's food intake. Another possibility is that reductions in nicotine exposure influence energy expenditure. For instance, leptin is a hormone produced by adipose tissue that plays a critical role in food intake, appetite, and energy expenditure (Klok, Jakobsdottir, & Drent, 2007; Pandit, Beerens, and Adan, 2017) and some studies have suggested that nicotine exposure affects sensitivity to leptin in humans (Hodge et al., 1997; Kryfti et al., 2015). While more research is needed to better understand how nicotine exposure alters weight, the findings of the present study are reassuring and suggest there would be few if any adverse consequences of implementing a nicotine reduction policy with regard to weight.

References

Aubin, H. J., Farley, A., Lycett, D., Lahmek, P., & Aveyard, P. (2012). Weight gain in smokers after quitting cigarettes: meta-analysis. *BMJ, 345*, e4439. doi:10.1136/bmj.e4439

Audrain-McGovern, J., & Benowitz, N. L. (2011). Cigarette smoking, nicotine, and body weight. *Clin Pharmacol Ther, 90*(1), 164-168. doi:10.1038/clpt.2011.105

Benowitz, N. L., Dains, K. M., Hall, S. M., Stewart, S., Wilson, M., Dempsey, D., & Jacob, P., 3rd. (2012). Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev, 21*(5), 761-769. doi:10.1158/1055-9965.EPI-11-0644

Benowitz, N. L., & Henningfield, J. E. (1994). Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N Engl J Med, 331*(2), 123-125. doi:10.1056/NEJM199407143310212

Benowitz, N. L., Nardone, N., Dains, K. M., Hall, S. M., Stewart, S., Dempsey, D., & Jacob, P., 3rd. (2015). Effect of reducing the nicotine content of cigarettes on cigarette smoking behavior and tobacco smoke toxicant exposure: 2-year follow up. *Addiction, 110*(10), 1667-1675. doi:10.1111/add.12978

Berman, M. L., & Glasser, A. M. (2019). Nicotine Reduction in Cigarettes: Literature Review and Gap Analysis. *Nicotine Tob Res, 21*(Suppl 1), S133-S144. doi:10.1093/ntr/ntz162

Bunney, P. E., Burroughs, D., Hernandez, C., & LeSage, M. G. (2016). The effects of nicotine self-administration and withdrawal on concurrently available chow and sucrose intake in adult male rats. *Physiol Behav, 154*, 49-59. doi:10.1016/j.physbeh.2015.11.002

Bush, T., Lovejoy, J. C., Deprey, M., & Carpenter, K. M. (2016). The effect of tobacco cessation on weight gain, obesity, and diabetes risk. *Obesity (Silver Spring), 24*(9), 1834-1841. doi:10.1002/oby.21582

Byron, M. J., Jeong, M., Abrams, D. B., & Brewer, N. T. (2018). Public misperception that very low nicotine cigarettes are less carcinogenic. *Tob Control, 27*(6), 712-714. doi:10.1136/tobaccocontrol-2017-054124

Chilcoat, H. D. (2009). An overview of the emergence of disparities in smoking prevalence, cessation, and adverse consequences among women. *Drug Alcohol Depend, 104 Suppl 1*, S17-23. doi:10.1016/j.drugalcdep.2009.06.002

Clark, M. M., Hurt, R. D., Croghan, I. T., Patten, C. A., Novotny, P., Sloan, J. A., ... & Loprinzi, C. L. (2006). The prevalence of weight concerns in a smoking abstinence clinical trial. *Addictive behaviors*, 31(7), 1144-1152.

Cooper, J., Borland, R., McKee, S. A., Yong, H. H., & Dugue, P. A. (2016). Depression motivates quit attempts but predicts relapse: differential findings for gender from the International Tobacco Control Study. *Addiction, 111*(8), 1438-1447. doi:10.1111/add.13290

Dermody, S. S., Tidey, J. W., Denlinger, R. L., Pacek, L. R., al'Absi, M., Drobes, D. J., . . . Donny, E. C. (2016). The Impact of Smoking Very Low Nicotine Content

Cigarettes on Alcohol Use. *Alcohol Clin Exp Res, 40*(3), 606-615. doi:10.1111/acer.12980

Diaz-Zavala, R. G., Castro-Cantu, M. F., Valencia, M. E., Alvarez-Hernandez, G., Haby, M. M., & Esparza-Romero, J. (2017). Effect of the Holiday Season on Weight Gain: A Narrative Review. *J Obes, 2017*, 2085136. doi:10.1155/2017/2085136

Etter, J. F. & Hughes, J. R. (2006) A Comparison of the Psychometric Properties of Three Cigarette Withdrawal Scales. *Addiction, 101*:362-372

Erlanson-Albertsson, C. (2005), How Palatable Food Disrupts Appetite Regulation. *Basic & Clinical Pharmacology & Toxicology*, 97: 61-73. https://doi.org/10.1111/j.1742-7843.2005.pto_179.x

Ferguson, S. G., Shiffman, S., & Gitchell, J. G. (2011). Nicotine replacement therapies: patient safety and persistence. *Patient Relat Outcome Meas, 2*, 111-117. doi:10.2147/PROM.S11545

Ferguson, S. G., Shiffman, S., Rohay, J. M., Gitchell, J. G., & Garvey, A. J. (2011). Effect of compliance with nicotine gum dosing on weight gained during a quit attempt. *Addiction, 106*(3), 651-656. doi:10.1111/j.1360-0443.2010.03244.x

Food and Drug Administration and U.S. Department of Health and Human Services (2018) Tobacco Product Standard for Nicotine Level of Combusted Cigarettes. Retreived from: https://www.federalregister.gov/d/2018-05345

Garvey, A. J., Kinnunen, T., Nordstrom, B. L., Utman, C. H., Doherty, K., Rosner, B., & Vokonas, P. S. (2000). Effects of nicotine gum dose by level of nicotine dependence. *Nicotine Tob Res, 2*(1), 53-63. doi:10.1080/14622200050011303

Gottlieb, S., & Zeller, M. (2017). A Nicotine-Focused Framework for Public Health. *N Engl J Med, 377*(12), 1111-1114. doi:10.1056/NEJMp1707409

Hatsukami, D. K., Benowitz, N. L., Donny, E., Henningfield, J., & Zeller, M. (2013). Nicotine reduction: strategic research plan. *Nicotine Tob Res, 15*(6), 1003-1013. doi:10.1093/ntr/nts214

Hatsukami, D. K., Luo, X., Jensen, J. A., al'Absi, M., Allen, S. S., Carmella, S. G., . . . Donny, E. C. (2018). Effect of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Biomarkers of Smoke Exposure: A Randomized Clinical Trial. *JAMA, 320*(9), 880-891. doi:10.1001/jama.2018.11473

Higgins, S. T., & Chilcoat, H. D. (2009). Women and smoking: an interdisciplinary examination of socioeconomic influences. *Drug Alcohol Depend, 104 Suppl 1*, S1-5. doi:10.1016/j.drugalcdep.2009.06.006

Higgins, S. T., Heil, S. H., Sigmon, S. C., Tidey, J. W., Gaalema, D. E., Hughes, J. R., . . . Tursi, L. (2017). Addiction Potential of Cigarettes With Reduced Nicotine Content in Populations With Psychiatric Disorders and Other Vulnerabilities to Tobacco Addiction. *JAMA Psychiatry, 74*(10), 1056-1064. doi:10.1001/jamapsychiatry.2017.2355

Higgins, S. T., Tidey, J. W., Sigmon, S. C., Heil, S. H., Gaalema, D. E., Lee, D., . . . Harfmann, R. F. (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*(10), e2019311. doi:10.1001/jamanetworkopen.2020.19311

Hodge, A. M., Westerman, R. A., De Courten, M. P., Collier, G. R., Zimmet, P. Z., & Alberti, K. G. M. M. (1997). Is leptin sensitivity the link between smoking cessation and weight gain?. International journal of obesity, 21(1), 50-53.

Hughes, J. R. (2007) Measurement of the effects of abstinence from tobacco. A qualitative review. *Psychol Addict Behav, 21*:127-137.

Hughes, J. R. (2020) Background on the Minnesota Tobacco Withdrawal Scale-Revised (MTWS-R). Retrieved from: http://www.med.uvm.edu/docs/background_and_references/behavior-and-health-documents/background_and_references.pdf?sfvrsn=f1189ddc_2

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry, 43*(3), 289-294. doi:10.1001/archpsyc.1986.01800030107013

Johnson, N. B., Hayes, L. D., Brown, K., Hoo, E. C., Ethier, K. A. (2014) CDC National Health Report: Leading Causes of Morbidity and Mortality and Associated Behavioral Risk and Protective Factors—United States, 2005-2013. *Morbidity and Mortality Weekly Report 63*(4), 3-27.

Klesges, R. C., Meyers, A. W., Klesges, L. M., & La Vasque, M. E. (1989). Smoking, body weight, and their effects on smoking behavior: a comprehensive review of the literature. *Psychol Bull, 106*(2), 204-230. doi:10.1037/0033-2909.106.2.204

Klok, M. D., Jakobsdottir, S., & Drent, M. L. (2007). The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obesity reviews*, 8(1), 21-34.

Krude, H., Biebermann, H., Schnabel, D., Tansek, M. Z., Theunissen, P., Mullis, P. E., & Gruters, A. (2003). Obesity due to proopiomelanocortin deficiency: three new cases and treatment trials with thyroid hormone and ACTH4-10. *J Clin Endocrinol Metab, 88*(10), 4633-4640. doi:10.1210/jc.2003-030502

Kryfti, M., Dimakou, K., Toumbis, M., Daniil, Z., Hatzoglou, C., & Gourgoulianis, K. I. (2015). Effects of smoking cessation on serum leptin and adiponectin levels. *Tobacco induced diseases*, 13(1), 1-7.

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W., & Zitman, F. G. (2010). Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of general psychiatry*, 67(3), 220-229.

Mercincavage, M., Saddleson, M. L., Gup, E., Halstead, A., Mays, D., & Strasser, A. A. (2017). Reduced nicotine content cigarette advertising: How false beliefs and subjective ratings affect smoking behavior. *Drug Alcohol Depend, 173*, 99-106. doi:10.1016/j.drugalcdep.2016.12.022

Mersha, A. G., Eftekhari, P., Bovill, M., Tollosa, D. N., & Gould, G. S. (2021). Evaluating level of adherence to nicotine replacement therapy and its impact on smoking cessation: a systematic review and meta-analysis. *Arch Public Health, 79*(1), 26. doi:10.1186/s13690-021-00550-2

Mineur, Y. S., Abizaid, A., Rao, Y., Salas, R., DiLeone, R. J., Gundisch, D., . . . Picciotto, M. R. (2011). Nicotine decreases food intake through activation of POMC neurons. *Science, 332*(6035), 1330-1332. doi:10.1126/science.1201889

Nardone, N., Donny, E. C., Hatsukami, D. K., Koopmeiners, J. S., Murphy, S. E., Strasser, A. A., . . . Benowitz, N. L. (2016). Estimations and predictors of non-

compliance in switchers to reduced nicotine content cigarettes. *Addiction, 111*(12), 2208-2216. doi:10.1111/add.13519

Ogden, C. L., Fakhouri, T. H., Carroll, M. D., Hales, C. M., Fryar, C. D., Li, X., & Freedman, D. S. (2017). Prevalence of Obesity Among Adults, by Household Income and Education - United States, 2011-2014. *MMWR Morb Mortal Wkly Rep, 66*(50), 1369-1373. doi:10.15585/mmwr.mm6650a1

Pacek, L. R., Vandrey, R., Dermody, S. S., Denlinger-Apte, R. L., Lemieux, A., Tidey, J. W., . . . Donny, E. C. (2016). Evaluation of a reduced nicotine product standard: Moderating effects of and impact on cannabis use. *Drug Alcohol Depend, 167*, 228-232. doi:10.1016/j.drugalcdep.2016.08.620

Pandit, R., Beerens, S., & Adan, R. A. (2017). Role of leptin in energy expenditure: the hypothalamic perspective. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 312(6), R938-R947.

Piper, M. E. (2015) Withdrawal: Explanding a key addiction construct. *Nicotine Tob Res, 17*: 1405-1415.

Rada, P., Jensen, K., & Hoebel, B. G. (2001). Effects of nicotine and mecamylamine-induced withdrawal on extracellular dopamine and acetylcholine in the rat nucleus accumbens. *Psychopharmacology*, 157(1), 105–110. https://doi.org/10.1007/s002130100781

Reinholz, J., Skopp, O., Breitenstein, C., Bohr, I., Winterhoff, H., & Knecht, S. (2008). Compensatory weight gain due to dopaminergic hypofunction: new evidence and own incidental observations. *Nutrition & metabolism*, 5, 35. https://doi.org/10.1186/1743-7075-5-35

Richter, K. P., Gibson, C. A., Ahluwalia, J. S., & Schmelzle, K. H. (2001). Tobacco use and quit attempts among methadone maintenance clients. *Am J Public Health, 91*(2), 296-299. doi:10.2105/ajph.91.2.296

Rupprecht, L. E., Koopmeiners, J. S., Dermody, S. S., Oliver, J. A., al'Absi, M., Benowitz, N. L., . . . Donny, E. C. (2017). Reducing nicotine exposure results in weight gain in smokers randomised to very low nicotine content cigarettes. *Tob Control, 26*(e1), e43-e48. doi:10.1136/tobaccocontrol-2016-053301

Rupprecht, L. E., Smith, T. T., Donny, E. C., & Sved, A. F. (2016). Self-Administered Nicotine Suppresses Body Weight Gain Independent of Food Intake in Male Rats. *Nicotine Tob Res, 18*(9), 1869-1876. doi:10.1093/ntr/ntw113

Sicras, A., Rejas, J., Navarro, R., Serrat, J., & Blanca, M. (2008). Metabolic syndrome in bipolar disorder: a cross-sectional assessment of a Health Management Organization database. *Bipolar Disord, 10*(5), 607-616. doi:10.1111/j.1399-5618.2008.00599.x

Stevens, J., Truesdale, K. P., McClain, J. E., & Cai, J. (2006). The definition of weight maintenance. *International journal of obesity*, 30(3), 391-399.

Sweeney, M. M., Antoine, D. G., Nanda, L., Geniaux, H., Lofwall, M. R., Bigelow, G. E., & Umbricht, A. (2019). Increases in body mass index and cardiovascular risk factors during methadone maintenance treatment. *J Opioid Manag, 15*(5), 367-374. doi:10.5055/jom.2019.0526

Tidey, J. W., Cassidy, R. N., & Miller, M. E. (2016). Smoking Topography Characteristics of Very Low Nicotine Content Cigarettes, With and Without

Nicotine Replacement, in Smokers With Schizophrenia and Controls. *Nicotine Tob Res, 18*(9), 1807-1812. doi:10.1093/ntr/ntw089

Tidey J. W., Colby S. M., Denlinger-Apte R. L., Goodwin, C., Cioe, P....Donny, E. C. (2019) Effects of 6-week use of very low nicotine content cigarettes in smokers with serious mental illness. *Nicotine Tob Res*. 21(suppl 1):S38-S45. doi:10.1093/ntr/ntz133

Tidey, J. W., Rohsenow, D. J., Kaplan, G. B., Swift, R. M., & Ahnallen, C. G. (2013). Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls. *Nicotine Tob Res, 15*(1), 121-129. doi:10.1093/ntr/nts098

Tuovinen, E. L., Saarni, S. E., Kinnunen, T. H., Ollila, H., Ruokolainen, O., Patja, K., ... & Korhonen, T. (2018). Weight concerns as a predictor of smoking cessation according to nicotine dependence: A population-based study. *Nordic Studies on Alcohol and Drugs*, 35(5), 344-356.

U.S. Department of Health and Human Services. (1988) The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

U.S. Department of Health and Human Services. (2020) Smoking Cessation. A Report of the Surgeon General. Atlanta, (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Volkow, N. D., Wang, G. J., & Baler, R. D. (2011). Reward, dopamine and the control of food intake: implications for obesity. *Trends in cognitive sciences, 15*(1), 37–46. https://doi-org.ezproxy.uvm.edu/10.1016/j.tics.2010.11.001

Weinberger, A. H., Kashan, R. S., Shpigel, D. M., Esan, H., Taha, F., Lee, C. J., . . . Goodwin, R. D. (2017). Depression and cigarette smoking behavior: A critical review of population-based studies. *Am J Drug Alcohol Abuse, 43*(4), 416-431. doi:10.3109/00952990.2016.1171327

West, R., Ussher, M., Evans, M., & Rashid, M. (2006) Assessing DSM-IV nicotine withdrawal symptoms: A comparison and evaluation of five different scales. *Psychopharm, 184*:619-627.

Williams, D. L., & Schwartz, M. W. (2005). The melanocortin system as a central integrator of direct and indirect controls of food intake. *Am J Physiol Regul Integr Comp Physiol, 289*(1), R2-3. doi:10.1152/ajpregu.00226.2005

Williamson, D. A., Bray, G. A., & Ryan, D. H. (2015). Is 5% weight loss a satisfactory criterion to define clinically significant weight loss?. *Obesity*, 23(12), 2319.

Winders, S. E. & Grunberg, N. E. (1989). Nicotine, Tobacco Smoke, and Body Weight: A Review of the Animal Literature. *Annals of Behavioral Medicine, 11*(4), 125-133.