THE IMPACT OF SMOKING VERY LOW NICOTINE CONTENT CIGARETTES ON ALCOHOL USE

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Product standards reducing the nicotine content in cigarettes could improve public health by reducing smoking behavior and toxicant exposure. However, relatively little is known about how the regulatory strategy could impact alcohol use. The primary objective of this project was to examine the effect of smoking cigarettes with varying nicotine levels on alcohol outcomes. Furthermore, the processes underlying the effect of smoking very low nicotine content (VLNC) cigarettes on alcohol outcomes were examined, including the role of nicotine exposure per se, as well as the indirect effects of cigarettes and withdrawal.

In a double-blind, randomized clinical trial, non-treatment seeking daily smokers (N = 840) were randomly assigned to smoke cigarettes for 6 weeks of varying nicotine content. This investigation focused on current drinkers (n = 476). The nicotine contents examined corresponded with a normal nicotine content (NNC) control condition (15.8 mg/g), a moderate nicotine content condition (5.2 mg/g), and several VLNC cigarette conditions (0.4 mg/g to 2.4 mg/g). Using latent growth curve models, each reduced nicotine content condition was compared to the NNC control condition with respect to the trajectories of average daily alcohol use and occurrence of binge drinking. Several moderating variables of these effects were also explored (i.e., gender, drinking to cope motives, baseline drinking level, history of problem drinking, nicotine dependence level). Furthermore, using mediation analyses, processes that may

explain the effect of VLNC cigarettes on alcohol outcomes were investigated, including changes in nicotine exposure, smoking behavior, and withdrawal.

Reducing the nicotine content of cigarettes appeared to reduce alcohol use and binge drinking, particularly among less nicotine dependent smokers. The reduction in alcohol use appeared to be driven by a combination of interrelated processes, notably nicotine exposure and smoking rate. An important subgroup, however, that warrants further study is highly nicotine dependent individuals, who tended to increase their drinking in response to nicotine reduction.

Regulatory strategies reducing the nicotine content in cigarettes may also impact health behaviors that are closely related to smoking, like alcohol use and binge drinking. It is necessary to broadly define the public health impact to include unintended health consequences on non-smoking behaviors.

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INTRODUCTION

As previously reviewed in Dermody and Donny (2014), cigarette smoking is the leading preventable cause of death in the United States, contributing to at least 400,000 deaths each year (Adhikari, Kahende, Malarcher, Pechacek, & Tong, 2009; Mokdad, Marks, Stroup, & Gerberding, 2004). In an effort to prevent these deaths, regulatory bodies around the world have worked to implement tobacco product standards to help individuals stop (and/or not start) smoking. The 2001 Institute of Medicine (IOM) report highlights that tobacco product regulations are critical methods to enhance national cessation rates (Stratton, Shetty, Wallace, & Bondurant, 2001). One such tobacco product regulation, as originally proposed by Benowitz and Henningfield (1994), involves mandating reduced nicotine levels in cigarettes below a "threshold" for dependence as a means of lessening the negative health impact of cigarettes (Zeller & Hatsukami, 2009). Nicotine is the main addictive substance in tobacco that sustains smoking (Corrigall, 1999; Harvey et al., 2004; USDHSS, 1988). Product standards that drastically reduce nicotine content of cigarettes are now possible due to the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which allows the Food and Drug Administration to reduce nicotine levels in cigarettes to non-zero levels (Congress, 2009).

This opportunity for nicotine regulations has prompted research to evaluate the public health impact of a nicotine reduction regulatory strategy (Zeller & Hatsukami, 2009). A growing literature suggests that smoking very low nicotine content (VLNC) cigarettes decreases nicotine

exposure, nicotine dependence and smoking (Benowitz et al., 2012; Donny, Houtsmuller, & Stitzer, 2007; Hatsukami et al., 2013a; Hatsukami et al., 2010a) and promotes abstinence (Hatsukami et al., 2010a). In general, the VLNC cigarettes used in these studies contain substantially reduced levels of nicotine in the tobacco (e.g., 2 mg/g; Benowitz & Henningfield, 1994; Benowitz et al., 2012) compared to conventional cigarettes (e.g., mean of 16 mg/g; Malson, Sims, Murty, & Pickworth, 2001; Kozlowski et al., 1998) resulting in substantially lower nicotine yields (< 0.2 mg) than cigarettes typically sold in the U.S. (0.8 mg). Importantly, they are distinguishable from 'light' or 'mild' cigarettes that use filter ventilation to reduce nicotine yields, which have been shown to promote compensatory smoking (Benowitz, 2001; Bernert et al., 2005; Hecht et al., 2005). In contrast, as a result of the reduced levels of nicotine in the tobacco itself, VLNC cigarettes have been shown to reduce smoking behavior with little evidence of lasting compensation (Donny et al., 2007; Hatsukami et al., 2013a; Hatsukami et al., 2013b; Hatsukami et al., 2010a) .

Enacting a low nicotine product standard for cigarettes (and possibly other tobacco products) requires evidence that the proposed standard would likely improve public health. While evidence will inherently emphasize the effects on smoking and exposure to related harmful smoke constituents, estimates of the public health impact should also include unintended consequences on non-smoking behaviors (Henningfield et al., 1998). One such non-smoking behavior of particular interest is alcohol use. This is because alcohol is widely used among smokers and is itself a leading contributor of preventable morbidity and death (Mokdad et al., 2004). In the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), 21.7% of the total population reported using both alcohol and tobacco products during the past year (Falk, Yi, & Hiller-Sturmhofel, 2006). Furthermore, co-use is higher among

important risk groups, such nicotine or alcohol dependent individuals (Falk et al., 2006). Given the prevalence and extent of co-use among smokers, it is important to determine if regulating tobacco products would have a causal effect on alcohol outcomes.

A causal link between alcohol and tobacco use is likely one of several factors that contribute to co-use (Neale & Kendler, 1995; Shiffman & Balabanis, 1995; McKee & Weinberger, 2013). Co-use may also be increased by shared genetic or environmental risk factors (Neale & Kendler, 1995; Shiffman, Balabanis, Fertig, & Allen, 1995a) without the behaviors being causally related (i.e., so-called "third variable" explanations). To the degree to which co-use results from shared risk factors, disrupting smoking will not likely affect drinking. Conversely, if smoking and drinking are causally linked, the consequences of smoking cigarettes (e.g., nicotine exposure, behavioral aspects of smoking) may impact drinking behavior (McKee, O'Malley, Shi, Mase, & Krishnan-Sarin, 2008; Shiffman et al., 1995). This potential causal relationship underlines the importance of determining if switching to VLNC cigarettes impacts drinking.

Despite the importance of understanding the effect of smoking VLNC cigarettes on alcohol use, it remains unknown how VLNC cigarettes would impact drinking. To date, only one study has examined the direct effect of VLNC cigarettes on drinking (Barrett, Tichauer, Leyton, & Pihl, 2006). In that study, college-aged men who smoked VLNC cigarettes drank less alcohol and reported fewer drinking urges during a single laboratory session than those who smoked normal nicotine content cigarettes. This suggests that nicotine reduction in cigarettes could reduce same-day drinking, which is consistent with a positive relation between nicotine exposure and alcohol use. This finding, however, warrants further study to understand the effect of recurrent VLNC cigarette use on drinking. Specifically, as described in more detail below, in

addition to reducing nicotine exposure, extended use of VLNC cigarettes reduces smoking behavior and increases the risk of withdrawal symptoms, which could each further impact drinking. Thus, it is critical to examine the effect of VLNC cigarettes on drinking over time and among individuals at risk of experiencing withdrawal symptoms, such as daily smokers (Coggins, Murrelle, Carchman, & Heidbreder, 2009; Shiffman, Paty, Gnys, Kassel, & Elash, 1995). Furthermore, having a more representative sample by including women in these investigations is important given known gender differences in sensitivity to the changes in nicotine content in cigarettes (Perkins et al., 2002; Perkins et al., 2006).

The primary objective of this dissertation was to evaluate the effect of smoking VLNC cigarettes on alcohol outcomes in a randomized clinical trial. Daily smokers were assigned to smoke cigarettes for 6 weeks with varying nicotine content corresponding with a normal nicotine content (NNC) control condition (15.8 mg/g), a moderate nicotine content condition (5.2 mg/g), and several VLNC cigarette conditions (0.4 mg/g to 2.4 mg/g). As described below, a reduction in the nicotine content of cigarettes may affect alcohol use through three causal pathways (Figure 1). Specifically, smoking VLNC cigarettes is expected to reduce nicotine exposure, reduce smoking behavior, and may increase the risk of withdrawal symptoms, which could all independently or jointly impact drinking.

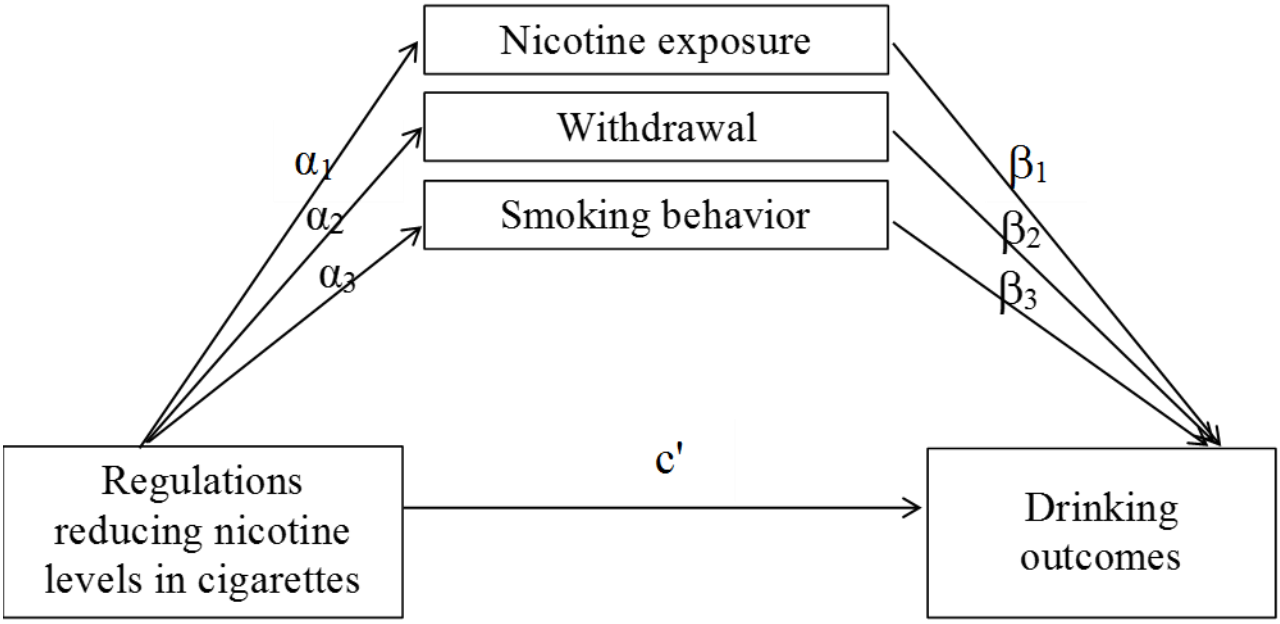

Figure 1. The processes linking nicotine reduction strategies to alcohol outcomes in a mediation framework

1.1 CAUSAL PATHWAYS LINKING CIGARETTE AND ALCOHOL USE

1.1.1 Nicotine Exposure

VLNC cigarettes immediately reduce nicotine delivery by substantially lowering the amount of nicotine in the tobacco (Hatsukami et al., 2010b). Ad libitum smoking of a VLNC cigarette results in lower plasma nicotine and cotinine levels, a nicotine metabolite, compared to smoking a standard cigarette (Benowitz, Jacob, & Herrera, 2006; Pickworth, Nelson, Rohrer, Fant, Henningfield, 1999). Immediately switching to VLNC cigarettes exclusively for one week (Hatsukami et al., 2013a) or 6 weeks (Hatsukami et al., 2013b; Hatsukami et al., 2010a) also markedly reduces urine levels of cotinine and nicotine equivalents with cotinine approaching

abstinent smoker levels within a week (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Hatsukami et al., 2013a). Thereafter, cotinine levels continue to decrease slowly (Hatsukami et al., 2010a). Similar, but more gradual, reductions in nicotine exposure markers are observed when smoking progressively reduced nicotine content cigarettes for up to 6 months (Benowitz et al., 2007, 2012).

Relatedly, the risk of compensatory nicotine exposure is low for cigarettes with very low nicotine content, perhaps because it is difficult to meaningfully increase nicotine exposure through increased smoking (Hatsukami et al., 2010b). As the nicotine content of tobacco in VLNC cigarettes is reduced, modified smoking (e.g., blocking ventilation holes of "light" cigarettes") will not markedly increase nicotine yield. As such, in order for nicotine intake to be substantially increased, one would need to use products with unaltered nicotine levels. For instance, using the nicotine patch alongside VLNC cigarettes results in higher levels of salivary cotinine than using VLNC cigarettes alone (Donny et al. 2007; Hatsukami et al., 2013b), despite smoking fewer VLNC cigarettes per day (Hatsukami et al., 2013b). Similarly, using non-medicinal products that contain nicotine (e.g., smokeless tobacco, e-cigarettes) could increase nicotine exposure. Little is known about multi-product use, however, because studies of VLNC cigarettes have limited other tobacco use by participants.

Reduced nicotine exposure may impact alcohol use, particularly in a subset of smokers. As previously described, smoking VLNC cigarettes *reduced* drinking relative to smoking normal nicotine content cigarettes in a single laboratory session among non-daily smoking men (Barrett et al., 2006). Similar findings have been reported among young adult men who were non-daily smokers administered placebo or nicotine containing patches (Acheson, Mahler, Chi, & de Wit, 2006; Barrett et al., 2006). In contrast, the opposite relation has been observed in other

subgroups of smokers. In particular, female non-daily smokers have exhibited *increased* alcohol use with a placebo relative to nicotine patch (Acheson et al., 2006). Similarly, placebo patch corresponded with increased drinking relative to nicotine patch among young adult daily smokers who drink heavily (McKee et al., 2008). Taken together, it appears that reduced nicotine exposure impacts alcohol use, but that the direction of the effect may depend on various factors such as gender, level of nicotine dependence or hazardous drinking.

Together, the findings in the literature suggest that short-term reductions nicotine exposure impacts alcohol use; however, the effect of nicotine reduction on drinking has not been examined longitudinally. The effect of nicotine reduction on drinking over time among daily smokers is not simple to predict based on the existing literature because, in several of the studies, participants arrive to the lab deprived of both smoking and nicotine. This methodological practice introduces the confounding effects of smoking behavior and withdrawal on drinking (see discussions below). As a result, direct evidence of the effects of nicotine per se on alcohol use remains limited. Several predictions can be made regarding this effect based on the existing literature focusing on the putative underlying processes. Furthermore, as the direction of the effect of nicotine exposure on alcohol use in prior studies is inconsistent, with nicotine either increasing or decreasing alcohol use, it is possible that the nature of the processes may differ between subgroups of smokers.

Nicotine may influence the effects of alcohol by (1) altering blood alcohol levels that correspond with an administered dose (i.e., altering alcohol metabolism) and (2) modulating the reinforcing effects of alcohol at a given blood alcohol level.

Nicotine could accelerate alcohol metabolism in several ways. Nicotine may increase liver metabolic enzymes like cytochrome P4502E1 (CYP2E1)(Lieber, 1994; Matsumoto et al.,

1996) as well as facilitate the initial metabolism of alcohol by gastric alcohol dehydrogenase (gADH)(Crabb, 1995) by slowing gastric emptying (Holt, Stewart, Adam, & Heading, 1980; Lim et al., 1993). The strongest evidence exists for the latter pathway because nicotine exposure has not been consistently shown to increase the availability of CYP2E1. Specifically, CYP2E1 levels are similar in human smokers compared to non-smokers, regardless of alcoholism history (Lucas et al., 1999; Lucas et al., 1995a; Lucas et al., 1995b). In contrast, nicotine appears to acutely slow gastric emptying in a dose-dependent fashion among adolescent and adult rats, and adult human daily smokers (Chen, Parnell, & West, 2001; Gritz et al., 1988, Johnson, Horowitze, Maddox, Wishart, & Shearman, 1991; Parnell, West, & Chen 2006). This is consistent with research that has detected delayed alcohol absorption as indicated by slower initial increases of blood alcohol levels among daily smokers exposed to nicotine administered by nasal spray and cigarettes compared to placebo (Johnson et al., 1991; Perkins et al., 1995) as well as in pre-clinical research (Chen et al., 2001). It is important to note that the effect of nicotine on blood alcohol levels have not been replicated in some pre-clinical (Collins, Burch, de Fiebre, & Marks, 1988) and clinical studies (McKee et al., 2008; Perkins, Fonte, & Grobe, 2000). Human studies with significant nicotine effects on blood alcohol levels tended to administer larger doses of alcohol (at least two standard drinks versus one or less) and took earlier blood alcohol level readings after administration (five minutes versus 10-25 minutes). Nevertheless, nicotine reduction due to VLNC cigarettes may increase alcohol blood levels by quickening gastric emptying and promoting alcohol absorption.

Nicotine may also affect alcohol use by impacting the reinforcing properties of alcohol. Nicotine enhances the reinforcing properties of other reinforcers through a non-associative process (Caggiula et al., 2009; Donny et al., 2003). Specifically, responding to other reinforcers

is enhanced following contingent and non-contingent nicotine administration (Barr, Pizzagalli, Culhane, Goff, & Evins, 2008; Chaudhri et al., 2006; Donny et al., 2003; Perkins & Karelitz, 2013). It also appears that nicotine may enhance alcohol reward, as described in a recent review by McKee and Weinberger (2013). Consistent with this mechanism, young adults who smoked normal nicotine content cigarettes worked harder on computer tasks to earn alcoholic beverages than individuals who smoked a VLNC cigarette (Barrett et al., 2006) and abstained from smoking overnight (Perkins et al., 2000) . Furthermore, nicotine patches increased the price male non-smokers would pay for alcohol relative to placebo; however, the opposite effect was observed among women (Acheson et al., 2006). Nicotine also increases operant responding for alcohol by male rats (Clark, Lindgren, Brooks, Watson, & Little, 2001; Prescott, Aggen, & Kendler, 2000). Overall, it appears that nicotine may increase responding for alcohol among dependent (Perkins et al., 2000) and non-daily smokers (Acheson et al., 2006; Barrett et al., 2006), which is consistent with the reinforcement-enhancing properties of nicotine on alcohol.

The reinforcement-enhancing effects of nicotine on alcohol use may also be explained by the ability of nicotine to enhance the subjective and behavioral effects of alcohol use (Zacny, 1989). The effects of alcohol are biphasic. At low doses and as blood alcohol levels increase, stimulant-like effects occur (Martin, Earleywine, Musty, Perrine, & Swift, 1993). In contrast, at high doses and as blood levels decrease, depressant-like effects are often experienced. Together, the relative stimulant and sedating effects of alcohol influence its reinforcing properties such that greater stimulating effects and diminished sedating effects tend to promote drinking (King, de Wit, McNamara, & Cao, 2011; Quinn & Fromme, 2011).

Research suggests that nicotine could enhance the reinforcing properties of drinking by adding to its stimulant-like effects (Kouri, McCarthy, Faust, & Lukas, 2004; Perkins et al., 1995)

while mitigating its depressant and sedating effects (Acheson et al., 2006; Perkins et al., 2000; Perkins et al., 1995; Ralevski et al., 2012; Zancy, 1989). These effects may be partly explained by the shared role of the nicotinic acetylcholine receptor (nAChR) system in the effects of nicotine and alcohol (see McKee & Weinberger, 2013, for review). Specifically, nicotine exerts its effects through the nAChR system (Benwell, Balfour, & Anderson, 1988; for review Buisson & Bertrand, 2002), which has also been implicated in the effects of alcohol (for review, Davis & de Fiebre, 2006; Dohrman & Reiter, 2003; Chi & deWit, 2003). Indeed, among non-smokers, a nAChR antagonist, mecamylamine, reduces subjective stimulant responses to alcohol (Blomqvist, Hernandez Avila, Van Kirk, Rose, & Kranzler, 2002; Chi & de Wit, 2003) even after controlling for blood alcohol levels (Blomqvist et al., 2002; Young, Mahler, Chi, & de Wit, 2005). Likewise, the nAChR partial agonist varenicline reduces alcohol self-administration among heavy drinking smokers (McKee et al., 2009). In the context of chronic smoking, desensitization of nAChRs due to nicotine may also play a role (Picciotto, Addy, Mineur, & Brunzell, 2008). Specifically, repeated exposure to nicotine may reduce the responsivity of particular nAChR subtypes to nicotine and other drugs. Hence, nicotine-induced changes in the function and/or number of nAChRs could mediate changes in the subjective effects of alcohol at a given blood concentration.

There appears be individual variability in effects of nicotine on the subjective effects of alcohol. Nicotine appears to enhance the stimulant-like effects more strongly among women and attenuate the depressant effects primarily among men (Perkins et al., 1995). This may help explain previously observed gender differences in drinking response to nicotine manipulations (Acheson et al., 2006). That is, men may drink more alcohol in response to nicotine as the attenuated depressant effects would facilitate increased drinking among men (i.e., by mitigating

the potentially undesirable depressant subjective effect). Furthermore, among relatively heavier drinkers, the opposite effect of nicotine on the subjective effects of drinking, and in turn, drinking behavior, has been observed. Specifically, nicotine exposure decreased, as opposed to increased, the intoxicating effects of drinking (McKee et al., 2008). This may help explain why McKee et al (2008) observed that nicotine exposure reduced alcohol use, as opposed to increased alcohol use. Thus, among some individuals, nicotine may instead reduce the intoxicating or stimulating effects of alcohol, which may correspond with reduced drinking. In the context of nicotine reduction, this pattern of relations would likely correspond with compensatory drinking.

Finally, the relative reinforcing properties of the stimulant versus depressant effects of alcohol may differ between individuals. These individual differences would, in turn, be expected to moderate the direction of the relation between nicotine and alcohol administration. For example, a subset of smokers who drink to cope with stress may prefer the sedating effects (Cooper, Frone, Russell, & Mudar, 1995). As a result, if nicotine mitigates the sedating effects among these individuals, the effect of nicotine on alcohol use may be undesirable. In order to compensate for the undesirable effect of nicotine on alcohol use, they may increase their drinking. In the context of nicotine reduction, reduced nicotine exposure may correspond with reductions in alcohol use.

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compensate for the undesirable effect of nicotine on alcohol use, they may increase their drinking. In the context of nicotine reduction, reduced nicotine exposure may correspond with reductions in alcohol use.

1.1.2 Nicotine Withdrawal

An anticipated consequence of nicotine reduction is the emergence of withdrawal symptoms including negative affect, cognitive impairment, and physical discomfort (Hughes, Higgins, & Hatsukami, 1990). Previous research has detected increased withdrawal symptoms after immediately switching to VLNC cigarettes (Hatsukami et al., 2010a, 2013b), but not while gradually switching to VLNC cigarettes over the course of six months (Benowitz et al., 2012). On average, withdrawal increases within one day of switching to VLNC cigarettes (Buchhalter, Schrinet, & Eissenberg, 2005) and returns to baseline levels within two weeks (Hatsukami et al., 2010a, 2013b). The withdrawal symptoms associated with immediately switching to VLNC cigarettes tend to be less severe than withdrawal following total smoking abstinence and select symptoms, such as craving, may not significantly increase at all (Benowitz et al., 2007; Buchhalter et al., 2005; Buchhalter, Schrinel, & Eissenberg, 2001; Donny et al., 2007; Hatsukami et al., 2010a). Immediately switching to VLNC cigarettes appears to specifically increase restlessness, impatience, difficulty concentrating (Buchhalter, Schrinel, & Eissenberg, 2005), irritability, and eating (Buchhalter, Schrinet, & Eissenberg, 2005; Donny & Jones, 2007).

On average, withdrawal symptoms after switching to VLNC cigarettes are likely transient; however, withdrawal symptoms may be of greater concern among certain subgroups of smokers, such as highly nicotine dependent smokers when they switch to the product for the first time. Furthermore, women report more withdrawal after smoking abstinence than men,

particularly negative affect (Evans, Blank, Sams, Weaver, & Eissenberg, 2006; Leventhal et al., 2007). Notably, although these individual differences are reliably observed in the context of smoking cessation, VLNC cigarettes appear to suppress withdrawal from overnight abstinence for women to a greater extent than men (Perkins & Karelitz, 2015). This may be due to pharmacological aspects of smoking, such as visual or olfactory cues, being particularly important predictors of smoking behavior among women (Perkins et al., 2000; Perkins, Jacobs, Sanders, & Caggiula, 2002). Thus, in the context of VLNC cigarette use, the sensory aspects of smoking may suppress withdrawal in such a way that gender differences are mitigated.

Withdrawal-induced negative affective and tension states could put smokers at greater risk for self-medicating with alcohol. For example, several motivational theories of alcohol use suggest that individuals may learn to drink alcohol in order to cope with negative affective states (Cooper et al., 1995; Wills & Shiffman, 1985). As smokers routinely alleviate withdrawal-induced negative affect by smoking (Baker, Brandon, & Chassin, 2004), smokers who do not experience complete withdrawal relief from smoking VLNC cigarettes may resort to coping with withdrawal with alternative substances. In fact, drinking to alleviate negative affect is a motive for drinking among many smokers (Novak, Burgess, Clark, Zvolensky, & Brown, 2003), and smoking urges during a quit attempt prospectively predict alcohol use (Businelle et al., 2013). As a result, a smoker's alcohol use may *increase* when withdrawal increases (i.e., on average, during the first two weeks of switching to VLNC cigarettes), particularly among smokers who tend to drink to cope with negative affect.

Consistent with the role of self-medicating nicotine withdrawal, smokers who demonstrated significantly elevated withdrawal symptoms after smoking abstinence increase their alcohol use relative to individuals who wore a nicotine containing patch (McKee et al.,

2008) or smoked a normal nicotine content cigarette (Palfai, Monti, Ostafin, & Hutchison, 2000). In contrast, in one study of smoking abstinent nicotine dependent smokers, participants did not increase their alcohol use (Perkins et al., 2000). It is unclear if the findings contradict the other studies because withdrawal levels were not reported. Regardless, the findings of these studies collectively suggest that alcohol use could increase among nicotine dependent smokers who experience withdrawal when switching to VLNC cigarettes.

Furthermore, smokers who have drinking to cope motives may be more likely to drink to cope with nicotine withdrawal compared to those who do not typically use alcohol as a coping strategy. For example, drinking to cope has been linked to individuals with a history of alcohol dependence (Carpenter & Hasin, 1999; Cooper et al., 1995). Consistent with alcohol dependence as a risk factor, smoking abstinence appears to predict increased drinking among hazardous drinkers (McKee et al., 2008; Palfai et al., 2000), but not moderate drinkers (Perkins, Fonte, & Grobe, 2000). Smoking abstinence, however, does not appear to predict self-reported drinking urges among alcohol dependent individuals early in recovery (Cooney, Cooney, Pilkey, Kranzler, & Oncken, 2003). Thus, a constellation of interrelated factors consistent with a history of problem drinking (e.g., current or past alcohol dependence, heavy drinking, and drinking to cope motives) may put a subset of smokers at risk for drinking to cope with withdrawal.

Despite the risk of self-medicating withdrawal symptoms, the transient nature of withdrawal suggests that compensatory drinking via this mechanism would be short-lived. On average, withdrawal after switching to VLNC cigarettes should dissipate within two weeks (Hatsukami et al., 2010b), which highlights a key risk period for compensatory drinking. Thereafter, negative affect and stress tend to decrease below pre-quit levels (for review, Kassel, Stroud, & Paronis, 2003) . As a result, over time, VLNC cigarettes could reduce negative affect

and stress processes by limiting nicotine exposure and promoting smoking cessation, which would reduce the need to self-medicate these symptoms by drinking.

1.1.3 Smoking as a Cue to Drink

As previously described, the primary mechanism by which nicotine reduction in cigarettes would improve public health is through a reduction in smoking behavior. Research suggests that individuals smoke a VLNC cigarette similarly to a usual brand cigarette when trying them for the first time. In particular, there are no significant differences in puffing behavior, expired carbon monoxide levels (Nadal, Chappell, & Samson, 1998; Rose & Behm, 2004), or tar exposure (Benowitz, Jacob, & Herrera, 2006) per cigarette beyond the first two VLNC cigarettes smoked among adults (MacQueen et al., 2012).

VLNC cigarette use tends to correspond with gradual reductions in the number of VLNC cigarettes smoked per day. On average, within the first week of switching to VLNC cigarettes, treatment-seeking individuals smoke VLNC cigarettes at a similar rate to normal nicotine content cigarettes (Hatsukami et al., 2010a; 2013a). Thereafter, VLNC cigarette use appears to decrease gradually (Hatsukami et al., 2010a; 2013a; 2013b), and in one study, reached significant reductions within two weeks and reductions of nearly 8 cigarettes per day after 6 weeks of use (Hatsukami et al., 2010a). Furthermore, non-treatment seekers, using the product exclusively in an in-patient setting for 8-days, reduced their smoking by approximately 4 VLNC cigarettes per day (Donny, Houtsmuller, & Stitzer, 2007). In cases where the nicotine content of cigarettes is progressively reduced over time in non-treatment seekers, reductions in cigarettes per day are relatively small and delayed (Benowitz et al., 2012). Thus, the reinforcing properties of VLNC

cigarettes may lessen over time such that smoking behavior gradually decreases, with more stark differences seen when the nicotine content of cigarettes is immediately reduced.

These changes in daily smoking levels due to VLNC cigarettes may impact alcohol use to the extent that cigarettes act as a cue for drinking. Research suggests that presenting drug cues, such as drug images, may promote drug urges and use (Carter & Tiffany, 1999). Specifically, images of alcoholic beverages have been shown to increase urges to drink among drinkers compared to non-alcohol cues (Drobes, 2002; George et al., 2001), particularly among alcoholics (Thomas, Drobes, & Deas, 2005). In addition to alcohol-specific cues, cigarettes may act as a cue for drinking (Shiffman, Balabanis, Fertig, & Allen, 1995). The repeated co-use of these substances among individuals may establish conditioned associations between them such that cigarettes or the act of smoking may cue subsequent drinking. As such, decreases in the number of cigarettes smoked per day due to VLNC cigarette use may, in turn, result in decreases in alcohol consumption given that the frequency of the cue (the cigarette) is diminished.

There is preliminary support for cigarettes acting as a cue for drinking. Among alcohol dependent smokers, smoking-related images have been shown to increase drinking urges compared to neutral and unpleasant images, producing similar effects as alcohol-related images (Drobes, 2002). While exposure to smoking-related images also increased drinking urges among social drinkers, the effect was not as robust. Similarly, among young adult smokers who are also heavy social drinkers, holding a lit cigarette did not influence drinking urges, expectancies, or volume consumed, compared to holding a pencil regardless if the individual was nicotine deprived or not (Palfai et al., 2000). Thus, it is possible that cigarettes are a weaker cue for drinking among social drinkers compared to alcohol dependent smokers because smoking frequently occurs without drinking. Specifically, smoking often follows a daily cycle (Chandra,

Shiffman, Scharf, Dang, & Shadel, 2007); whereas, normative drinking among smokers does not occur daily and is concentrated on weeknights or weekends (Jackson, Colby, & Sher, 2010; Shiffman, 2009). In contrast, among alcohol dependent smokers, an extensive history of alcohol and smoking co-use may condition cigarettes as a cue for drinking. Thus, particularly among alcohol dependent or heavy drinking smokers, switching to VLNC cigarettes could reduce alcohol use by reducing smoking frequency and thus limiting opportunities for cigarettes to cue drinking.

What remains unknown, however, is how reductions in the nicotine content of cigarette would impact the extent to which cigarettes cue drinking. It is also anticipated that the very low levels of nicotine in cigarettes could undermine the effectiveness of cigarettes to cue drinking. As previously described, nicotine appears to the primary factor through which smoking increases the reinforcing process of alcohol. Thus, if the nicotine in regular cigarettes acts as a discriminative stimulus that predicts enhanced alcohol reward, smoking VLNC cigarettes would not be expected to produce the same effect on drinking. Instead, over time, cigarettes would come to predict low (not high) doses of nicotine, and may not correspond with the same urge to drink. As a result, after repeated use, VLNC cigarettes may not cue drinking as strongly as conventional cigarettes.

1.2 SUMMARY

Only one study has directly examined, in a single laboratory session of non-daily college-aged male smokers, the effect of VLNC cigarettes on drinking (Barrett et al., 2006). The reviewed literature highlights the importance of extending these findings in several ways. First,

additional research is needed to examine the effects of VLNC cigarettes on drinking beyond one session of co-use. As the processes that are believed to link VLNC cigarette use to drinking appear to unfold over time, their relative influence on drinking could change in a time-dependent matter. As a result, the effect of VLNC cigarettes on drinking on the first day of switching to the product could be meaningfully different from the effect several weeks later. As nicotine reduction in cigarettes has been proposed as a potential regulatory strategy to reduce the harmful impact of smoking, it is critical to examine how the intervention effects unfold over time. In particular, a longitudinal investigation would help identify key periods in which the regulatory strategy may have a detrimental impact on alcohol outcomes, which may need to be addressed if the regulation is enacted.

Second, the effect of VLNC cigarettes on drinking needs to be examined in additional subgroups of smokers, particularly those who may be at risk of increasing their alcohol consumption in response to the intervention. The literature suggests that increased alcohol use is most likely to occur among individuals who self-medicate nicotine withdrawal by drinking. Self-medicating withdrawal-induced negative affect may be of concern for individuals who tend to experience more severe withdrawal in response to smoking abstinence, such as women and daily smokers who are highly nicotine dependent. Moreover, another risk group is individuals who tend to drink to cope with negative affect, such as individuals with a history of alcohol dependence and heavy drinkers.

Third, additional research is needed to clarify the mechanisms that link smoking and drinking. As previously described, by asking participants to abstain from smoking, research confounds the effects of nicotine, smoking behavior, and withdrawal on drinking. It is widely accepted that nicotine, smoking behavior, and withdrawal are interrelated, which makes it

important to understand their shared effects on drinking. Importantly, when simply looking at the effect of VLNC cigarettes on drinking and ignoring the underlying process, it is quite possible that no effect would be observed. This would be particularly true if each of these processes have unique effects on drinking, which in some cases may cancel each other out. Thus, exploring these unique effects is warranted regardless of the strength of the effect of VLNC cigarettes on drinking and will provide support for different theoretical models underlying cigarette and alcohol co-use.

1.3 CURRENT STUDY

The current study was designed to address the gaps in the current literature regarding the relation between nicotine reduction in cigarettes and drinking in several ways. The **first aim** was to directly determine the impact of smoking VLNC cigarettes on alcohol use in daily smokers for the first time. This was accomplished as part of a double-blind, randomized clinical trial in which daily smokers (N = 840) were randomly assigned to smoke cigarettes of varying nicotine content for 6 weeks. The nicotine contents examined corresponded with a normal nicotine content (NNC) control condition (15.8 mg/g), a moderate nicotine content condition (5.2 mg/g), and several VLNC cigarette conditions (0.4 mg/g to 2.4 mg/g). The primary paper that the data was collected for evaluated the dose-response relationship between nicotine content in cigarettes and smoking outcomes (Donny et al., Under Review). The results suggested that, by the end of the study, individuals assigned to smoke VLNC cigarettes (with 2.4 mg/g nicotine or less) had reduced exposure to nicotine and smoked fewer cigarettes per day than the NNC control

condition. In contrast, reduced nicotine content cigarettes did not significantly increase withdrawal.

Based on the observed effects of VLNC cigarette use on reductions in nicotine exposure and smoking behavior on drinking in the primary paper, it was hypothesized in the present investigation that the intervention would similarly reduce alcohol use and binge drinking. Furthermore, given the time course of the hypothesized mechanisms described below, it was hypothesized that the total effect of the intervention on drinking would change over the course of the 6 week study. Specifically, VLNC cigarette use is expected to decrease alcohol use over time, outside of a short-term risk period immediately following switching to VLNC cigarettes.

The **second aim** of the project was to examine individual differences in the relation between nicotine reduction in cigarettes and alcohol outcomes. The effect of nicotine reduction was predicted to be strongest among individuals who experienced the greatest amount of nicotine reduction, which would likely include individuals who were compliant when smoking study cigarettes with the lowest nicotine content. Similarly, these effects were expected to be relatively more robust among individuals who are believed to be more sensitive to dose changes in nicotine (e.g., men) and for whom smoking and drinking frequently go hand-in-hand (e.g., heavy drinkers and those with a history of problem drinking). In contrast, it was expected that individuals who are at risk of withdrawal symptoms may not benefit as much from the intervention with respect to changes in drinking (e.g., women, individuals who are more highly nicotine dependent, and individuals who report drinking to cope motives), particularly if they attempt to self-mediate these symptoms via drinking. Thus, particularly early in the intervention, risk of withdrawal symptoms could mitigate any reduction in drinking.

The **third aim** of the investigation was to examine the processes underlying the effect of VLNC cigarette use on alcohol use, particularly change in total nicotine exposure assessed by nicotine biomarkers, changes in smoking behavior, and symptoms of nicotine withdrawal. It was hypothesized that switching to VLNC cigarettes would immediately and drastically reduce nicotine exposure and gradually decrease smoking behavior relative to NNC controls. Based on the reviewed literature, each of these processes are expected to be positively related to drinking, and thus, correspond with similar reductions in alcohol use. At the same time, VLNC cigarette use may modestly increase withdrawal early in the study, which could in turn, increase alcohol use. Although the primary investigation of this data with the total sample did not identify an increase in withdrawal in response to nicotine reduction in cigarettes, subgroups of individuals may be at risk for withdrawal. As a result, the present investigation attempted to examine some of these subgroups when examining this process.

2.0 METHODS

2.1 PARTICIPANTS

Between August 2013 and July 2014, adult daily smokers who were at least 18 years old were recruited. Participants were recruited using flyers, direct mailings, television, radio, and other advertisements from communities surrounding the University of Pittsburgh, Brown University, Johns Hopkins, University of Minnesota-Masonic Cancer Center, University of Minnesota-Duluth, Duke University, MD Anderson Cancer Center, University of California-San Francisco, Moffitt Cancer Center, and University of Pennsylvania. The advertisements read "Smokers who want to try new cigarettes that may or may not lead to reduced smoking are wanted for research. Participants will be paid for participation."

Eligibility was determined during an initial phone screen and in-person screening. Inclusion criteria included being at least 18 years old, smoking at least five cigarettes per day for at least 1 year, and breath carbon monoxide (CO) levels greater than 8 ppm (if less than or equal to 8 ppm, then reading on NicAlert Strip test must be greater than 2). Exclusion criteria included intention to quit smoking in next 30 days or seeking/participating in smoking cessation treatment, quit attempt in the past 30 days resulting in greater than three days of abstinence, having participated in a research study during the past three months that required changes in nicotine or tobacco products used for more than one day, regular use of other tobacco products or

frequent binge drinking (i.e., more than 9 of past 30 days), any significant or unstable medical or psychiatric conditions, suicidal ideation in past month or attempt in past 10 years, schizophrenia and schizoaffective disorder, currently taking anticonvulsant medications, positive illicit drug toxicology screen (other than cannabis), pregnancy or breastfeeding, illiteracy, and smoking 'roll your own' cigarettes exclusively.

In total, 1270 individuals met the phone screen eligibility criteria and signed an informed consent prior to participation. Of these participants, 840 individuals were eligible based on the in-person screening and agreed to participate in the study. One randomized participant was excluded from all analyses as they were found to be ineligible by the local Internal Review Board. The present study examined the subset of the participants who reported drinking any alcohol during the past month at the screening visit or reported any alcohol use during the two week baseline period. This resulted in a total sample size of 476 of 839 individuals (57%) for the current analyses.

2.2 STUDY DESIGN

The study was a 7-arm, double-blind randomized trial. The duration was 8 weeks, including a 2 week baseline period and 6 week experimental period. During the baseline period, participants smoked their usual brand cigarettes and completed baseline assessments at two laboratory sessions. Following baseline, participants were randomly assigned to smoke cigarettes of varying nicotine content, including: 1) 0.4 mg/g; 2) 0.4 mg/g – HT (high tar); 3) 1.3 mg/g nicotine; 4) 2.4 mg/g; 5) 5.2 mg/g; 6) 15.8 mg/g (NNC control group); and 7) usual cigarette brand (usual brand control group). The study cigarettes were supplied by NIDA (NOT-

DA-14-004). The various nicotine levels were selected in order to determine the "threshold" nicotine content for sustaining cigarette use anchored around a 0.17 mg nicotine yield, as hypothesized by Benowitz and Henningfield (1994). This yield would be expected from the cigarettes in the present study with a nicotine content of 2.4 mg/g or less.

Each week, participants were provided with a 14-day supply of cigarettes free of charge (tailored to their usual consumption). Participants were instructed not to use other cigarettes during the study; however, there was no incentive to use the cigarettes exclusively nor penalty for the use of other cigarettes, tobacco products, or nicotine-containing products. Participants completed weekly laboratory assessments, which involved various self-report, interviewer, behavioral, cognitive, and biological measures (relevant measures to this study are described in detail below). Weekly counseling sessions were provided aimed at increasing study compliance.

During baseline and experimental periods, an Interactive Voice Response (IVR) system allowed participants to respond to daily questions using their phone or phone provided by the study. The participants were asked questions about their smoking behavior as well as withdrawal symptoms the week before and after randomization (more detailed information about the questions is provided in the Measures section). The IVR system called each participant once per day at a time of his or her choosing. In cases when the participant missed the call, the IVR system made up to three additional attempts to reach the participant at each subsequent hour. Participants could also call the IVR system directly instead of waiting to receive the daily phone call. To encourage compliance with the daily IVR calls, the participants received daily earnings that increased with consistent compliance as well as weekly bonuses for perfect compliance. Perfect compliance involved completing approximately 50 phone calls, which corresponded with a $160 payment.

2.3 MEASURES

The timing of each measure examined in the present study is summarized in Table 1. Outside of the daily IVR measures, all assessments occurred during the weekly laboratory visits.

Table 1. Timing of assessments for each measure of interest

	Baseline		Experiment (post-randomization)					
Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
TLFB		X	X	X	X	X	X	X
SMAST	X							
Drinking to Cope Motives	X							
Nicotine biomarkers		X		X				X
Daily cigarette use (IVR)	X	X	X	X	X	X	X	X
MNWS	X	X	X	X	X	X	X	X
FTND	X			X				X

2.3.1 Alcohol Outcomes

Participants' daily alcohol use and binge drinking was assessed retrospectively using an interviewer-administered timeline follow-back (TLFB) questionnaire (Sobell & Sobell, 1992). The measure consisted of participants' retrospective recall of the number of "standard drinks" (i.e., 12 oz. of beer, 5 oz. of 12%-alcohol wine, 1.5 oz. 80-proof distilled spirits) consumed on each of the previous days since their last session. To assess binge drinking, participants also indicated the days they consumed 5 or more (men) or 4 or more (women) alcoholic drinks within a 2 hour period. The alcohol use variables examined included the average number of standard drinks per day consumed during the last 7 days of the baseline period and the average number of drinks per day consumed between each weekly laboratory visit. During the same time frames, weekly binge drinking was examined as a dichotomous outcome representing any occurrence of binge drinking. A dichotomous outcome, as opposed to count outcome was used due to the

infrequency of individuals reporting more than one binge between visits (i.e., in any week, only between two and four percent of the sample reported two or more binges).

Several steps were taken to promote accurate reporting. Each staff member completed training on the TLFB that was standardized across the sites including reading a standard operating procedure, in-person instruction, standardized training videos, and repeated observation while administering the TLFB to three participants at the beginning and midpoint of the study. Furthermore, standardized forms and supplemental materials were used across the sites, including a TLFB Calendar, Standard Drink Card (a visual aid to help the participant report his or her drinking and convert beverages to a standard drink), and Definitions of Tobacco Products List.

2.3.2 Smoking Behavior

Daily cigarette use was assessed using the IVR system. During the baseline period, participants responded to the question, "How many cigarettes did you smoke yesterday?" The day following random assignment to study product, participants separately reported the number of study and non-study cigarettes they used each day with the following questions: "How many study cigarettes did you smoke yesterday?" and "How many other cigarettes (not given to you by the study) did you smoke yesterday?" The baseline average of cigarettes smoked per day was computed using the average number of cigarettes smoked during last seven days of the baseline period. Following randomization, the average number of all cigarettes smoked per day (both study and non-study cigarettes) was computed for each week.

2.3.3 Nicotine Withdrawal

Withdrawal symptoms were measured weekly using the 15-item Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986). The present study focused on the 8 most validated items including negative affect (i.e., irritability, anxiety, depressed mood), craving, physical symptoms (i.e., increased appetite, restlessness, insomnia), and cognitive symptoms (i.e., difficulty concentration). Participants rated these symptoms during the past week using the following responses: "none", "slight", "mild", "moderate", and "severe." The average score was computed at each visit. The items appeared to be reliable at each time point (Cronbach's alpha .83, .85, .84, .81, .80, .81, and .82 for baseline to Week 6, respectively).

2.3.4 Nicotine Exposure

Nicotine exposure biomarkers were assessed using first void urine sample of the day. The samples were analyzed to determine total nicotine equivalents (TNE), which has been established as a useful measure of daily nicotine exposure (Hukkanen, Jacob, & Benowitz, 2005; Scherer et al., 2007). TNE was computed as the sum of nicotine and six metabolites, which included total nicotine, total cotinine, total trans 3'-hydroxycotinine (with total referring to sum of the analyte and respective glucuronide conjugate), and nicotine-N-oxide. TNE was adjusted for creatinine to account for urinary output volume.

2.3.5 Nicotine Dependence

Nicotine dependence was assessed using the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The responses to the 6-items were summed resulting in scores ranging from 0 to 10, with higher scores suggesting higher levels of dependence.

2.3.6 Alcohol Dependence Symptoms

Drinking problems were assessed with the short-form of the Michigan Alcohol Screening Test (SMAST) (Selzer, Vinokur, & Rooijen, 1975). The SMAST includes 13 yes or no questions about one's perceptions of their drinking and the presence of associated consequences. In concurrence with existing literature, a cut-off of 5 was used to indicate a history of problem drinking (Fleming & Barry, 1989; Selzer et al., 1975).

2.3.7 Alcohol Use History

Baseline drinking status was assessed using an alcohol use questionnaire adapted from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Specifically, participants were asked, "How long it has been since you last used alcohol?" with the following response options: "within the past 30 days", "more than 30 days, but within the past year", "more than a year ago", and "I never drank any alcohol in my life." Participants who reported drinking within the past 30 days were identified as current drinkers. Individuals who indicated that they

had not used alcohol within the past 30 days, but reported any alcohol use during the two week baseline period of the TLFB were also identified as current drinkers.

2.3.8 Drinking to Cope Motives

Participants responded to five items that assessed the tendency to use alcohol as a way of coping from Cooper et al.'s (1994) Drinking Motives Questionnaire-Revised. The items assessed the extent to which the participant drinks to forget problems, help with depressed or anxious mood, forget worries, cheer up, or to improve confidence. Possible responses to each item ranged from 0 to 4, which corresponded with "almost never/never", "some of the time", "half of the time", "most of the time", and "almost always/always", respectively. The items demonstrated acceptable internal reliability ($\alpha = .80$) and were averaged together to derive a single drinking to cope motives score.

3.0 ANALYTIC OVERVIEW

Analyses were conducted in the structural equation modeling (SEM) framework using Mplus 7.2 (Muthén & Muthén, 1998-2010). Missing data were accounted for using a full information maximum likelihood estimation method, ML, which determines model estimates using all available data. A sequence of analytic steps were used to address the following aims:

Aim 1: To determine the impact of smoking VLNC cigarettes on alcohol outcomes (i.e., alcohol use, binge drinking), latent growth curve models for each alcohol outcome were estimated, and the main effect of the intervention was examined on these trajectories. Additional analyses took into account the effect of non-compliance.

Aim 2: To investigate individual differences of the impact of smoking VLNC cigarettes on alcohol outcomes, several baseline variables were examined as moderators of the effect examined in Aim 1 (i.e., gender, drinking levels, nicotine dependence, history of problem drinking, drinking to cope motives).

Aim 3: To examine the processes contributing to these effects, mediation analysis was used to examine the extent to which study condition impacted the intermediate processes of interest (i.e., changes in nicotine exposure, cigarette smoking, and withdrawal), and in turn, influenced drinking.

4.0 AIM 1: THE IMPACT OF SMOKING VLNC CIGARETTES ON ALCOHOL OUTCOMES

A primary objective of this investigation was to determine, for the first time in daily smokers, the impact of smoking VLNC cigarettes on alcohol use over time. In the first set of analyses, the dose-related effects of reduced nicotine were examined. This was accomplished by evaluating the impact of the nicotine content of cigarettes on repeatedly-measured alcohol outcomes (i.e., alcohol use, binge drinking). The nicotine contents examined corresponded with a NNC control condition (15.8 mg/g), a moderate nicotine content condition (5.2 mg/g), and several VLNC cigarette conditions (0.4 mg/g to 2.4 mg/g). It was hypothesized that smoking VLNC cigarettes would reduce alcohol use and binge drinking relative to smoking NNC control cigarettes. As the extent of differences between each reduced nicotine condition and the normal nicotine control would likely be impacted by non-compliance (i.e., use of non-study cigarettes with normal nicotine content), the role of non-compliance in the strength of relations between smoking VLNC cigarettes and alcohol outcomes was also considered.

4.1 AIM 1: STATISTICAL ANALYSES

The effects of the moderate and VLNC cigarette conditions, relative to the NNC control condition, were evaluated on change over time in alcohol outcomes. The change over time in

alcohol outcomes during the 6 week trial was described using latent growth curve models of weekly alcohol use and binge drinking. Then, the change over time (i.e., slope of alcohol outcome trajectories) were predicted by each reduced nicotine condition (relative to the NNC control).

Separate latent growth curve models were examined to describe changes in alcohol use and binge drinking. For the latent growth curve models for both alcohol use and binge drinking, the intercept factor loadings were fixed to 1 and the slope factor loadings were fixed to reflect the equal intervals between the visits and to estimate the intercept at the baseline visit. The functional form of the change over time was determined by examining the relative fit indices of several trajectory shapes, including linear, quadratic, and piecewise. The corresponding factor loadings for each trajectory shape are summarized in Table 2.

Table 2. Factor loadings for latent intercept and slope factors for linear, quadratic, and piecewise functional forms

	Intercept (Int)	Slope 1 (Sl1)	Slope 2 (Sl2)
Intercept Centered at Baseline			
Linear	1, 1, 1, 1, 1, 1, 1	0, 1, 2, 3, 4, 5, 6	N/A
Quadratic	1, 1, 1, 1, 1, 1, 1	0, 1, 2, 3, 4, 5, 6	0, 1, 4, 9, 25, 36
Piecewise	1, 1, 1, 1, 1, 1, 1	0, 1, 2, 2, 2, 2, 2	0, 0, 0, 1, 2, 3, 4
Intercept Centered at Week 6			
Linear	1, 1, 1, 1, 1, 1, 1	-6, -5, -4, -3, -2, -1, 0	N/A
Quadratic	1, 1, 1, 1, 1, 1, 1	-6, -5, -4, -3, -2, -1, 0	36, 25, 16, 9, 4, 1, 0
Piecewise	1, 1, 1, 1, 1, 1, 1	-2, -1, 0, 0, 0, 0, 0	-4, -4, -4, -3, -2, -1, 0

Note. The timing of visits was equally spaced with about seven days between each visit (means: 6.98 – 7.28 days between visits). The number of days between visits did not significantly differ by treatment condition (*p*'s .49 - .90). This supported the use of equally spaced factor loadings for the slope terms. Thus, to reflect the time passed between visits, study results refer to weekly patterns of each outcome.

For the piecewise model, the inflection point was chosen a priori at Week 2. Week 2 was chosen based on the study hypotheses of the timeframe of withdrawal and nicotine reduction, instances when mediators were measured (i.e., nicotine exposure was measured at baseline, Week 2, and Week 6), and identification of the model (i.e., latent linear slope factors need minimum of 3

indicators for identification purposes). This resulted in a model with two slope terms: The first slope corresponded with the change in the alcohol outcome during first two weeks of the study and the second slope corresponding with the final four weeks of the study.

When using latent growth curve models to estimate the change over time in alcohol use, it was important to take into account that the alcohol use outcome was not normally distributed. Alcohol use was a continuous, positively skewed outcome (see Figure 2 for depiction of baseline distribution). The extent of the skew and kurtosis each week tended to exceed the recommended cut-offs of 3 and 7, respectively[1], which can lead to incorrect rejections of models and downwardly biased p-values (Finch, West, & MacKinnon, 1997; Hoyle, 2014; Olsson, Foss, Troye, & Howell, 2000).

[1] From baseline to week 6, skewness statistics obtained in SPSS were 3.20, 2.78, 2.77, 2.02, 3.21, 2.35, and 1.82, respectively, and kurtosis statistics were 16.23, 11.42, 11.71, 5.13, 17.79, 6.97, and 4.13.

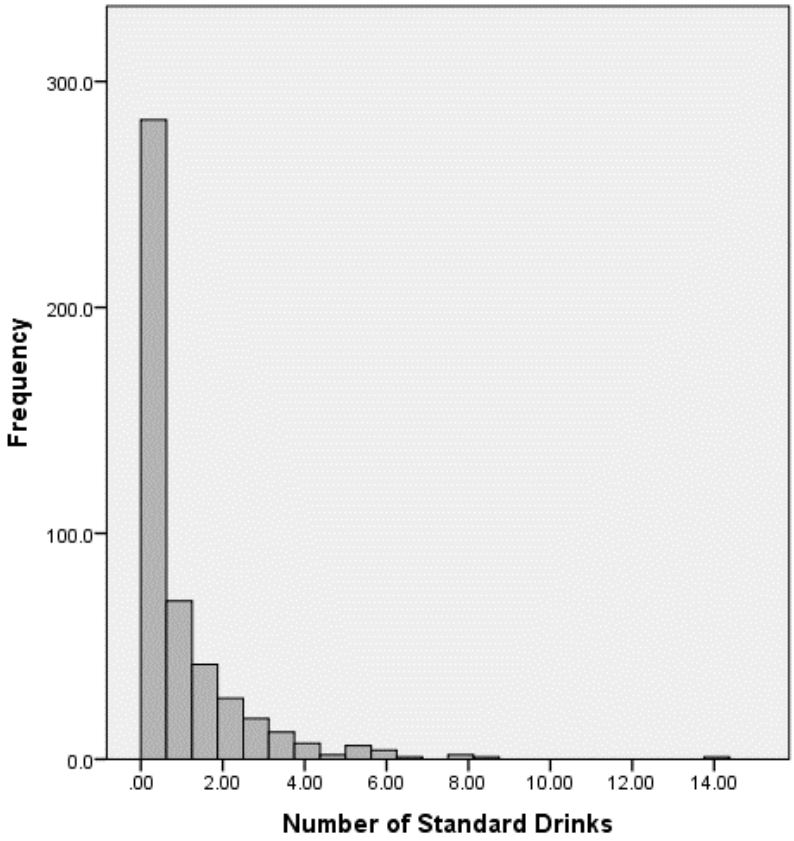


Figure 2. Baseline distribution of average number of standard drinks consumed per day

A recommended approach to address non-normality is to conduct significance testing using bias-corrected confidence intervals obtained from bootstrapping (Hoyle, 2014; Yung & Bentler, 1996). In the context of structural equation modeling, bootstrapping has been shown to produce confidence intervals that are robust against non-normality. In contrast, the binge drinking outcome was dichotomous. As a result, bootstrapping was not required. Instead, a robust estimation method, MLR, was used to handle missing data using maximum likelihood estimation.

Once the best fitting trajectory shape to the alcohol outcome was determined, the dose-response relationship between the nicotine content of the study cigarette and alcohol outcome was evaluated. Specifically, the slope(s) of each alcohol outcome was regressed on a dummy-

coded predictor comparing the NNC control condition (i.e., coded as '0') to each reduced nicotine content condition (i.e., coded as '1'). The resulting regression coefficient indicated if the slope differed between the NNC control condition and reduced nicotine content condition. A secondary analysis compared NNC control condition to usual brand condition, in order to determine if they could be combined for subsequent analyses. Together, this resulted in five a priori pairwise comparisons.

Then, the effect of non-compliance on alcohol outcomes was considered. Prior research of individuals assigned to smoke the 0.4 mg/g cigarettes has identified a TNE cut-off value of 6 nmol/mL as indicating any non-compliance and 12 nmol/mL indicating some non-compliance (i.e., about 10% of cigarettes smoked are usual brand; Denlinger et al., 2015). The present study used these cut-off values, for individuals assigned to the 0.4 mg/g normal and high tar conditions only, to create dummy-coded variables for biomarker confirmed non-compliance. These indicators were examined as predictors of the alcohol outcome trajectories.

Analyses were conducted with and without the following covariates to determine the sensitivity of the findings to controlling for their effects: gender, age, baseline cigarettes per day, baseline FTND score without cigarettes per day item, and minority status.

4.2 AIM 1: BASELINE CHARACTERISTICS

The present study examined a total of 476 alcohol users, including 418 individuals who reported drinking within the past 30 days at baseline. An additional 58 individuals were included in the analyses who denied drinking within the past 30 days but reported alcohol use during the baseline TLFB period. Baseline characteristics of the sample are provided in Table 3.

Table 3. Demographics and baseline smoking and drinking characteristics

Variable	Level/Unit	Overall	Usual Brand	15.8 mg/g	5.2 mg/g	2.4 mg/g	1.3 mg/g	0.04 mg/g	0.04 mg/g HT
N		415	73	64	61	67	71	60	80
Age	Years	38.88(13.61)	37.26(12.76)	39.93(14.20)	39.39(13.70)	40.16(12.63)	38.77(14.63)	40.38(14.16)	37.48(13.42)
Sex	Female	41.9	38.4	39.1	39.3	37.3	45.1	45.0	46.3
Race	Non-Hispanic White	59.5	61.6	57.8	50.8	59.7	62.0	45.0	60.0
	Black	33.3	38.4	37.5	41.0	32.8	28.2	36.7	27.5
Education	High school or less	35.2	43.8	32.8	42.6	31.3	36.6	33.3	322.5
	Some college or more	64.8	56.2	67.2	57.4	68.7	63.4	66.7	67.5
Menthol	Menthol Smoker	47.5	49.3	54.7	50.8	59.7	49.3	48.3	53.8
CPD		14.76 (7.32)	13.69(7.62)	14.81(7.50)	14.97(7.21)	14.75(7.05)	14.98(7.43)	14.52(6.80)	15.66(7.51)
FTND	Total score	4.59 (2.27)	4.44(2.18)	4.50(2.50)	4.87(2.14)	4.61(2.31)	4.52(2.40)	4.48(2.14)	4.93(2.13)
Alcohol use	Drinks per day	0.90 (1.48)	.68(.97)	1.11(2.02)	1.12(1.65)	1.09(1.82)	0.80(1.27)	1.05(1.51)	0.78(1.12)
Binge	Any binge	11.6	11.0	9.4	11.5	11.9	11.0	16.7	11.9

Note. Means (standard deviations) are reported for continuous outcomes and proportions are reported for dichotomous/categorical outcomes. None of the baseline characteristics significantly differed between the study conditions, which was determined using omnibus chi-square tests for dichotomous outcomes (*p*'s > .59) and one-way ANOVAs for continuous outcomes (*p*'s > .39).

On average, at baseline, participants were 38.88 years old (standard deviation [SD] = 13.61), smoked 14.76 cigarettes per day (SD = 7.62), and were moderately nicotine dependent (FTND = 4.59, SD = 2.27). The participants were primarily male (58.1%), non-Hispanic White (59.5%), completed at least some college (64.8%), and were non-Menthol cigarette smokers (52.5%). At baseline, participants averaged approximately 0.90 standard drinks per day and 11.6% reported at least one binge drinking episode. Baseline characteristics did not significantly differ across the study conditions, which was determined using omnibus chi-square tests for dichotomous outcomes (*p*'s > .59) and one-way ANOVAs for continuous outcomes (*p*'s > .39).

4.3 AIM 1: RESULTS: THE IMPACT OF REDUCED NICOTINE CONTENT CIGARETTES ON ALCOHOL USE

4.3.1 Modeling Alcohol Use Trajectories

The overall change in alcohol use over time was best described by the piecewise model. This was determined based on the goodness of model fit of each trajectory shape as well as the relative fit between trajectory shapes. The model fit indices and corresponding parameter estimates for the linear, quadratic, and piecewise trajectory shapes in the total sample are summarized in Table 4.

Table 4. Model fit and estimates for examined trajectory shapes for alcohol use and binge drinking outcomes

	Linear	Quadratic	Piecewise	Selected Model
	Alcohol use			
Fit Indices	$X^2 = 89.31$ $p < .001$ RMSEA = .08 (.06, .10) CFI = .97; TLI = .97 AIC = 9527; BIC = 9577	$X^2 = 78.98$ $p < .001$ RMSEA = .08 (.06, .10) CFI = .97; TLI = .97 AIC 9524; BIC 9591	$X^2 = 58.78$ $p < .001$ RMSEA = .07(.04, .09) CFI = .98; TLI = .98 AIC = 9504; BIC = 9571	Piecewise (due to lower RMSEA, AIC, BIC; and CFI and TLI closer to 1).
Parameter Estimates[1]	Int 1.03** (0.91-1.20) Int Var 1.89** (1.19-3.27) Sl1 .03** (0.01, 0.05) Sl1 Var .02** (0.01-0.04)	Int 1.03** (.90, 1.19) Int Var 1.86** (1.21, 3.20) Sl1 .05* (.01, .08) Sl1 Var .01 (-.03, .06) Sl2 -.01 (-.01, .01) Sl2 Var .002 (-.001, .01)	Int .98** (.85, 1.10) Int Var 1.55** (.83, 2.42) Sl1 .09** (.05, .14) Sl1 Var .01 (-.11, .12) Sl2 .01 (-.02, .03) Sl2 Var .04* (.01, .07)	
	Binge Drinking			
Fit Indices	$X^2 = 123.15$ $p = .43$ AIC = 2231; BIC = 2252	$X^2 = 118.74$ $p = .44$ AIC 2235; BIC 2272	$X^2 = 119.90$ $p = .41$ AIC 2236; BIC 2273	Linear (due to smaller AIC, BIC; and non-significant slopes or variance terms for more complex trajectory shapes).
Parameter Estimates	Int 3.14*** (2.63, 3.65) Int Var 4.82*** (2.50, 7.13) Sl1 .09 (-.03, .21) Sl1 Var .07* (.01, .14)	Int 3.45*** (2.58, 4.32) Int Var 5.99** (1.38, 10.59) Sl1 .46† (-.08, 1.00) Sl1 Var .33 (-.61, 1.28) Sl2 -.07 (-.15, .01) Sl2 Var .01 (-.01, .04)	Int 3.27*** (2.42, 4.12) Int Var 5.14* (.85, 9.43) Sl1 .26 (-.19, .46) Sl1 Var .03 (-.97, 1.03) Sl2 -.02 (-.23, .18) Sl2 Var .19 (-.08, .45)	

Note. Parameter estimates include intercept (Int) and slope (Sl) terms, and their corresponding variances (Var). For quadratic trajectories, Sl1 corresponds with the linear change and Sl2 corresponds with quadratic change during the 6 week study. For piecewise trajectories, Sl1 corresponds with the linear change during the first 2 weeks and Sl2 corresponds with the linear change during the last 4 weeks.
† $p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$

Conventional cut-off criteria for adequate model fit was used, including the root mean square error of approximation (RMSEA) and its 90% confidence interval (CI) having values less than .05, and the comparative fit index (CFI) with values close to .95 or greater (Browne, Cudeck,

Bollen, & Long, 1993; Hu & Bentler, 1999).[2] As needed, the relative fit for each trajectory shape to the data were determined using nested model chi-square testing (for linear vs quadratic) and relative fit indices (for piecewise vs quadratic and linear). The piecewise model exhibited acceptable model fit. Furthermore, consistent with improved fit relative to the linear and quadratic models, the piecewise model exhibited the lowest AIC and BIC values, smaller RMSEA and chi-square, and CFI closest to 1.[3] The final piecewise trajectory shape is depicted in Figure 3. On average, alcohol use levels significantly increased from baseline to week 2 (Sl_1 = 0.09, 95% CI .05 - .14, $p < .01$), and then did not change for the remainder of the study (i.e., weeks 2 to 6) (Sl_2 = 0.01, 95% CI -.02 - .03, $p > .10$).

[2] Non-significant chi-square tests are also indicative of good model fit, but are prone to be sensitive to small deviations in fit in large samples using real world data (Browne et al., 1993; Hu & Bentler, 1999), and as a result, was not heavily emphasized as an index of absolute model fit in this study.

[3] The relative fit for each functional form was also compared both using log transformed alcohol use outcome and robust maximum likelihood, which are two alternative methods of addressing non-normal dependent variables. Both methods replicated the conclusion that the piecewise model was the best fitting model.

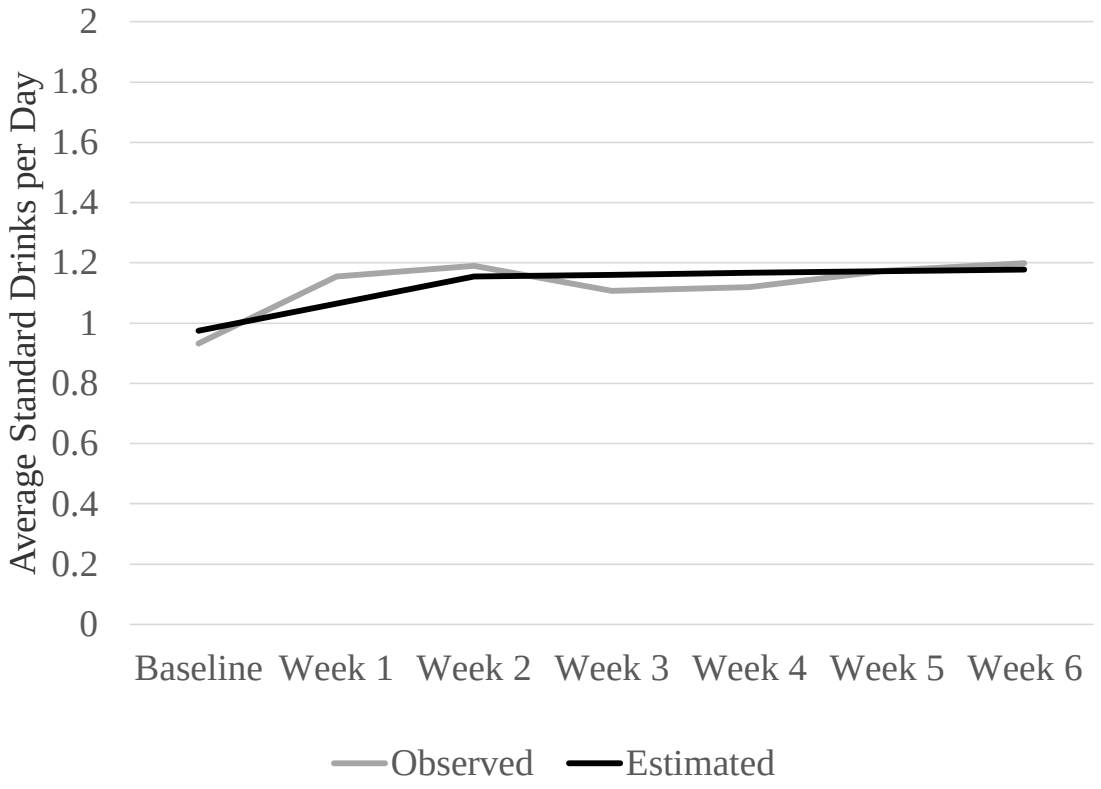
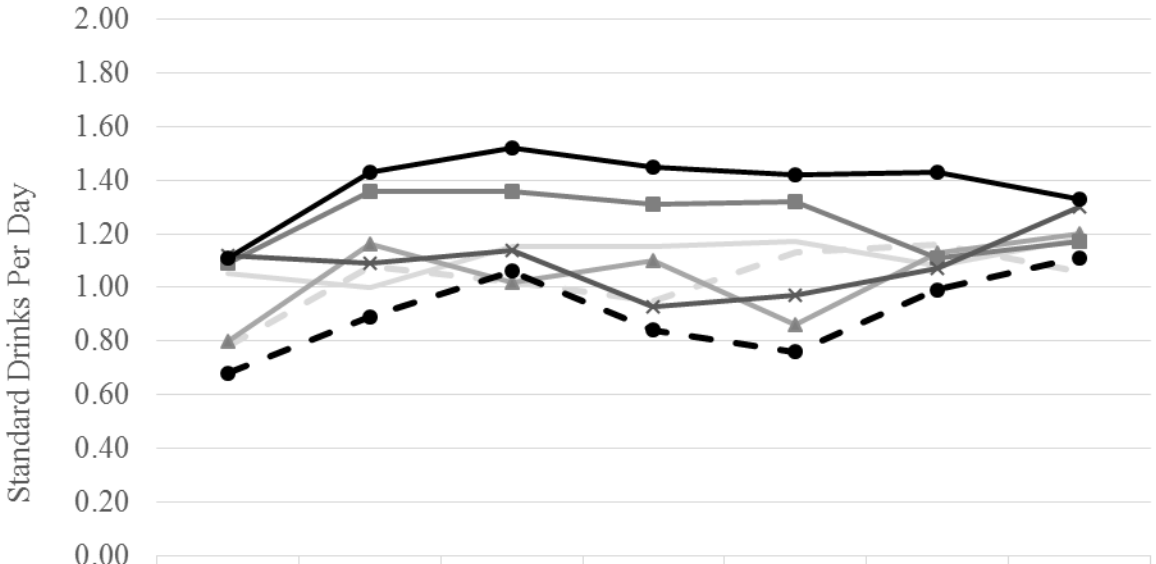


Figure 3. Best fitting piecewise trajectory shape for alcohol use levels relative to the observed alcohol use values

4.3.2 The Effect of Nicotine Reduction on Alcohol Use Trajectories

Then, the effect of the moderate and VLNC cigarette conditions, relative to the NNC control condition, on piecewise change in alcohol use was examined (the observed number of standard drinks in each condition are summarized in Figure 4). Given the piecewise change in alcohol use, this was accomplished by examining the effect of the aforementioned dummy-coded reduced nicotine content conditions (e.g., NNC control coded as '0' and 0.4 mg/g condition coded as '1') on both the slope term representing the change during the first two weeks of the

study (i.e., Slope 1) as well as the slope term for the change during the last four weeks of the study (i.e., Slope 2).



	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
0.4-HT	0.78	1.08	1.02	0.95	1.13	1.16	1.06
0.4	1.05	1.00	1.15	1.15	1.17	1.08	1.18
1.3	0.80	1.16	1.02	1.10	0.86	1.13	1.20
2.4	1.09	1.36	1.36	1.31	1.32	1.11	1.17
5.2	1.12	1.09	1.14	0.93	0.97	1.07	1.30
15.8	1.11	1.43	1.52	1.45	1.42	1.43	1.33
UB	0.68	0.89	1.06	0.84	0.76	0.99	1.11

Figure 4. Observed levels of average number of standard drinks consumed per day in each condition

The effects of the reduced nicotine content conditions relative to the NNC control cigarette are summarized in Table 5.[4]

[4] Baseline alcohol use levels did not differ significantly between study cigarette control and reduced nicotine conditions (p's > .10) or usual brand condition (p > .05). Thus, baseline drinking levels were not controlled for in the analyses.

Table 5. Effect of smoking cigarettes with reduced nicotine content on alcohol outcomes

	Usual brand	5.2	2.4	1.3	0.4	0.4 HT
Unadjusted Estimates						
Alcohol Use						
Slope 1	-.13 (-.27, .05)	-.18* (-.36, -.04)	-.08 (-.28, .15)	-.15† (-.33, .01)	-.16† (-.34, .04)	-.11 (-.28, .07)
Slope 2	.07 (-.04, .19)	.09 (-.02, .21)	-.03 (-.14, .08)	.05 (-.06, .18)	.03 (-.07, .14)	.02 (-.10, .11)
Binge drinking						
Slope 1	-.13 (-.34, .07)	.14 (-.11, .24)	-.14 (-.35, .08)	-.003 (-.19, .19)	0.12 (-.07, .31)	.04 (-.35, .52)
Covariate-Adjusted Estimates						
Alcohol Use						
Slope 1	-.15 (-.32, .07)	-.18* (-.24, .01)	-.08 (-.27, .10)	-.14† (-.33, .02)	-.16† (-.39, .03)	-.12 (-.28, .03)
Slope 2	.07 (-.06, .17)	.08 (-.03, .20)	-.02 (-.13, .08)	.05 (-.07, .16)	.04 (-.06, .15)	.02 (-.09, .14)
Binge Drinking						
Slope 1	-.12 (-.34, .09)	.14 (-.09, .36)	-.13 (-.34, .09)	0.02 (-.16, .21)	0.16† (-.02, .35)	.03 (-.07, .58)

Note. Unstandardized path coefficients (95% confidence interval) are reported in the table. Confidence intervals for alcohol use outcome are bias corrected using bootstrapping procedure. Slope 1 corresponds with change during the first 2 weeks of the study; slope 2 corresponds with change during the last 4 weeks of the study. The binge drinking slope represented linear change throughout the duration of the study. No covariates were included in the unadjusted analyses. Adjusted analyses control for gender, age, minority race/ethnicity, and baseline cigarettes per day and FTND scores (without cigarettes per day item).
† $p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$

During the first two weeks, on average, alcohol use significantly increased. There were no significant differences in this increase between the NNC condition and the 0.4 mg/g HT and 2.4 mg/g conditions. The 0.4 mg/g and 1.3 mg/g conditions demonstrated a marginally smaller increase relative to the NNC control condition (0.04 mg/g: b = -.16, 90% CI: -.32, -.002; 1.3 mg/g: b = -.15, 90% CI: -.29, -.01). The moderate nicotine condition (5.2 mg/g) exhibited a significantly smaller increase relative to the NNC cigarette (see Figure 5; b = -.19, 95% CI: -.37, -.04, $p < .05$).

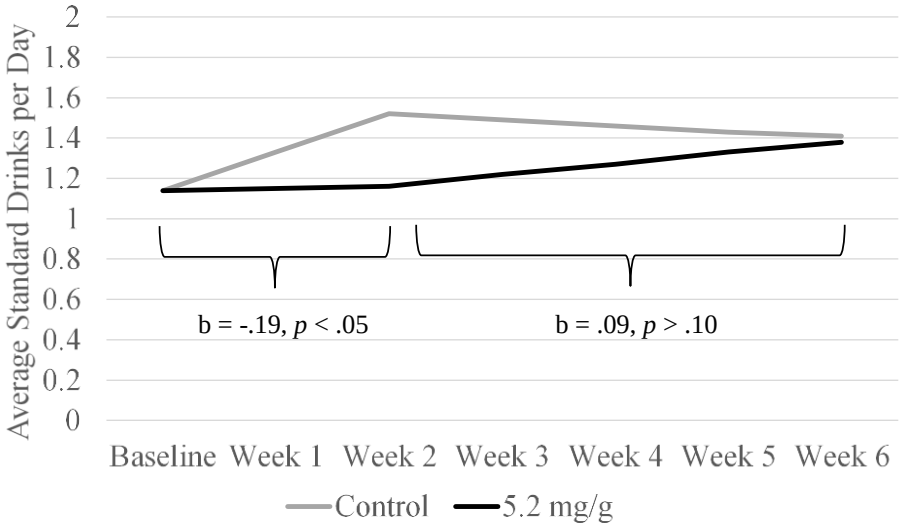


Figure 5. Estimated differences between the 5.2 mg/g and study control cigarette in alcohol use trajectories after adjusting for covariates

During the last four weeks, none of the conditions had significantly different slopes during the final four weeks (*p*'s > .10; Table 5). Thus, on average, alcohol use did not change during the last four weeks for any of the nicotine content conditions. The pattern of findings did not change after controlling for the effects of minority race/ethnicity, gender, and baseline age, cigarettes per day, and FTND (see lower panel of Table 5).[5]

4.3.3 The Effect of Combined VLNC Cigarette Conditions on Alcohol Use Trajectories

As there was no clear dose-response relationship between the nicotine content of cigarettes and alcohol use (i.e., non-significant or marginal differences in the same direction), the VLNC conditions were combined (0.4 HT, 0.4, 1.3, and 2.4 mg/g conditions) and the main effect

[5] The intercept for the alcohol use trajectory was also centered to Week 6 to determine if these differential slopes corresponded with significantly different drinking levels at the end of the trial. Alcohol use levels at Week 6 did not significantly differ between the NNC control cigarette condition and usual brand or reduced conditions (*p*'s > .10; results not shown).

analyses were reexamined. This approach was taken as a way to increase the sample size, thus increasing statistical power to detect differences. The results of these comparisons are summarized in Table 6 and Figure 6.

Table 6. Effect of smoking VLNC cigarettes on alcohol outcome trajectories relative to study and usual brand controls

Control Condition:	**Study cigarette**	**Usual Brand**
	Unadjusted Estimates	
	Alcohol Use	
Slope 1	-.12† (-.28, .02)	.01 (-.17, .10)
Slope 2	.01 (-.07, .10)	-.04 (-.12, .04)
	Binge Drinking	
Slope 1	.01 (-.45, .22)	.15† (-.01, .31)
	Adjusted Estimates	
	Alcohol Use	
Slope 1	-.12† (-.28, .02)	.03 (-.16, .13)
Slope 2	.01 (-.07, .11)	-.04 (-.12, .04)
	Binge Drinking	
Slope 1	.03 (-.13, .18)	.17† (.000, .34)

Note: Unstandardized path coefficients (95% confidence intervals) are reported. VLNC comparison group includes combined 0.4, 0.4 HT, 1.3, and 2.4 reduced nicotine conditions. Slope 1 corresponds with change during the first 2 weeks of the study; slope 2 corresponds with change during the last 4 weeks of the study. The binge drinking slope represented linear change throughout the duration of the study. Adjusted analyses control for gender, age, minority race/ethnicity, and baseline cigarettes per day and FTND scores (without cigarettes per day item).
† p < .10; $^{*}p$ < .05; $^{**}p$ < .01; $^{***}p$ < .001

The VLNC cigarette condition exhibited a marginally smaller increase in alcohol use during the first two weeks relative to the NNC condition (see Figure 8; b = -.12, 90% CI: -.28, -.01)[6], but no differences were observed during the last four weeks. There were no significant differences in the change in alcohol use between the VLNC cigarette conditions and usual brand. The effects did not change after including covariates (see lower panel of Table 6).

[6] The marginal difference was replicated when only examining the 0.4 mg/g and 1.3 mg/g conditions.

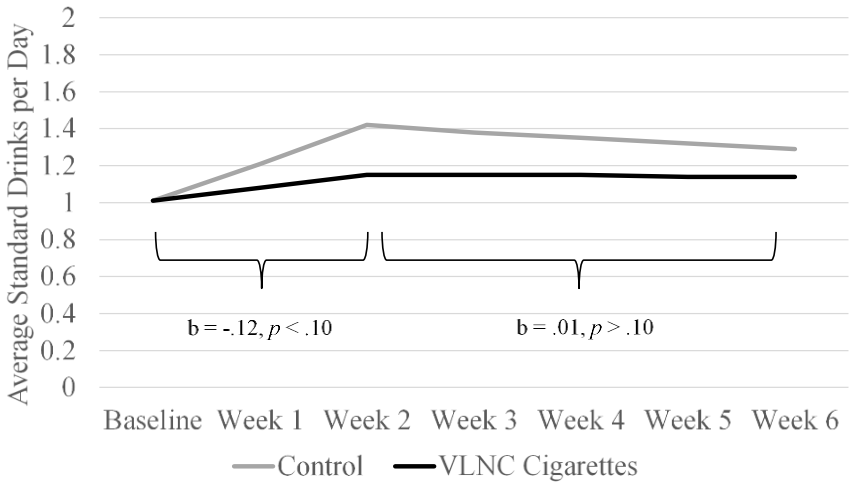


Figure 6. Alcohol use trajectories for combined VLNC cigarette conditions relative to study control cigarette after adjusting for covariates

4.3.4 The Effect of Non-Compliance on Alcohol Use Trajectories

Lastly, the effect of non-compliance, assessed by nicotine biomarkers, on alcohol use was explored. The effect of non-compliance was examined among individuals in the 0.4 mg normal tar and high tar conditions (n = 137).[7] The TNE distributions at Week 2 and Week 6 are depicted in Figure 7.

[7] Individuals who were missing biomarker data were assumed to be non-compliant.

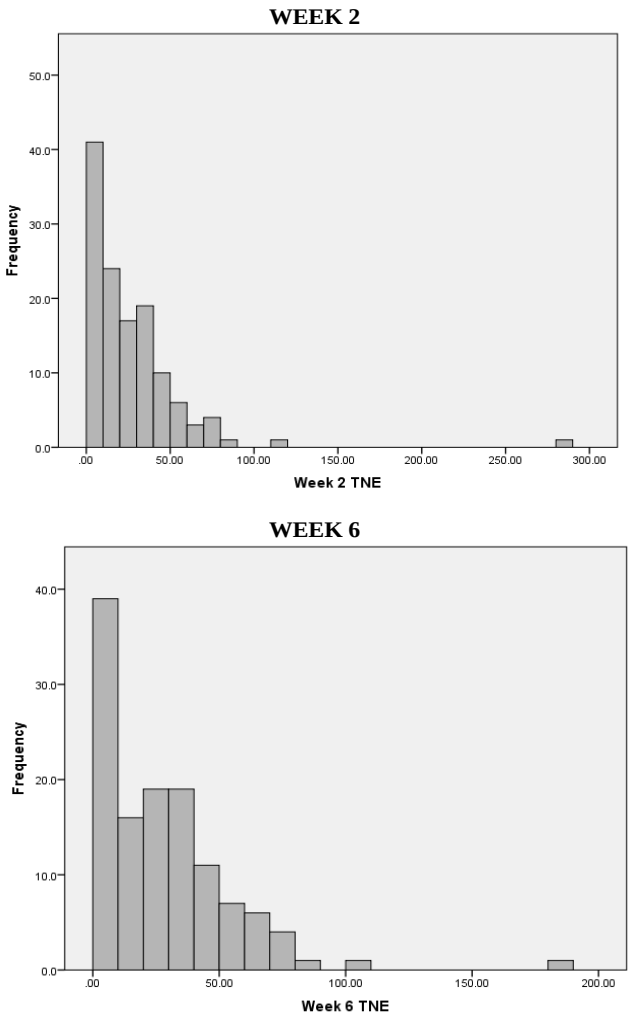


Figure 7. Distribution of observed TNE in the lowest nicotine content conditions (0.4 mg/g) at Week 2 and Week 6

Using a strict cut-off value of 6 nmol/mL, non-compliance was not associated with change in alcohol use during the first two weeks (74% non-compliant: b = .08, 95% CI: -.11, .28) or the last four weeks (76% non-compliant: b = -.15, 95% CI: -.47, .31). When a more lenient cut-off value of 12 nmol/mL was used, non-compliance was unrelated to change in alcohol use during the first two weeks (65% non-compliant, b = .01, $p > .10$, 95% CI: -.11, .30); however, non-compliance was associated with a significant increase in alcohol use during the last four weeks

relative to compliance (69% non-compliant, b = .13, $p < .05$, 95% CI: .05, .24).[8] The alcohol use trajectories for compliant and non-compliant individuals are depicted in Figure 8.

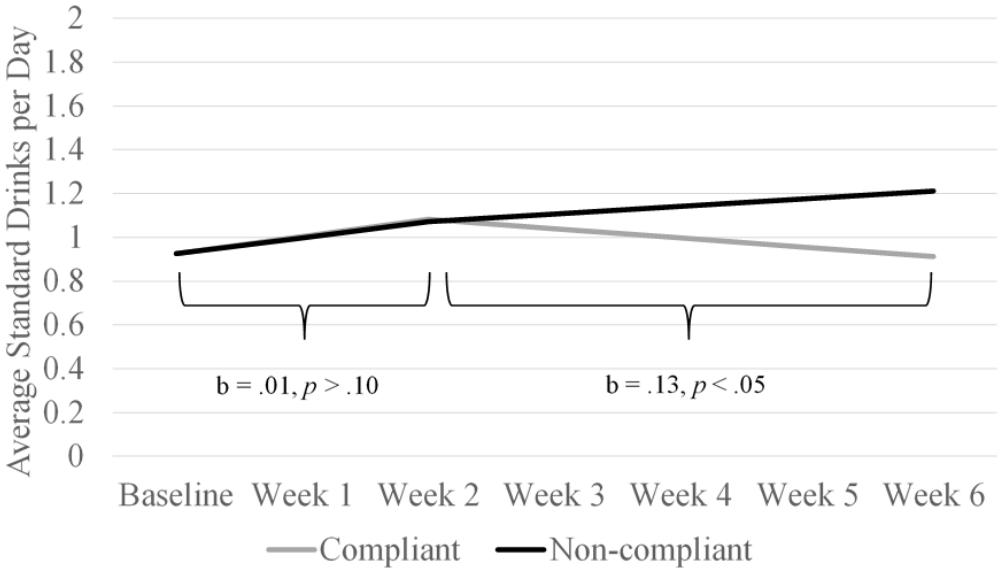


Figure 8. The relation between non-compliance and changes in alcohol use among individuals in the lowest nicotine content conditions (0.4 mg/g)

4.4 AIM 1: RESULTS: THE IMPACT OF REDUCED NICOTINE CONTENT CIGARETTES ON BINGE DRINKING

4.4.1 Modeling Binge Drinking Trajectories

The overall change over time in binge drinking was best described by a linear trajectory (see Table 4 for model fit for linear, quadratic, and piecewise models). The linear model exhibited

[8] Non-compliance was not predicted by baseline alcohol use levels.

acceptable model fit. It also appeared to have relatively better model fit, as it exhibited the lowest AIC and BIC values. Furthermore, adding the quadratic term did not significantly improve model fit based according to a non-significant chi-square test for nested models (χ^2 = 2.90, df = 4, p = .57). As a result, the proceeding analyses relied on the linear trajectory shape (depicted in Figure 9) when testing for study effects. On average, there was a non-significant increase in binge drinking over the 6 week period (Slope = .09, 95% CI: -.03, .21); however, there was significant individual variability in the slope suggesting that some individuals increased their binge drinking while others decreased.

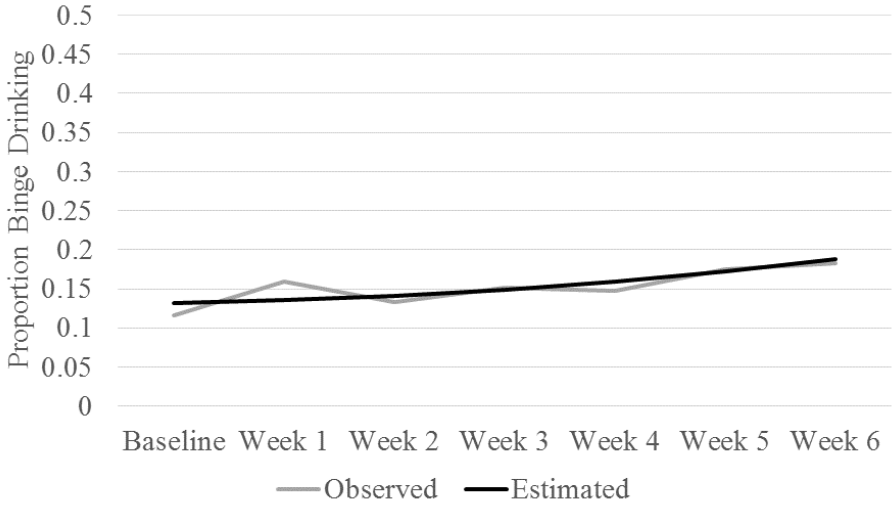
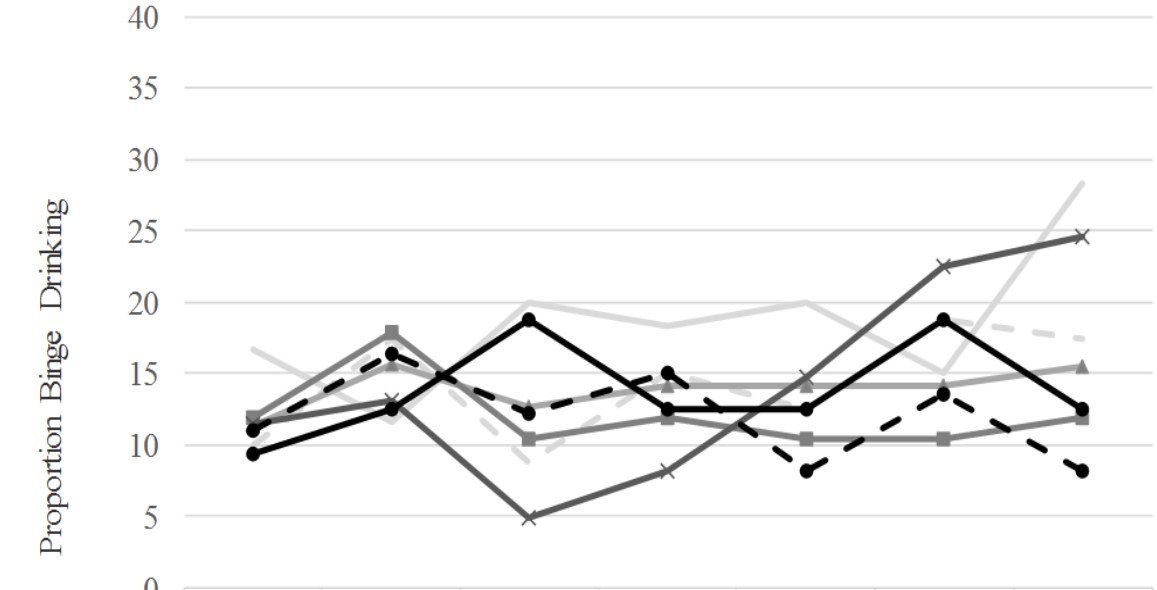


Figure 9. Best fitting linear trajectory shape for binge drinking relative to the observed values

4.4.2 The Effect of Nicotine Reduction on Binge Drinking Trajectories

The effect of the moderate and VLNC cigarette conditions, relative to the NNC control condition, on linear change in binge drinking was examined (observed proportions of binge drinking by condition is summarized in Figure 10).



	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
0.4-HT	10	17.5	8.8	15	12.5	18.8	17.5
0.4	16.7	11.7	20	18.3	20	15	28.3
1.3	11.3	15.7	12.7	14.1	14.1	14.1	15.5
2.4	11.9	17.9	10.4	11.9	10.4	10.4	11.9
5.2	11.5	13.1	4.9	8.2	14.8	22.6	24.6
15.8	9.4	12.5	18.8	12.5	12.5	18.8	12.5
UB	11	16.4	12.3	15.1	8.2	13.6	8.2

Figure 10. Observed proportion of individuals reporting any binge drinking by condition

This was accomplished by examining the effect of each dummy-coded reduced nicotine condition on the linear slope term that represented overall change during the 6 week study. The corresponding results are summarized in Table 5.[9] There were no significant differences in binge drinking slope between reduced nicotine content conditions and NNC condition (*p*'s: .20 - .97).[10] These findings largely remained unchanged after adding the covariates (see Table 6);

[9] The study conditions did not differ significantly with respect to baseline binge drinking levels (*p*'s: .26 - .93), thus only the relation between study condition and the slope terms were estimated in the final models.
[10] There were no significant differences in binge drinking occurrence at Week 6 between the normal nicotine content control cigarette and reduced nicotine content conditions (*p*'s .19 - .97).

however, the lowest nicotine content cigarette (0.4 mg/g) exhibited marginally faster increases in binge drinking relative to the NNC cigarette (b = .16, SE = .08, p = .08), which corresponded with marginally higher levels of binge drinking at Week 6 (b = 1.00, SE = .56, p = .08).

4.4.3 The Effect of Combined VLNC Cigarette Conditions on Binge Drinking Trajectories

While the 0.4 mg/g condition appeared to have a marginal increase in binge drinking relative to the NNC condition, this increase was likely driven by the unusually high prevalence of binge drinking from Week 5 (15%) to Week 6 (28%), which is expected to be a spurious finding.[11] With the exception of the 0.4 mg/g condition, the VLNC cigarette conditions exhibited similar patterns of binge drinking relative to the NNC cigarette condition. Thus, as there was no clear dose-response relationship between the nicotine content of cigarettes and binge drinking, again, the four VLNC cigarette conditions were combined and compared to the NNC control condition.

The results of these comparisons are summarized in Table 6. Change in binge drinking did not differ between VLNC cigarette conditions and NNC control cigarette (b = .01, SE = .08, p = .56). There was a marginal increase binge drinking in the VLNC cigarette conditions relative to the usual brand condition (b = .15, SE = .08, p = .07). The effects did not substantively change after including covariates (Table 6 lower panel).

[11]The difference in slope between the 0.4 mg/g and NNC control condition was non-significant when only examining the first 5 weeks of the trial (p = .73).

4.4.4 The Effect of Non-Compliance on Binge Drinking Trajectories

The effect of non-compliance on binge drinking was then examined. When examining the effect of non-compliance among individuals in the 0.4 mg/g normal tar and high tar conditions (n = 137), the strict cut-off value of 6 nmol/mL was not significant associated with change in binge drinking (b = -.14, SE = .11, p = .21). The lack of relation was replicated with the more lenient cut-off value of 12 nmol/mL (b = .05, SE = .24, p = .83).

4.5 AIM 1: SUMMARY

The hypothesis that smoking cigarettes with reduced nicotine content would reduce alcohol outcomes relative to NNC cigarettes was partially supported. Smoking cigarettes with reduced nicotine content corresponded with significantly smaller (for the moderate nicotine 5.2 mg/g condition) or marginally smaller (for the two lowest VLNC conditions: 0.4 mg/g and 1.3 mg/g) initial increases in alcohol use. During the subsequent four weeks, however, the nicotine content of study cigarettes was not related to changes in alcohol use. A similar pattern of findings was seen when the VLNC cigarettes conditions were combined. The lack of association during the last four weeks may be partly attributed to non-compliance, as it appeared that non-compliance was associated with increased drinking during this time frame.

The hypothesis that nicotine reduction would reduce binge drinking was not supported. Smoking cigarettes with reduced nicotine content did not significantly impact changes in binge drinking during the study relative to the NNC cigarette. The pattern of findings was replicated

after combining the VLNC cigarette conditions. Non-compliance did not appear to impact the pattern of findings in the lowest nicotine conditions.

5.0 AIM 2: INDIVIDUAL DIFFERENCES OF THE IMPACT OF VLNC CIGARETTES ON ALCOHOL OUTCOMES

An objective of this study was to examine if the effect of VLNC cigarettes on alcohol outcomes differed between subgroups of smokers. A number of individual difference factors were proposed in the introduction due to suspected differences in response to VLNC cigarettes specifically, as well as the interrelatedness of smoking and drinking more generally. The individual difference factors examined included gender, baseline drinking status (i.e., intercept term of alcohol outcome trajectory), alcohol dependence symptoms, baseline drinking to cope motives, and baseline FTND score.

While the moderation analyses were generally exploratory, there were select a priori hypotheses based on the existing literature:

1. The effect of nicotine reduction will be relatively robust among individuals who are believed to be more sensitive to changes in nicotine dose (e.g., men) and for whom smoking and drinking frequently go hand-in-hand (e.g., heavy drinkers and those with a history of problem drinking).
2. As withdrawal symptoms may mitigate any reduction in drinking in response to nicotine reduction, it is expected that individuals who are at risk of withdrawal symptoms may not benefit as much from the intervention with respect to changes in

drinking (e.g., women, individuals who are more highly nicotine dependent, and individuals who report drinking to cope motives).

5.1 AIM 2: STATISTICAL ANALYSES

Moderation analyses were conducted to determine if the effect of VLNC cigarette use on change in alcohol outcomes differed as a function of baseline characteristics. These analyses focused exclusively on the combined VLNC cigarette conditions (n = 278) and normal nicotine content (NNC) control condition (n = 64).[12] This was achieved in Mplus by regressing the slope term(s) on three variables: the two main effects comprising the interaction (i.e., intervention effect, demographic effect) as well as the computed product of these variables. With the exception of baseline drinking status, which was examined as a continuous latent variable, each moderating variable was made into a dichotomous variable using a median split (i.e., FTND, baseline drinking to cope motives) or predetermined clinical cut-off (i.e., for alcohol dependence symptoms). The significance of each interaction effect was tested in separate models.

Significant interactions ($p < .05$) were probed using simple slope analyses. Simple slope analyses included plotting the adjusted slopes for four subgroups (e.g., paired combinations of

[12] The usual brand condition was not combined with the NNC control condition given the differential pattern of findings relative to the combined VLNC cigarette condition. As a number of factors may differentiate the usual brand and NNC control conditions (e.g., expectancy effects about nicotine content, different sensory characteristics, or other constituents in the tobacco), the moderation analyses focused on the a priori comparisons between the NNC cigarette alone and combined VLNC conditions.

study and control cigarettes with high and low levels on moderator) using the adjusted estimated means plots available via the plot subcommand in Mplus. For dichotomous moderators, the significance of the VLNC at the low and high level of the moderator were obtained from the original moderation analyses (i.e., VLNC effect at low level of moderator - when moderator is set to zero) and an additional analysis in which the moderator was reverse-coded (i.e., VLNC effect at high level of moderator – when reverse-coded moderator equals zero).

5.2 AIM 2: RESULTS

Descriptive statistics of the dichotomous moderating variables and corresponding cut-off values are summarized in Table 7.

Table 7. Proportion of participants endorsing "high level" of each moderator variable in each condition

	% female	% FTND > 5	% "High" coping motives[1]	% SMAST > 4
mg/g	VLNC Cigarette Conditions			
0.4	45	47	45	33
0.4 (HT)	46	45	44	21
1.3	45	38	50	22
2.4	37	42	42	28
All VLNC[2]	44	42	45	24
	Normal Nicotine Content Control Condition			
15.8	35	37	39	30

[1]The median value for drinking to cope motives was 0.2 (range 0 to 3.2). "High" coping motives was operationalized as a score greater than 0.2.
[2]All VLNC includes 0.4 mg/g, 0.4 mg/g (HT), 1.3 mg/g, and 2.5 mg/g conditions.

5.2.1 Individual Differences in Impact of VLNC Cigarettes on Alcohol Use

The results of the moderation tests of the relation between smoking VLNC cigarettes relative to the study cigarette control on alcohol use, adjusted for covariates, are summarized in Table 8.

Table 8. Moderators of effect of smoking VLNC cigarettes on drinking outcomes relative to the NNC control cigarette adjusting for covariates

Moderator	**Alcohol Use**		**Binge drinking**
	Slope 1	Slope 2	Slope 1
Gender	.13 (-.18, .39)	.15 (-.04, .30)	-.08 (-.38, .23)
FTND	.32† (-.01, .61)	-.14 (-.34, .03)	.37* (.01, .74)
Alcohol motives	-.11 (-.44, .20)	.18* (.01, .62)	-.06 (-.32, .34)
Baseline drinking	-.05 (-.18, .15)	.06 (-.21, .17)	.05 (-.07, .18)
SMAST	-.24 (-.63, .25)	.07 (-.24, .56)	.12 (-.22, .45)

Note. Unstandardized path coefficients (standard errors) are reported. Slope 1 corresponds with change during the first 2 weeks of the study; slope 2 corresponds with change during the last 4 weeks of the study. The binge drinking slope represented linear change throughout the duration of the study. Analyses control for gender, age, minority race/ethnicity, and baseline cigarettes per day and FTND score (without cigarettes per day item).
† $p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$

Given the piecewise functional form of alcohol use, the association of the interaction term was examined for both slopes (i.e., slope 1: change during first two weeks; slope 2: change during last four weeks).

When examining moderators of the effect of VLNC cigarettes on change in alcohol use, few moderators were identified. The moderated effect alcohol motives (slope 2: b = .18, 95% CI: .01, .62) reached statistical significance.[13] The simple slopes of the moderating effect of alcohol motives is depicted in Figure 11. During the last four weeks, for individuals with high drinking to cope motives, there was a marginally smaller reduction in alcohol use among individuals smoking the VLNC cigarettes than NNC cigarettes (b = .13, $p < .10$, 90% CI: .03,

[13] The analysis included a subset of participants who responded to these items (n = 302), which due to the computer skip algorithm, only included individuals who endorsed any alcohol use during the past month at the baseline visit.

.27). In contrast, among individuals with low drinking to cope motives, VLNC cigarette use was unrelated to changes in alcohol use (b = -.05, p > .10, 95% CI: -.19, .08).

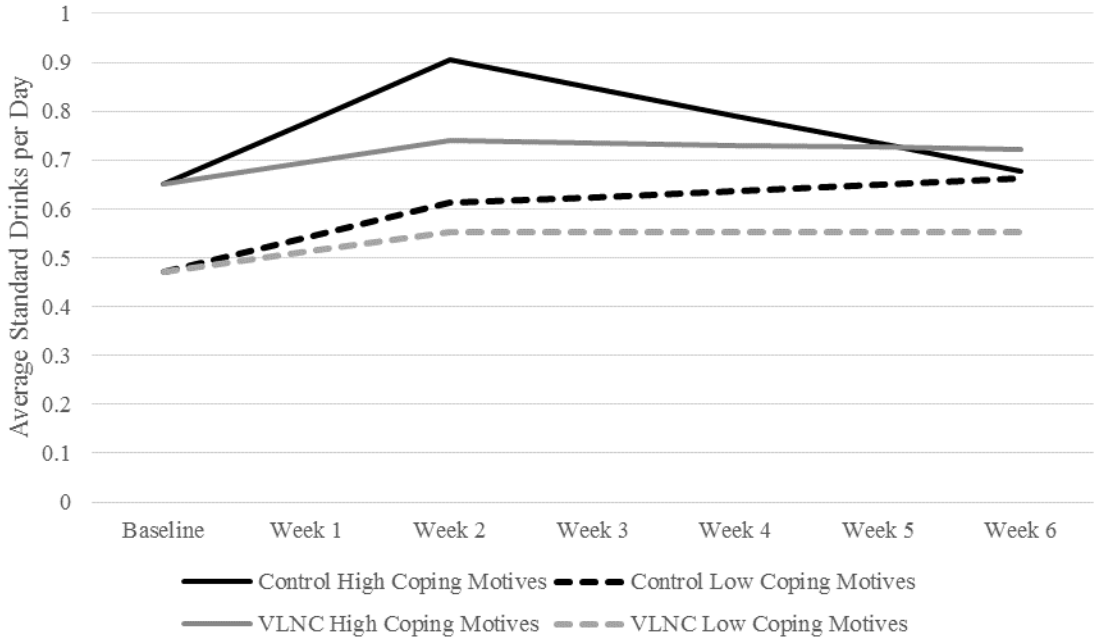


Figure 11. The effect of VLNC cigarettes on alcohol use is moderated by drinking to cope motives

There was also a trend for a moderated effect of baseline FTND score on changes in alcohol use during the first two weeks (slope 1: b = .32, $p < .10$, 95% CI: -.01, .61). While the effect was marginal, it was interpreted given the similar, but significant, moderation effect seen for binge drinking (described below). The simple slopes are depicted in Figure 12. During the first two weeks, individuals with relatively low FTND scores exhibited a significantly reduced rate of increase in alcohol use when smoking VLNC cigarettes relative to the NNC control (b = -.24, $p < .01$, 95% CI: -.47, -.01). In contrast, individuals with relatively high FTND scores showed no effect of smoking VLNC cigarettes on alcohol use (b = .16, $p > .10$, 95% CI: -.15, .41).

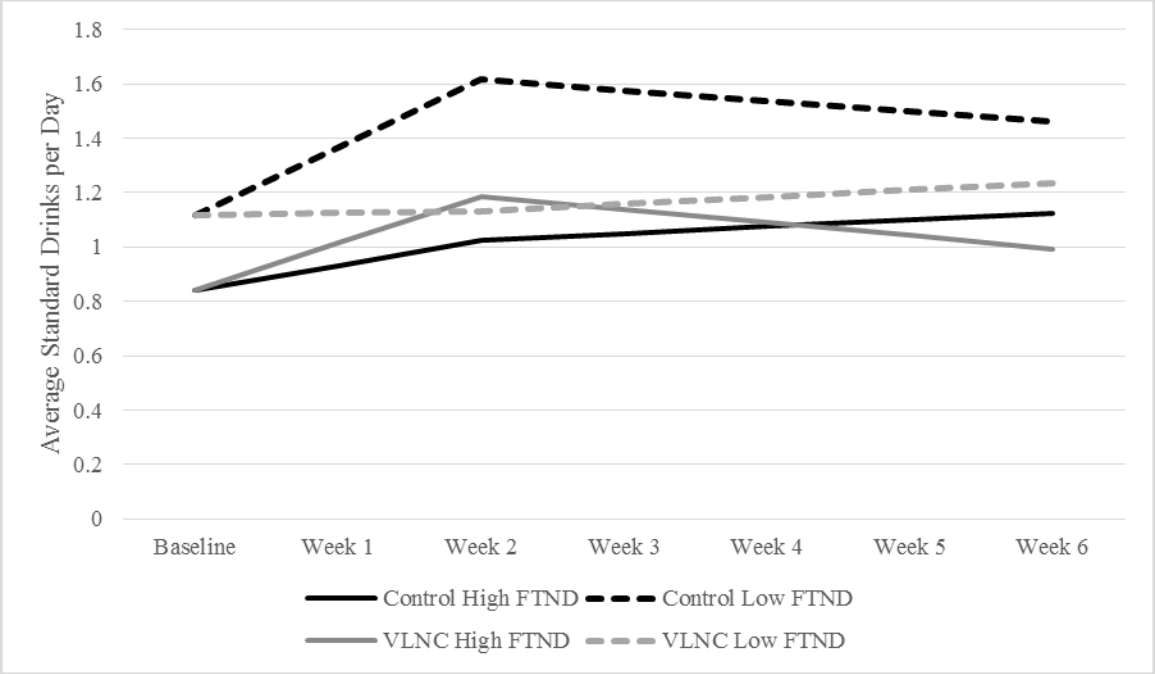


Figure 12. The effect of VLNC cigarettes on alcohol use is moderated by baseline nicotine dependence score

To better understand the moderating role of FTND score, exploratory analyses were conducted using additional indices of nicotine dependence. First, time to first cigarette smoked was examined as a moderator. Time to first cigarette is one of the FTND items which is believed to play an important role in the predictive ability of the FTND (Haberstick et al., 2007; Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989). The marginal moderating role of FTND score was replicated when examining a cut-off of smoking within 5 minutes of waking (b = .63, 90% CI: .08, .69).[14] That is, individuals who smoke within five minutes of waking (i.e., more dependent individuals) did not change their drinking in response to VLNC cigarettes; whereas, individuals who smoke after five minutes of waking (i.e., less dependent individuals)

[14] The cut-off was chosen based on a median split. The item responses included after 60 minutes (response for 10% of sample), 31 – 60 minutes (16% of sample), 6 – 30 minutes (38% of sample), and within 5 minutes (36% of sample).

showed a relative decrease in alcohol use during the first two weeks when smoking VLNC cigarettes as opposed to NNC cigarettes. Second, the total score on the Wisconsin Inventory of Smoking Dependence Motives (WISDM; Piper et al., 2008), another measure of dependence, was examined as a moderator using a median split (median = 40.5). WISDM score was not a significant moderator of the effect of VLNC cigarettes on change in alcohol use during the first two weeks (b = .17, p > .10, 95% CI: -.13, .45) or last four weeks (b = -.05, p > .10, 95% CI: -.21, .13).

Several moderated effects were not supported. Specifically, the interaction terms with gender, and baseline alcohol use levels, and alcohol dependence symptoms (SMAST), were not significantly associated with either alcohol use slope (p's > .10).

5.2.2 Individual Differences in the Impact of VLNC Cigarettes on Binge Drinking

The results of the moderation tests of the relation between smoking VLNC cigarettes relative to NNC control cigarette on binge drinking, adjusted for covariates, are summarized in Table 8. The results describe the association of each interaction term with the linear change in binge drinking occurrence.

The only supported moderating individual difference factor was baseline FTND (p = .046). The simple slopes are depicted in Figure 13.

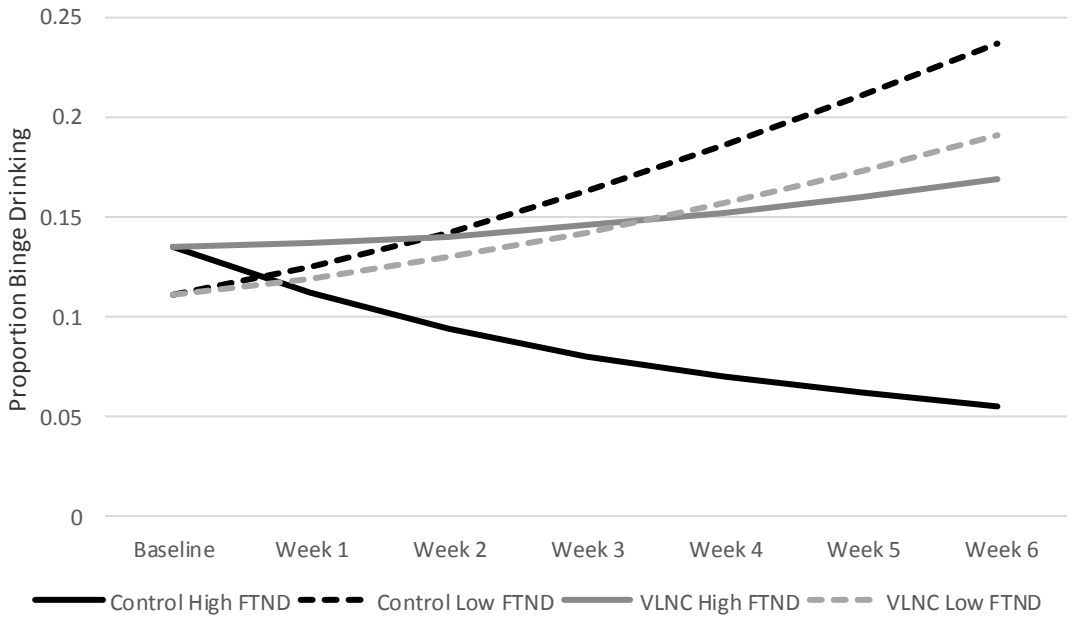


Figure 13. The effect of VLNC cigarettes on alcohol use is moderated by baseline nicotine dependence score

Specifically, the simple slopes suggested that for relatively less nicotine dependent individuals there was no difference in the change in binge drinking slope between VLNC cigarette and NNC conditions (b = -.07, p = .42). In contrast, there was a marginal effect among individuals with relatively high FTND scores (b = .31, SE = .17, p = .06). Specifically, high-FTND individuals who smoked VLNC cigarettes exhibited a marginal increase in binge drinking during the study relative to individuals who smoked NNC cigarettes.

The moderating role of nicotine dependence, however, was not replicated with alternative indicators of dependence. Although the effects were in the same direction, differential effects of VLNC cigarettes on changes in binge drinking were not statistically significant for individuals who smoke their first cigarette within five minutes of waking (b = .49, SE = .37, p = .18) or for higher dependence level based on WISDM total score (b = .20, SE = .15, p = .18).

The interaction terms with gender, and baseline alcohol use levels, alcohol dependence symptoms, and alcohol motives were not significantly associated with the binge drinking slope (*p*'s .40 - .65).

5.3 AIM 2: SUMMARY

The hypothesis that the effect of VLNC cigarettes on alcohol outcomes is moderated by nicotine dependence, assessed by the FTND, was supported. Nicotine dependence moderated the association of VLNC cigarette use on both alcohol use and binge drinking. Among less nicotine dependent individuals, VLNC cigarette use significantly reduced alcohol use during the first two weeks. There was no effect of VLNC cigarette use on binge drinking. In contrast, among more nicotine dependent individuals, there was no effect of VLNC cigarettes on alcohol use; however, when examining binge drinking, VLNC cigarette use was associated with a significant increase in binge drinking relative to smoking NNC cigarettes.

No additional moderators were systematically supported. Thus, it appeared that the effect of VLNC cigarettes on alcohol outcomes was not moderated by gender, baseline drinking level, history of problem drinking, or drinking to cope motives.

6.0 AIM 3: THE PROCESSES UNDERLYING THE EFFECTS OF VLNC CIGARETTES ON ALCOHOL OUTCOMES

Lastly, a goal of this investigation was to determine if VLNC cigarette influenced alcohol outcomes through several hypothesized intermediate processes: Nicotine exposure, cigarette smoking, and withdrawal. Specifically, it was hypothesized that VLNC cigarette use would reduce nicotine exposure and cigarettes per day, which, in turn, would reduce alcohol use and binge drinking. The role of cigarettes per day, however, may not emerge until the later time points in the study because reductions in cigarettes per day in response to VLNC cigarette use tend to be delayed. At the same time, however, VLNC cigarettes may increase withdrawal symptoms that could, in turn, increase drinking as ways of coping with the withdrawal.

Finally, select moderated mediation models were investigated to determine if these process vary based on individual difference factors believed to impact (1) sensitivity to nicotine reduction, and in turn, the relation between nicotine and alcohol outcomes (i.e., gender, nicotine dependence, history of alcohol problems); (2) risk for experiencing withdrawal, and in turn, the risk for self-medication withdrawal by drinking (i.e., gender, drinking to cope motives, history of alcohol problems, nicotine dependence); (3) and the ability of cigarettes to act as a cue to drink (i.e., gender, history of problem drinking).

6.1 AIM 3: STATISTICAL ANALYSES

Mediation analyses were conducted to examine the extent to which VLNC cigarettes impacted intermediate processes of interest (i.e., nicotine exposure, withdrawal, and cigarette smoking), and in turn, the extent to which the intermediate processes impacted drinking. Initially, each mediator was tested separately. The effect of each mediator was determined by taking the product of the effect of VLNC cigarettes on change in mediator (i.e., alpha pathway) with the effect of the change in mediator on the alcohol outcome (i.e., beta pathway). To estimate the statistical significance of the mediated effect, a bootstrapping method was implemented. This method estimated a 95% confidence interval that takes into account nonnormality of the distribution of the mediated effect (MacKinnon, Lockwood, & Williams, 2004).

Change in nicotine exposure was examined as a mediator by investigating if changes in TNE in response to VLNC cigarette use corresponded with concurrent changes in alcohol use or binge drinking. Change in TNE was examined as a mediator in two ways. One method involved using observed TNE (level of nicotine biomarkers), controlling for baseline TNE. The second method used percent reduction in TNE relative to baseline (i.e., [baseline TNE – experimental TNE]/[baseline TNE]). Specifically, percent change in TNE relative to baseline was calculated to correspond with each alcohol slope term (e.g., percent change during first two week, last four weeks, or across entire six week period).

Changes in withdrawal and cigarettes per day were tested as mediators using parallel process models. Parallel process models simultaneously estimate the latent growth curves of the mediator and alcohol outcome, which allows for estimating the relations between concurrent changes in the mediator and outcome (Cheong, MacKinnon, & Khoo, 2003). The parallel process models required two analytic steps. First, a latent growth curve was fit to the repeated

measures of the mediators. If model fit was acceptable, the same trajectory shape was chosen for the mediator as the dependent variable. Second, the parallel process model was estimated. The estimated model involved examining the effect of VLNC cigarettes on the trajectory of the mediator, and in turn, the relation of the trajectory of the mediator with the alcohol outcome. As the specific pathways examined depended on the chosen trajectory shape of the mediators and outcome, the specific estimated pathways that were estimated and why are described in the results section below.

For each mediation analysis, specific moderated mediation pathways were investigated using the approach outlined by Preacher et al (2007). The moderation analyses were identical to the prior moderation analyses with a few exceptions. First, moderators of the pathway from VLNC cigarette use to the mediator, and in turn, the mediator to the dependent variable were examined simultaneously. Second, product terms between observed variables and latent variables were created using the Mplus xwith command (e.g., moderating effect of nicotine dependence on the relation between the latent withdrawal slope and alcohol use slope). All other steps were identical to the aforementioned moderation analyses.

Lastly, significant mediators were examined together in one model. Examining the mediators in one model allowed for examining to what extent the processes are independent from each other. The specific models examined were based on the mediating processes that were supported, and thus, are described in detail in the Results section.

6.2 AIM 3: RESULTS: MEDIATING ROLE OF NICOTINE EXPOSURE

6.2.1 Alcohol Use

The model used to test the mediating role of observed nicotine biomarkers (TNE) in the effect of VLNC cigarettes on alcohol use is depicted in Figure 14.[15] Due to the piecewise trajectory in alcohol use, two mediation pathways were tested. The first pathway was comprised of the effect of VLNC cigarettes on Week 2 TNE, and in turn, the relation of Week 2 TNE with changes in alcohol use during the first two weeks (i.e., Slope 1 Alcohol). The second pathway examined the mediating role of TNE at Week 6 in changes in alcohol use during the last four weeks (i.e., Slope 2 Alcohol).

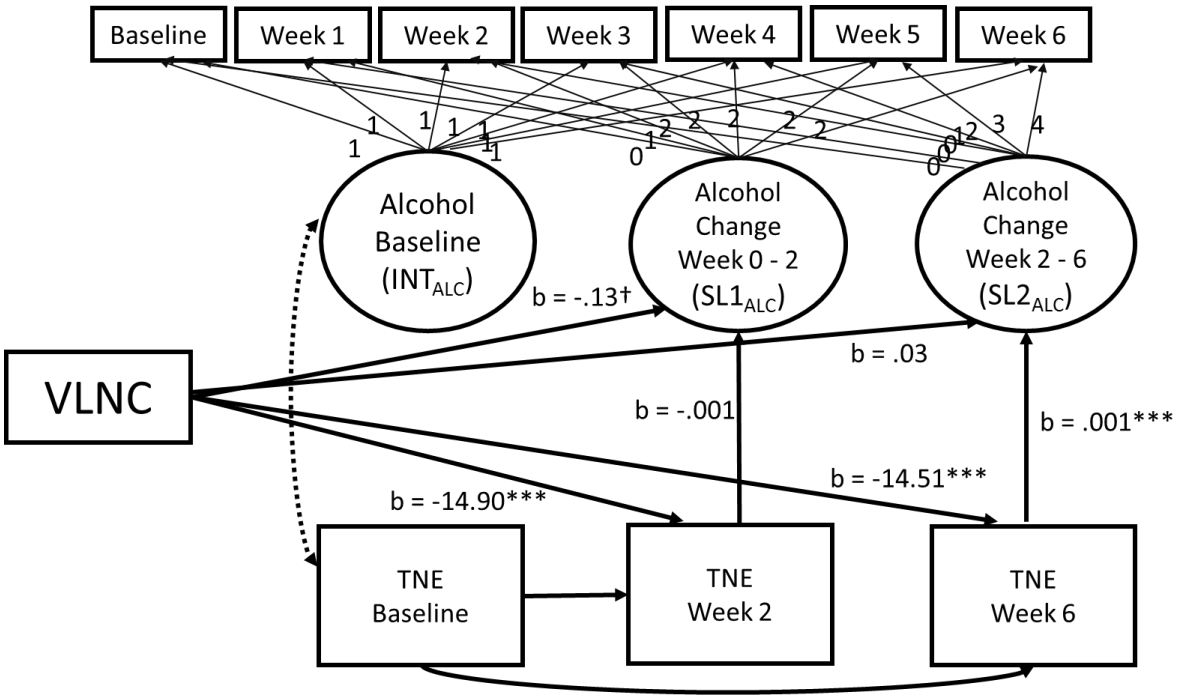


Figure 14. The mediating role of nicotine exposure in the effect of VLNC cigarette use on alcohol use

[15] The analyses excluded 5 individuals with missing or baseline total nicotine equivalents less than 3, which is lower than would be expected for a daily smoker (TNE < 3). Thus, it is suspected that may have been former, light/non-daily, or non-smokers.

TNE at Week 2 did not significantly mediate the relation between VLNC cigarettes and initial changes in alcohol use. While VLNC cigarette use was associated with significantly lower TNE at Week 2 (b = -14.90, $p < .001$; see observed TNE values in Figure 15), TNE was not, in turn, associated with changes in alcohol use (b = -.001, $p > .10$).

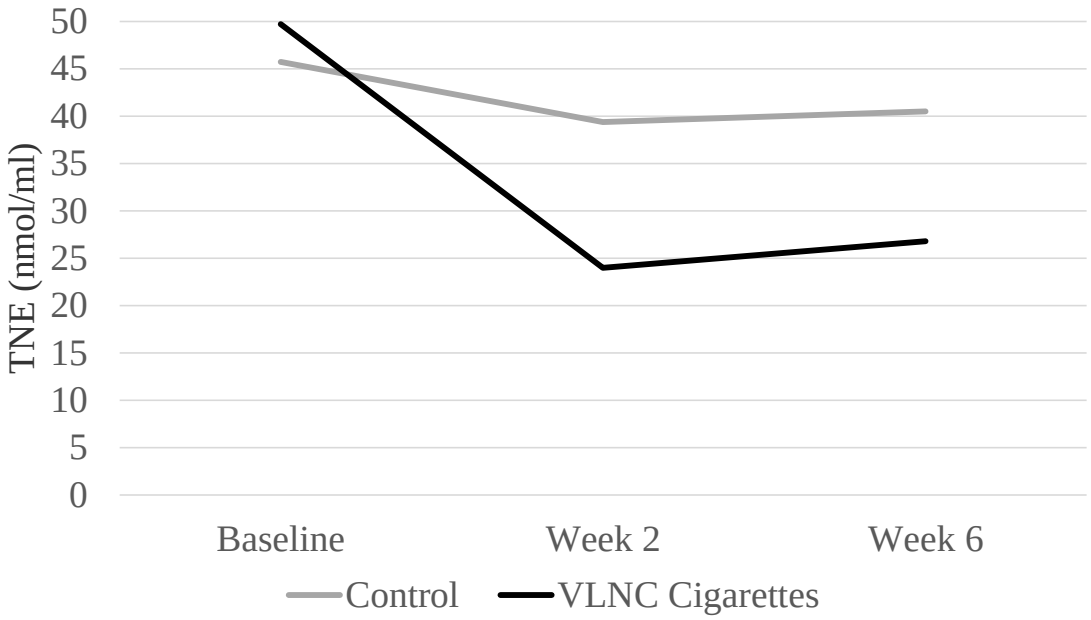


Figure 15. TNE levels for individuals assigned to smoke VLNC or NNC cigarettes

TNE at Week 6, however, significantly mediated the effect of VLNC cigarettes on changes in alcohol use during the last four weeks. VLNC cigarette use was associated with significantly lower Week 6 TNE ($\alpha = -14.51$, $p < .001$; see observed Week 6 TNE in Figure 15). Lower Week 6 TNE was, in turn, significantly associated with smaller increases in alcohol use from Week 2 to Week 6 ($\beta = .001$, $p < .001$). The significant pathways corresponded with a significant mediating effect ($\alpha\beta = -.02$, $p < .05$, 95% CI: -.04, -.001).

Using moderated mediation analyses, gender, nicotine dependence level, and history of problem drinking were not significant moderators of the mediated effect. While each of these factors appeared to moderate the association between VLNC cigarette use on TNE at Week 2

and Week 6 (*p's* < .001), the factors did not moderate the relations between TNE and alcohol use (*p*'s > .10). Lower TNE levels at Week 2 and Week 6 following VLNC cigarette use relative to NNC cigarette use were seen for females, and individuals who were more nicotine dependent, and individuals who did not have a history of problem drinking.

A different pattern of findings was supported when examining the same mediating pathways but with percent reduction in TNE, not absolute level of TNE, as the mediating variable. The results are depicted in Figure 16.

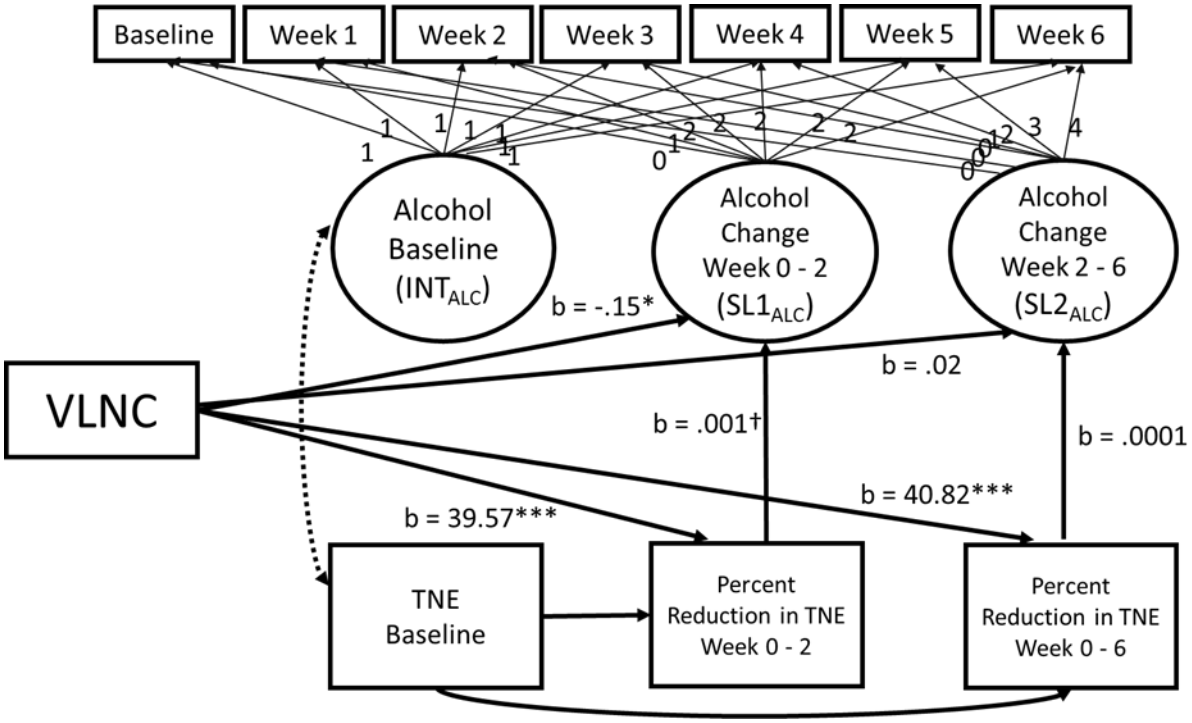


Figure 16. The mediating role of percent reduction in nicotine exposure in the effect of VLNC cigarette use on alcohol use

Again, percent reduction in nicotine biomarkers did not appear to mediate the effect of VLNC cigarettes on change in nicotine exposure from baseline to Week 2. While VLNC cigarette use was associated with a greater reduction in TNE from baseline to Week 2 (α = 39.57, *p* < .001; see observed values in Figure 17), a greater percent reduction in TNE was marginally associated

with an *increase* in alcohol use from baseline to Week 2 (β = .001, $p < .10$). As the latter effect was not significant, a mediating pathway was not supported (αβ = .03, 95% CI: -.02, .08).

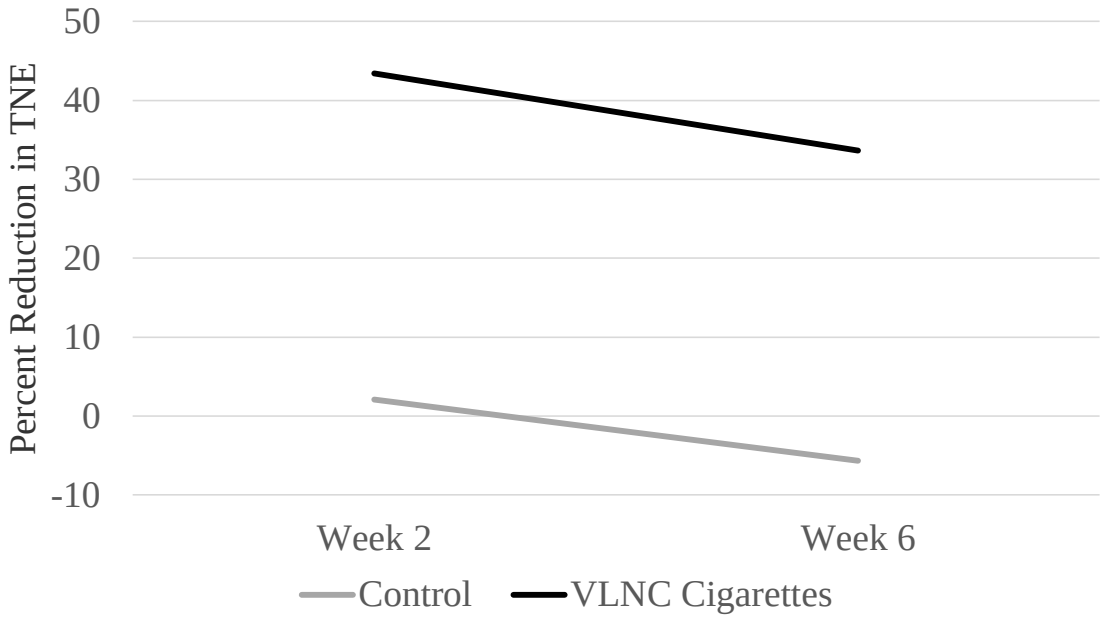


Figure 17. Percent reduction in TNE levels relative to baseline for individuals assigned to smoke VLNC or NNC cigarettes

Percent reduction in TNE was also not a significant mediator of the effect of VLNC cigarettes on change in alcohol use from Week 2 to Week 6. While VLNC cigarette use corresponded with a greater reduction in TNE from baseline to Week 6 (α = 40.82, $p < .001$), this percent reduction in TNE, in turn, was unrelated to changes in alcohol use (β = .0001, $p > .10$). As the second pathway was not supported, a mediating pathway was not identified.

Using moderated mediation analyses, gender, nicotine dependence level, and history of problem drinking were not significant moderators of the mediated effect. While each of these factors appeared to moderate the association between VLNC cigarette use on percent reduction in TNE at Week 2 and Week 6 (*p's* < .001), the factors did not moderate the relations between TNE and alcohol use (*p*'s > .10). A greater percent reduction in TNE was seen for individuals

who were less nicotine dependent (as opposed to more nicotine dependent), who had a history of problem drinking, or who were male.

6.2.2 Binge Drinking

The model testing the mediating role of TNE in the effect of VLNC cigarettes on binge drinking is depicted in Figure 18.

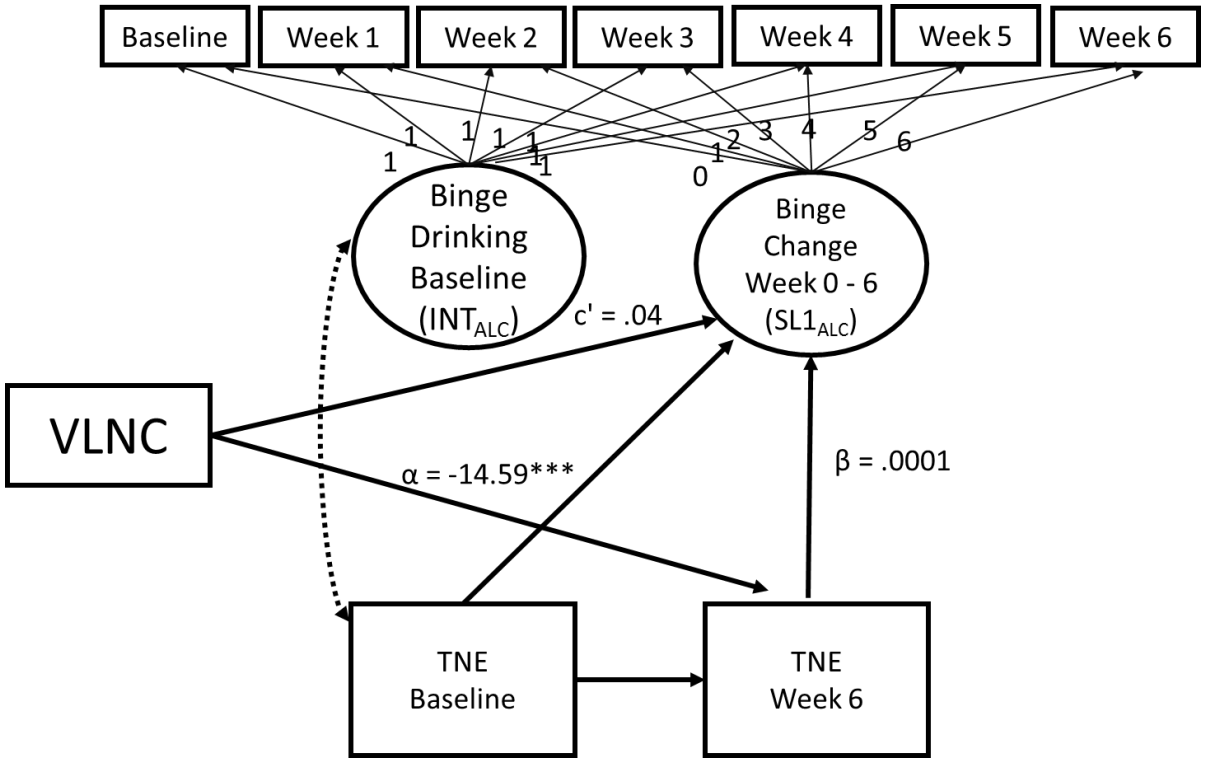


Figure 18. The mediation role of nicotine exposure in the effect of VLNC cigarette use on binge drinking

TNE at Week 6 did not mediate the effect of VLNC cigarette use on binge drinking. VLNC cigarette use was unrelated to change in binge drinking during the 6 week study (c' = .05, p > .10), consistent with aforementioned analyses. There was also no indirect effect of VLNC cigarette use on change in binge drinking, as Week 6 TNE was not significantly associated with change in binge drinking (β = .0001, p > .10).

When nicotine dependence level, history of problem drinking, and gender were examined as moderators of the mediation pathway, the only supported moderator was nicotine dependence level. Specifically, nicotine dependence level (assessed by FTND) moderated both the association between VLNC cigarette use and Week 6 TNE (b = 9.56, p = .03), as well as the association between Week 6 TNE and change in binge drinking from baseline to Week 6 (b = -.007, p = .02). Simple slope analyses demonstrated that for less nicotine dependent individuals, VLNC cigarette use was associated lower Week 6 TNE than the normal nicotine content control (α = -11.55, p < .001), and in turn, lower TNE was marginally associated with reductions in binge drinking (β = .004, p < .10, 90% CI: .001, .01). This corresponded with a marginal mediated effect such that VLNC cigarette use reduced binge drinking via lower levels of nicotine biomarkers ($\alpha\beta$ = -.04, 90% CI: -.10, -.001). In contrast, among more nicotine dependent individuals, VLNC cigarette use was also associated with even lower TNE relative to NNC cigarette use (α = -19.07, p < .001). Lower nicotine biomarker levels were, in turn, marginally related to an *increase* in binge drinking relative to normal nicotine content control (β = -.003, p < .10, 90% CI: -.01, -.001). This corresponded with a significant mediating effect in the opposite direction as was seen for less dependent individuals ($\alpha\beta$ = .06, p < .05, 95% CI: .003, .18).

Percent reduction in TNE did not mediate the relation between VLNC cigarette use and binge drinking (see Figure 19). While VLNC cigarette use was associated with a significantly larger percent reduction in TNE between baseline and Week 6 (α = 39.59, p < .001), this was not, in turn, associated with concurrent changes in binge drinking (β = .0001, p > .10). As a result, the mediation pathway through percent reduction in TNE was not supported.

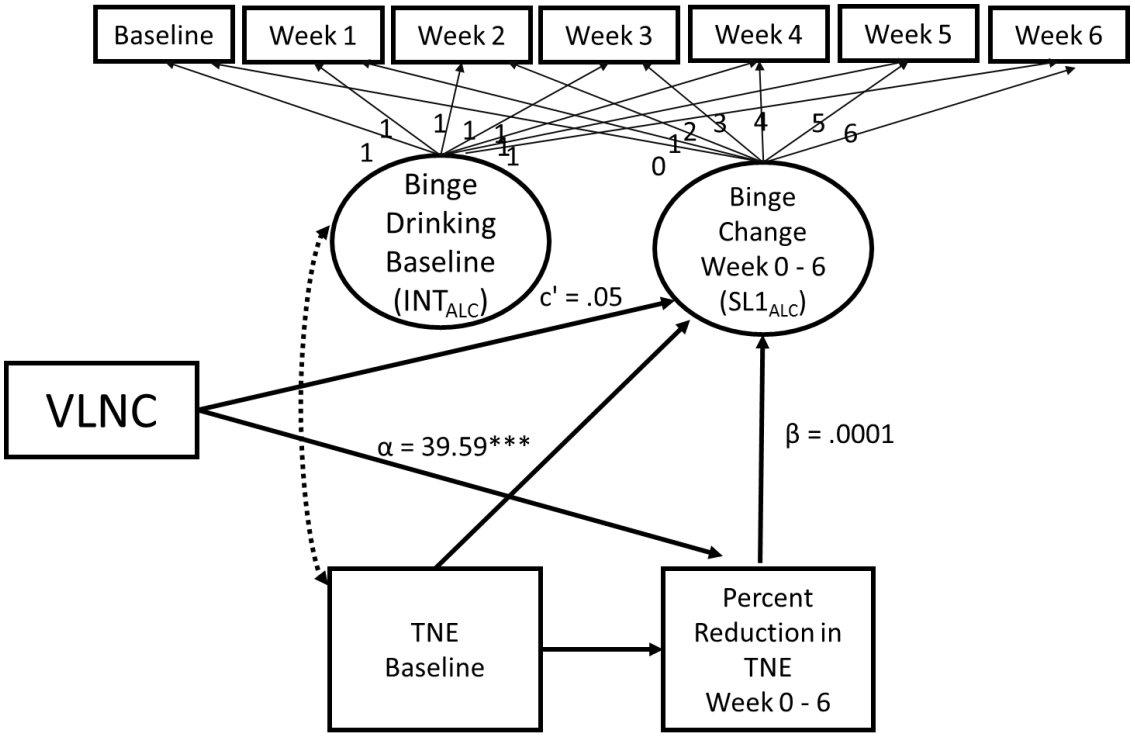


Figure 19. The mediation role of percent reduction in nicotine exposure in the effect of VLNC cigarette use on alcohol use

Again, when nicotine dependence level, history of problem drinking, and gender were examined as moderators of the mediation pathway, only nicotine dependence level was a significant moderator of the mediation pathway. Nicotine dependence level moderated the association between VLNC cigarette use and percent reduction in nicotine biomarkers (b = -.56, $p < .001$) and the association between percent reduction on change in binge drinking (b = .42, $p = .01$). For less nicotine dependent individuals, there was a significant mediated effect ($\alpha\beta$ = -.09, $p < .05$, 95% CI: -.23, -.002). Specifically, among less dependent individuals, VLNC cigarette use was associated a greater percent reduction in TNE during the 6-week study than normal nicotine content cigarette use ($\alpha = 55.67$, $p < .001$), and in turn, greater percent reduction in TNE was significantly associated with a reduction in binge drinking (β = -.002, $p < .05$). For more nicotine dependent individuals, VLNC cigarette was not associated with a significant percent

reduction in TNE (α = 14.22, 95% CI: -7.61, 34.10). Greater reductions in TNE, however, were marginally associated with an *increase* in binge drinking, as opposed to a decrease (β = .002, 90% CI: .001, .004). As a result, percent reduction in TNE did not appear to mediate the relation between VLNC cigarette use and binge drinking among highly dependent individuals (αβ = .03, 95% CI: -.01, .11).

6.3 AIM 3: RESULTS: MEDIATING ROLE OF WITHDRAWAL

When examining the mediating role of withdrawal, the change in withdrawal and alcohol outcomes was represented by an alternative latent growth model. The alternative latent growth model involved estimating the initial increase in withdrawal at Week 1, as opposed to the increase from Baseline to Week 2 (like what was done for the alcohol use outcome). This was accomplished by including baseline withdrawal as a covariate in the analyses, as opposed to including it as part of the growth process (see bottom half of Figure 20).

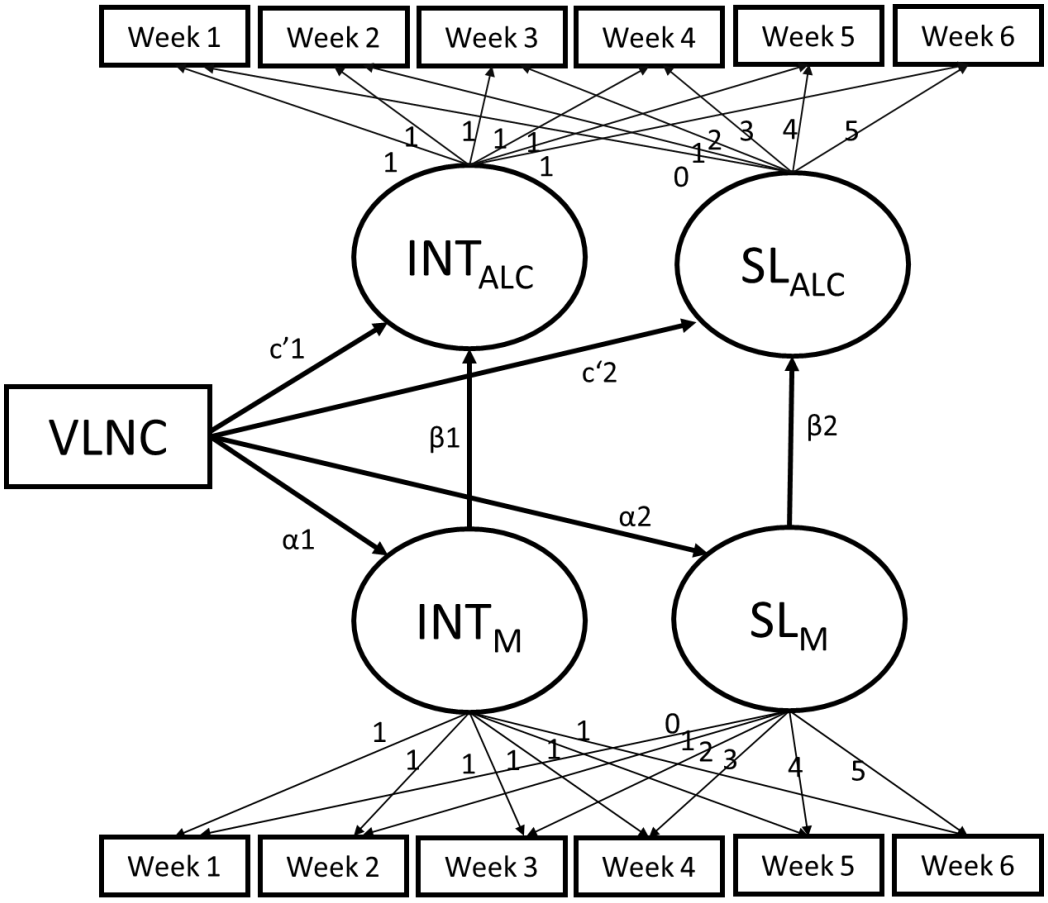
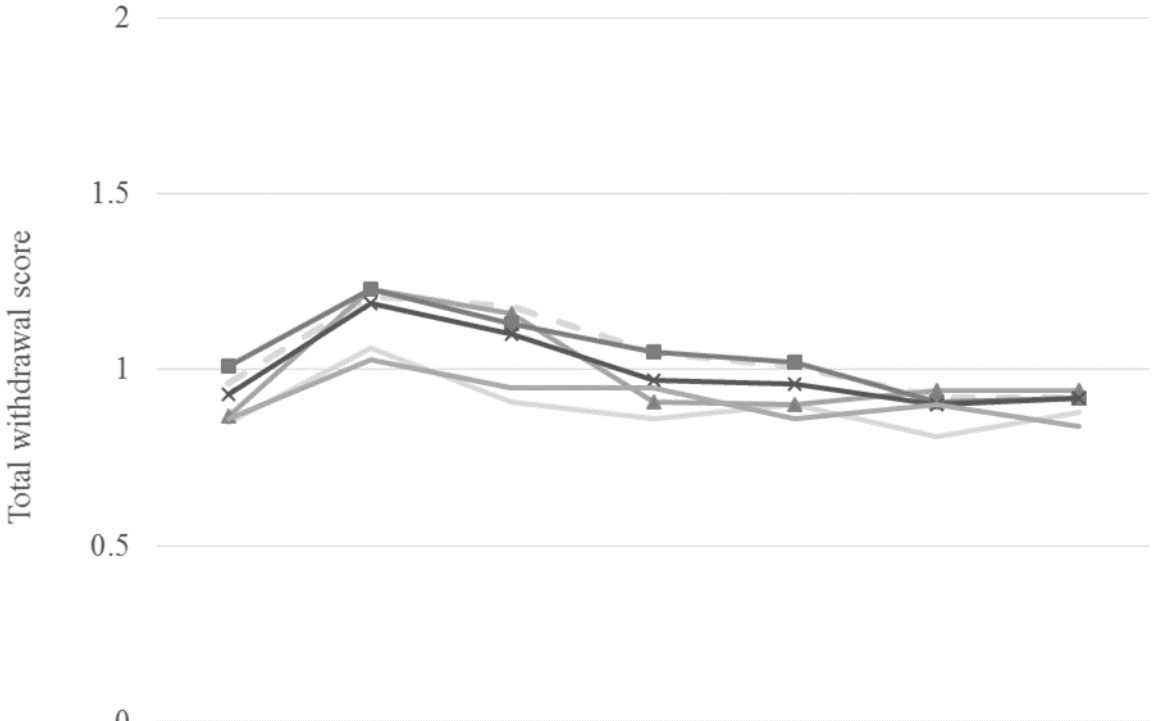


Figure 20. Alternative parallel process model testing the mediating pathways between VLNC cigarette use and alcohol outcomes

The rationale for using this alternative model was that withdrawal symptoms, as well as corresponding differences between the VLNC cigarette condition and control, peaked at Week 1 not Week 2[16] (see observed values in Figure 21).

[16] The observed withdrawal scores demonstrated that withdrawal tended to be higher at Week 1 than Week 2. This was confirmed when attempting to fit the piecewise growth curve model to the data as freeing the Week 1 factor loading significantly improved model fit.



	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
0.4-HT	0.96	1.21	1.18	1.05	1.01	0.92	0.92
0.4	0.85	1.06	0.91	0.86	0.9	0.81	0.88
1.3	0.87	1.23	1.16	0.91	0.9	0.94	0.94
2.4	1.01	1.23	1.13	1.05	1.02	0.91	0.92
VLNC	0.93	1.19	1.1	0.97	0.96	0.9	0.92
15.8	0.86	1.03	0.95	0.95	0.86	0.9	0.84

Figure 21. Observed values of withdrawal by condition

As a result, examining change in withdrawal from baseline to Week 2 with a piecewise model would likely underestimate any initial compensatory drinking that would occur in response to withdrawal (see estimated piecewise trajectory in Figure 22 for example of underestimation issue).[17] In contrast, the alternative model maximized the precision in estimating the levels of

[17] A piecewise latent growth curve model with an inflection point at Week 1, as opposed to Week 2 in the original analyses, would not be possible due to model non-identification. Specifically, three or more observations are needed to identify a linear slope in latent growth curve models.

the mediator and alcohol outcomes at Week 1, as it is estimated directly as the intercept, and the slopes represent the change after Week 1.

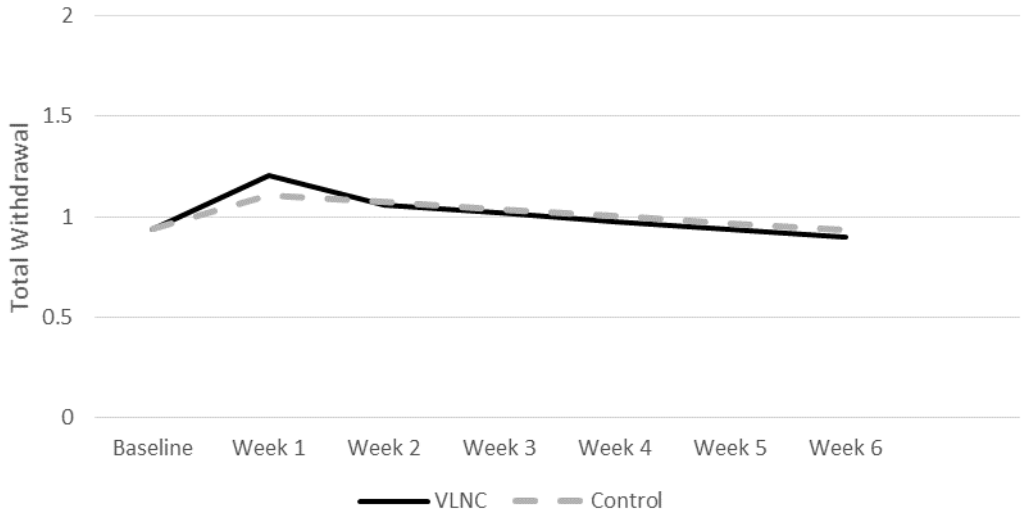


Figure 22. Depiction of underestimation of VLNC cigarette effects on withdrawal when including baseline levels in growth model

From Week 1 to Week 6, both withdrawal and the alcohol outcomes exhibited linear change. A linear latent growth model adequately fit the total withdrawal outcome from Week 1 to Week 6 (depicted in Figure 23; $\chi^2 = 22.40$, $p = .13$; RMSEA = .04, 90% CI: .001 - .07, CFI = .99, TFI = .99).

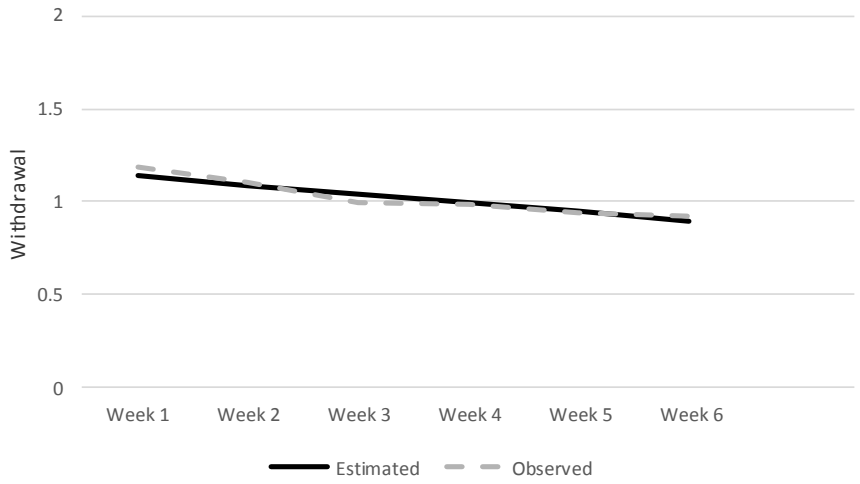


Figure 23. Best fitting trajectory shape for changes in withdrawal relative to the observed values

The average withdrawal score at Week 1 was 1.14 (p < .001), and, on average, this score decreased during the following 5 weeks (b = -.05, SE = .01, p < .001). Similarly, for alcohol use and binge drinking trajectories, the best fitting trajectory shape was linear (see Table 9).

Table 9. Model fit and estimates for examined trajectory shapes without baseline levels for alcohol use and binge drinking outcomes

	Linear	Quadratic	Piecewise	Selected Model
		Alcohol use		
Fit Indices	X^2 = 38.71 p = .001 RMSEA = .07 (.04, .09) CFI = .98; TLI = .98 AIC = 5956; BIC = 5998	X^2=29.06 p = .004 RMSEA = .07 (.04, .10) CFI = .99; TLI = .98 AIC 5954; BIC 6011	X^2=30.64 p = .002 RMSEA = .07(.04, .10) CFI = .98; TLI = .98 AIC = 5956; BIC = 6013	Linear (due to non-significant chi-square; lower RMSEA, AIC, BIC; and CFI and TLI closer to 1).
Parameter Estimates[1]	Int 1.20** (1.04,1.42) Int Var 2.21** (1.19,3.27) Sl1 -.01 (-.04, .02) Sl1 Var .02 (-0.003,0.05)	Int 1.21** (1.05, 1.46) Int Var 2.46** (1.26, 4.18) Sl1 -.02 (-.11, .07) Sl1 Var .23 (-.21, .56) Sl2 .003 (-.01, .02) Sl2 Var .007 (-.003, .02)	Int 1.21** (1.04, 1.45) Int Var 2.47** (1.32, 4.20) Sl1 -.02 (-.10, .04) Sl1 Var .14 (-.09, .34) Sl2 .002 (.01, .04) Sl2 Var .06* (.01, .11)	
		Binge Drinking		
Fit Indices	X^2 = 80.31 p = .03 AIC 1462; BIC 1481	X^2=83.13 p = .01 AIC 1468; BIC 1503	X^2=78.63, p = .02 AIC 1469; BIC 1504	Linear (due to smaller AIC, BIC; and non-significant slopes or variance terms for more complex trajectory shapes).
Parameter Estimates	Int 2.61*** (2.06, 3.17) Int Var 3.74** (1.37, 6.11) Sl1 -.04 (-.22, .13) Sl1 Var .16* (.01, .31)	Int 2.91*** (1.91, 3.91) Int Var 5.52* (.06, 10.98) Sl1 .13 (-.66, .91) Sl1 Var 1.03 (-.80, 2.86) Sl2 -.03 (-.17, .12) Sl2 Var .03 (-.03, .09)	Int 2.57*** (1.66, 3.47) Int Var 3.56† (-.65, 7.77) Sl1 -.11 (-.69, .46) Sl1 Var .24 (-.58, 7.77) Sl2 .02 (-.33, .37) Sl2 Var .14 (-.20, .48)	

Note. Parameter estimates include intercept (Int) and slope (Sl) terms, and their corresponding variances (Var). The intercept is estimated at Week 1. For quadratic trajectories, Sl1 corresponds with the linear change and Sl2 corresponds with quadratic change. For piecewise trajectories, Sl1 corresponds with the linear change from Week 1 to 3, and Sl2 corresponds with the linear change from Week 4 to 6.
*† p < .10; *p < .05; **p < .01; ***p < .001*

For alcohol use, on average, participants consumed 1.20 standard drinks per day during Week 1 (int = 1.20, p < .001), and there was no change in levels of alcohol use from Week 1 to Week 6 (slope = -.01, p > .10). For binge drinking, 16% of the sample reported binge drinking during Week 1, and rates of binge drinking did not significantly change between Week 1 and Week 6 (b = -.04, p = .64).

Given the linear change in both the mediating and outcome processes, the mediating effects were estimated using the parallel process model depicted in Figure 20. The model depicts two mediation pathways for withdrawal. The first mediating pathway for withdrawal involved the effect of VLNC cigarettes on Week 1 withdrawal, and in turn, the association of Week 1

withdrawal on Week 1 alcohol outcome (controlling for baseline levels of smoking and the alcohol outcome). Second, the effect of VLNC cigarettes on changes in withdrawal from Week 1 to Week 6 was examined, and in turn, the relation of those changes in withdrawal with changes in alcohol outcome from Week 1 to Week 6.

When examining alcohol use, withdrawal was not supported as a mediator.[18] Specifically, at Week 1, VLNC cigarettes were not associated with withdrawal (α_1 = .06, p > .10, 95% CI: -.08, .17), and in turn, withdrawal was not associated with alcohol use (β_1 = .22, p > .10, 95% CI: -.04, .50). Similarly, when examining changes in the mediator and alcohol use from Week 1 to Week 6, VLNC cigarette use was unrelated to change in withdrawal (α_2 = -.01, p > .10, 95% CI: -.04, .02) and change in withdrawal was not associated with concurrent changes in alcohol use (β_2 = .22, p > .10, 95% CI: -.17, .70). Taken together, on average, the effect of VLNC cigarettes on alcohol use did not appear to be mediated by withdrawal.

No moderated mediation pathways were supported. The examined moderators included nicotine dependence level, history of problem drinking, gender,[19] and drinking to cope motives. None of these variables significantly moderated the relation between VLNC cigarettes and withdrawal. As a result, it did not appear that any of these subgroups experienced elevated withdrawal symptoms in response to VLNC cigarette use that would, in turn, lead to self-medication by drinking.

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[18] The pattern of findings was identical when baseline levels of alcohol use and withdrawal were included in the growth process. Specifically, the resulting trajectories for withdrawal and alcohol use were both piecewise functions. Changes in withdrawal during the first two weeks and last four weeks did not mediate the effect of VLNC cigarette use on alcohol use.

[19] The moderating effect of gender on the relation between VLNC cigarette use and withdrawal was marginal. Men appeared to exhibit marginal increase in withdrawal during the first week when smoking VLNC cigarettes relative to NNC cigarettes; whereas, for women, there was no significant difference in Week 1 withdrawal between VLNC cigarette and NNC cigarettes.

For the binge drinking model, withdrawal was also not supported as a mediator. VLNC cigarette use was unrelated to Week 1 withdrawal (α_1 = .07, SE = .06, p = .24) or changes in withdrawal between Week 1 and 6 (α_2 = -.01, SE = .02, p = .44).[20] Furthermore, withdrawal at Week 1 was not associated with Week 1 binge drinking (β_1 = .07, SE = .06, p = .24) and changes in withdrawal in the following weeks was unrelated to concurrent changes in binge drinking (β_2 = -.45, SE = .58, p = .44). As a result, neither mediation pathway through withdrawal was supported.

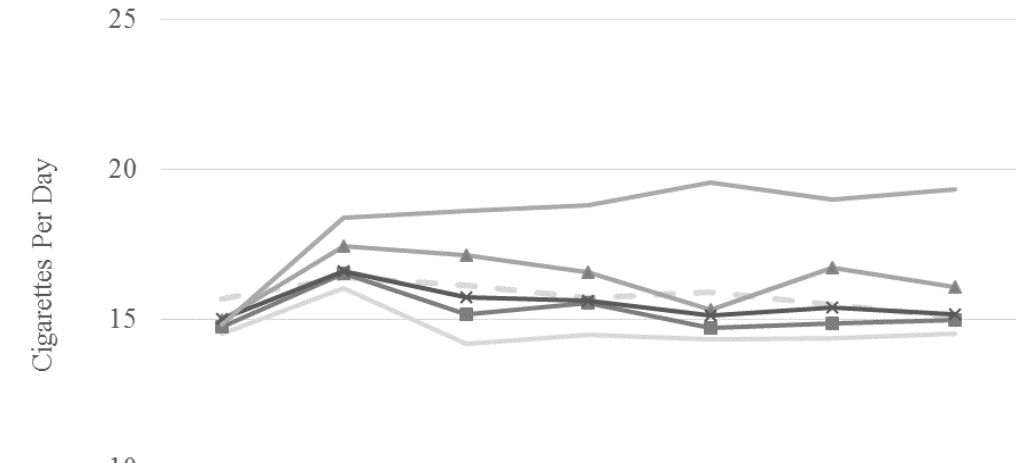
Again, like what was seen for alcohol use, moderated mediation was not supported because none of the examined variables (nicotine dependence level, history of problem drinking, gender, and drinking to cope motives) moderated the relation between VLNC cigarettes and withdrawal.

6.4 AIM 3: RESULTS: MEDIATING ROLE OF WITHDRAWAL

Like with withdrawal, the alternative latent growth curve model was used to examine the effect of VLNC cigarette use on change in cigarettes per day over time (observed values are depicted in Figure 24) and, in turn, the effect of cigarettes per day on alcohol outcomes.[21]

[20] The results were identical when baseline levels of binge drinking and withdrawal were included in the growth process. This involved examining the mediated effect of changes in withdrawal during the first two weeks and last four weeks on the linear change in binge drinking (from baseline to Week 6).

[21] When including baseline cigarettes per day in the growth model, model modification indices indicated that cigarettes per day at Week 1 significantly deviated from the estimated trajectory. While freeing the Week 1 factor loading led to mediator models with acceptable fit, a consequence of this approach was that the initial increase in cigarettes per day was underestimated.



	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
0.4-HT	15.66	16.39	16.12	15.7	15.9	15.49	15.06
0.4	14.52	16.01	14.17	14.46	14.32	14.37	14.51
1.3	14.98	17.45	17.14	16.57	15.31	16.71	16.07
2.4	14.75	16.53	15.17	15.55	14.71	14.85	14.96
VLNC	15.02	16.61	15.73	15.61	15.12	15.39	15.17
15.8	14.81	18.38	18.6	18.8	19.55	19	19.35

Figure 24. Observed values of total cigarettes per day (study + non-study) by condition

Change from Week 1 (intercept) to Week 6 appeared to be linear and is depicted in Figure 25 (acceptable model fit: $\chi^2 = 40.98$, $p < .001$; RMSEA = .07, 90% CI: .046 - .10, CFI = .98, TFI = .98). On average, participants smoked 16.52 cigarettes per day at Week 1 ($p < .001$). Cigarettes per day did not significantly change from Week 1 to Week 6 (b = -.08, SE = .06, $p = .15$).

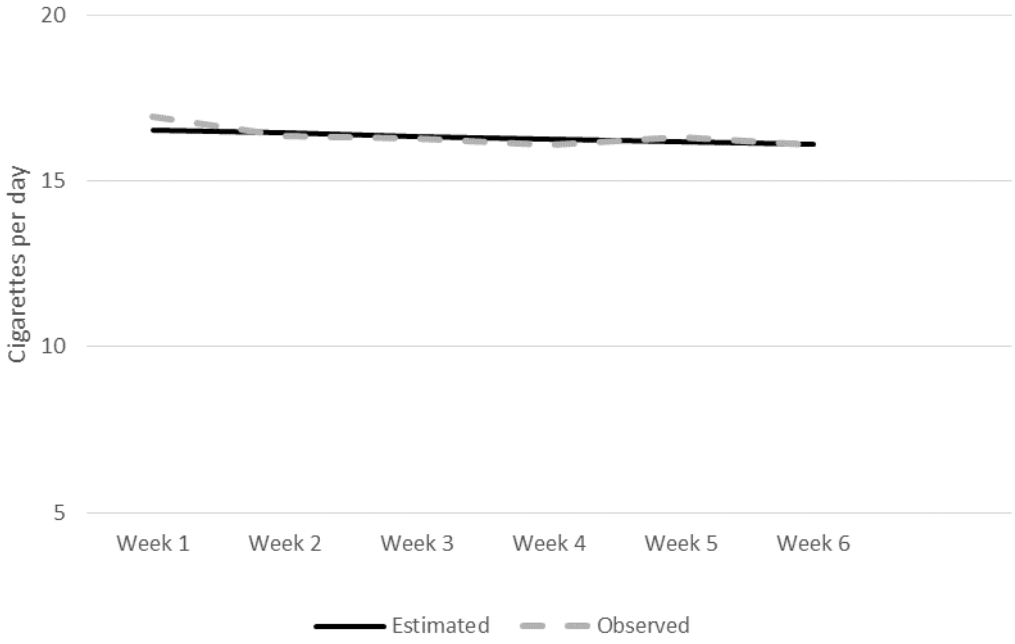


Figure 25. Best fitting trajectory shape for changes in cigarettes per day relative to the observed values.

Cigarettes per day appeared to mediate the relation between VLNC cigarette use and alcohol use, but only after Week 1. Like with withdrawal, the mediation pathways were estimated using the parallel process model depicted in Figure 20. At Week 1, mediation was not supported. VLNC cigarette use corresponded with a significant decrease in smoking level at Week 1 relative to the NNC control cigarette (α_1 = -2.01, p < .01, 99% CI: -3.78, -.31). Fewer cigarettes per day at Week 1 were not, in turn, associated with lower alcohol use levels at Week 1 (β_1 = .02, p > .10, 95% CI: -.10, .05). When examining mediation from Week 1 to Week 6, VLNC cigarettes predicted a reduction in smoking levels relative to NNC control cigarettes (α_2 = -.67, p < .01, 99% CI: -1.12, -.24). Furthermore, reductions in cigarettes per day corresponded with significant reductions in alcohol use during Weeks 1 to 6 (β_2 = .04, p < .05, 95% CI: .001,

.08). These significant pathways corresponded with a significant mediation pathway ($\alpha_2\beta_2$ = -.03, p < .05, 95% CI: -.07, -.004).[22]

When testing for moderated mediation, neither gender nor history of alcohol problems appeared acted as moderators. In particular, gender and alcohol problems did not moderate the association between VLNC cigarette use and smoking or the association between smoking and alcohol use (p's > .10). As a result, the mediating pathway did not appear to vary as a function of gender or problem drinking history.

For the binge drinking outcome, cigarettes per day did not appear to mediate the effect of VLNC cigarettes. At Week 1, VLNC cigarettes were associated with cigarettes per day (α_1 = -1.94, p = .007, 99% CI: -3.79, -.09); however, cigarettes per day was unrelated to Week 1 binge drinking (β_1 = .03, p = .36, 95% CI: -.03, .09). Similarly, while VLNC cigarettes were associated with reductions in cigarettes per day from Week 1 to Week 6 relative to the normal nicotine content control cigarette (α_2 = -.65, p < .001, 99% CI: -1.11, -.26), this was not, in turn, associated with changes in binge drinking during the same period (β_2 = .09, p = .61, 95% CI: -.08, .13). Thus, neither mediating pathway was supported.

Gender and history of alcohol problems were not supported as moderators of the mediated pathway through cigarettes per day. Specifically, gender and alcohol problems did not moderate the association between VLNC cigarette use and smoking or the association between smoking and alcohol use (p's > .10).

[22] The mediated effect was replicated when including baseline levels in the growth process. Specifically, both alcohol use and cigarettes per day changed in a piecewise fashion. Changes in cigarettes per day in the first two weeks were unrelated to concurrent changes in alcohol use. During the last four weeks, changes in cigarettes per day were significant and positively related to changes in alcohol use. This corresponded with a significant mediated effect.

6.5 AIM 3: RESULTS: UNIQUE MEDIATION PATHWAYS: DISSAGGREGATING THE MEDIATING EFFECTS OF NICOTINE EXPOSURE AND CHANGES IN CIGARETTES PER DAY

Additional analyses were conducted to investigate if the mediating pathways supported in prior analyses uniquely explained changes in alcohol outcomes. Alcohol use was the only alcohol outcome in which multiple mediating pathways was supported. Specifically, the effect of VLNC cigarettes on changes in alcohol use during the last four weeks of the study was mediated by reduced nicotine exposure. Furthermore, at approximately the same time frame -- the last five weeks of the study, the effect of VLNC cigarettes on changes in alcohol use was mediated by changes cigarettes per day. As the effects of changes in cigarettes per day on alcohol use could, in part, be explained by the effect of smoking on nicotine exposure, additional analyses were warranted to attempt to disaggregate these interrelated processes.

Independent mediating effects of nicotine exposure and changes in cigarettes per day were tested and supported using the model depicted in Figure 26 (refer to the black lines).

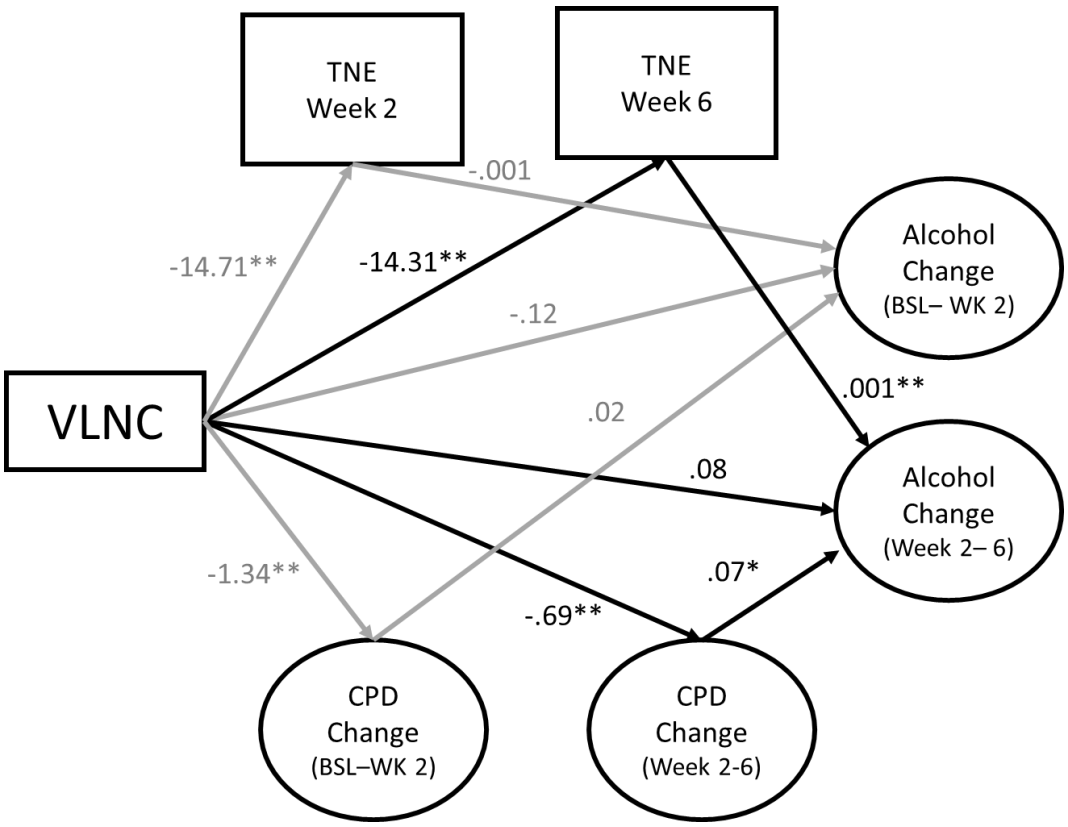


Figure 26. The unique mediating effect of nicotine exposure and changes in cigarettes per day on alcohol use

VLNC cigarette use was associated with reduced TNE levels at Week 6, which in turn, was associated with reductions in alcohol use from Week 2 to Week 6. These significant pathways corresponded with a significant mediating effect (mediated effect = -.05, 95% CI: -.18, -.10), even after controlling for the associations between cigarettes per day and alcohol use. At the same time, VLNC cigarette use was associated with significant reductions in cigarettes per day between Week 2 and 6 relative to the NNC control condition. Reductions in cigarettes per day were associated with concurrent reductions in alcohol use. This resulted in a significant mediated effect over and above the mediated effect of TNE (mediated effect = -.02, 95% CI: -.05, -.003). Taken together, both TNE and changes in cigarettes per day independently mediated the effect of VLNC cigarettes.

6.6 AIM 3: SUMMARY

The present study supported that the effect of VLNC cigarettes on alcohol outcomes was partly explained by reduced nicotine exposure. On average, VLNC cigarette use, relative to NNC cigarette use, was associated with significantly lower levels of nicotine exposure at Week 2 and Week 6. During the last four weeks, but not the first two weeks, lower nicotine exposure was associated with reduced alcohol use. The same pattern of findings was seen when examining the mediating role of nicotine exposure for binge drinking among less nicotine dependent individuals. In contrast, more nicotine dependent individuals tended to increase their binge drinking in response to nicotine reduction.

The hypothesis that withdrawal would mediate the effect of VLNC cigarettes on alcohol outcomes was not supported for alcohol use or binge drinking. The present investigation found no differences in withdrawal between the NNC and VLNC cigarette users. Moreover, withdrawal did not covary with alcohol use or binge drinking.

Finally, the hypothesis that cigarettes per day would mediate the effect of VLNC cigarettes on alcohol outcomes was supported. This mediation pathway was supported for alcohol use, but not for binge drinking. Reductions in cigarettes per day in response to VLNC cigarette use corresponded with a concurrent reductions in alcohol use, particularly during the last 4 to 5 weeks of the study. This mediated pathway did not appear to be entirely explained by co-occurring changes in nicotine exposure.

7.0 SUMMARY AND CONCLUSIONS

Enacting a low nicotine product standard for cigarettes is expected to improve public health by reducing exposure to nicotine and harmful smoke constituents (Benowitz & Henningfield, 1994; Zeller & Hatsukami, 2009). Reducing nicotine exposure may have cascading effects on a closely-related health behavior, alcohol use (Dermody & Donny, 2014). Changes in alcohol use in response to repeated VLNC cigarette use, however, has not been examined. The present study sought to address this gap in the literature by examining the impact of smoking VLNC cigarettes for 6 weeks on alcohol outcomes, including alcohol use and binge drinking. These relations were examined in the context of a larger multisite clinical trial in which participants were randomly assigned to smoke VLNC cigarettes (Donny et al., Under Review). The aim of the original investigation was to determine the dose-response relationship between the nicotine content of cigarettes and smoking-related outcomes. The overarching aim of the present investigation, however, was to determine the impact of smoking VLNC cigarettes on alcohol outcomes in daily smokers for the first time.

7.1 AIM 1: THE IMPACT OF SMOKING VLNC CIGARETTES ON ALCOHOL OUTCOMES

In the total sample of drinkers, the hypothesis that smoking cigarettes with reduced nicotine content would *directly* reduce alcohol outcomes relative to smoking cigarettes with normal nicotine content cigarettes was partially supported. This effect was seen on alcohol use in the early weeks of the study. On average, alcohol use levels increased during the first two weeks of the study, and then stabilized. Smoking cigarettes with reduced nicotine content corresponded with significantly smaller (for the moderate nicotine 5.2 mg/g condition) or marginally smaller (for the two lowest VLNC conditions: 0.4 mg/g and 1.3 mg/g) initial increases in alcohol use relative to NNC cigarette use.

The trend during the first two weeks was most consistent with prior laboratory studies of non-daily male smokers. Prior studies of non-daily male smokers have found that briefly reducing nicotine exposure, using VLNC cigarettes or placebo patch versus their nicotine containing counterparts, resulted in reduced alcohol use (Acheson et al., 2006; Barrett et al., 2006). In contrast, among non-daily smoking women or daily smokers, reduced nicotine exposure via placebo patch increased alcohol (Acheson et al., 2006; McKee et al., 2008). An important factor distinguishing these studies, which may have also impacted the findings in the present study, was the extent to which participants experienced withdrawal symptoms. Unlike prior research of daily smokers that administered nicotine by patch (McKee et al., 2008), VLNC cigarettes largely suppressed withdrawal and thus may have prevented any compensatory drinking. As a result, potentially due to the successful suppression of withdrawal, VLNC cigarette use corresponded with a relative decrease in alcohol use, as opposed to compensatory drinking.

During the subsequent four weeks, however, the nicotine content of study cigarettes was not *directly* related to patterns of alcohol use. Ultimately, the relatively small differences in early alcohol use patterns between the VLNC cigarette and NNC condition, as well as the non-significant increase seen in subsequent weeks in the moderate nicotine condition, corresponded with no group differences in Week 6 alcohol use.

It is important to note, that the non-significant direct effects of smoking VLNC cigarettes on alcohol use during the last four weeks may have been partly due to non-compliance. Non-compliance was prevalent in the VLNC cigarette conditions. In the lowest nicotine content condition, the prevalence of non-compliance was 65% and 69% at Weeks 2 and Week 6, respectively (using a relatively liberal nicotine biomarker cut-off value). Non-compliant participants showed a significant increase in alcohol use during the last four weeks compared to compliant participants, which suggests that non-compliance could have mitigated the strength of the effect of VLNC cigarettes on alcohol use during this timeframe.

The present study was the first to examine the effect of nicotine reduction on risky drinking, specifically binge drinking. It was hypothesized that VLNC cigarettes would impact alcohol use and binge drinking in similar ways. This hypothesis, however, was not supported as there were several notable differences in the pattern of findings for changes in alcohol use and binge drinking. For instance, while alcohol use increased during the study, on average, binge drinking patterns did not change during the 6 week study. This suggests that while study participation increased alcohol use, the increases in alcohol use did not correspond with an effect on binge drinking.

Another key difference was that VLNC cigarette use appeared to have no overall effect on binge drinking compared to the NNC control. One trend was identified, in the lowest nicotine

content group (0.4 mg/g), in which binge drinking *increased*. This trend was not systematic across other conditions with comparable nicotine content (i.e., 0.4 mg/g high tar group) or across time, thus it may not be a reliable effect. For instance, there was a sizeable increase in the prevalence of binge drinking between Week 5 (15%) and Week 6 (28.3%). After combining the VLNC cigarette conditions, the trend was not replicated relative to the NNC cigarette condition.

Furthermore, non-compliance did not appear to impact changes in binge drinking. Compliant and non-compliant individuals in the lowest nicotine content conditions appeared to have similar patterns of binge drinking. Thus, for the typical participant, it is nicotine reduction in cigarettes did not impact binge drinking.

7.2 INDIVIDUAL DIFFERENCES OF THE IMPACT OF SMOKING VLNC CIGARETTES ON ALCOHOL OUTCOMES

It was hypothesized that the effect of VLNC cigarettes on alcohol outcomes may be moderated by a number individual difference factors that may impact sensitivity to changes in nicotine dose, the extent to which smoking and drinking co-occur, and risk of withdrawal. While several moderators were considered (i.e., gender, history of problem drinking, drinking to cope motives, baseline drinking, level of nicotine dependence), only one moderator was consistently supported. The supported moderator was level of nicotine dependence, assessed by the FTND, which moderated the associations of VLNC cigarette use on both alcohol use and binge drinking.

When considering alcohol use, VLNC cigarette use significantly reduced alcohol use only among less nicotine dependent individuals. In particular, VLNC cigarette use corresponded with a relative reduction in alcohol use during the first two weeks compared to NNC cigarette

use. The pattern of findings with less dependent smokers is similar to what has been supported among non-daily smokers (Barrett et al., 2006), and suggests that among these individuals VLNC cigarette use may in fact decrease alcohol use over time.

In contrast, among more nicotine dependent individuals, there was no effect of VLNC cigarette use on alcohol use. This pattern of findings was anticipated as more highly nicotine dependent may respond to VLNC cigarette use in such a way that would mitigate the effect on alcohol use, such as non-compliance or experiencing effects of withdrawal that would lead to increased (as opposed to decreased) drinking. A recent secondary data analysis of a VLNC cigarette trial sheds some light on this issue by demonstrating that high nicotine dependence, as assessed by FTND, corresponded with compensatory smoking behaviors (Bandiera et al., 2015). These compensatory smoking behaviors, including increases in cigarettes per day, resulted in greater nicotine and toxicant exposure in the context of nicotine reduction. In the present study, these compensatory behaviors likely undermined the extent of nicotine reduction, and in turn, mitigated any positive effect of VLNC cigarette use on drinking. For instance, when looking at percent reductions in biomarkers, highly nicotine dependent individuals assigned to VLNC cigarettes did not demonstrate a significant percent reduction in nicotine biomarkers over the course of the study (14% reduction) relative to NNC controls (56% reduction). The relative importance of this process to others (such as withdrawal) in explaining this disparity is described in more detail below (as part of the discussion about processes underlying the effect of VLNC cigarette use on drinking).

Level of nicotine dependence also impacted the effect of reducing the nicotine content of cigarettes on binge drinking. Reducing the nicotine content of cigarettes was not associated with binge drinking for individual with relatively lower nicotine dependence. In contrast, more highly

nicotine dependent individuals who were assigned to smoke VLNC cigarettes exhibited increased binge drinking during the study relative to individuals who smoked NNC cigarettes. This pattern of findings is more in line with compensatory drinking in response to nicotine reduction among more highly dependent individuals, which is described in more detail below. Taken together, this suggests that VLNC cigarettes may have a beneficial effect on alcohol use among less dependent smokers, but may increase the risk of binge drinking among more dependent smokers.

7.3 AIM 3: THE PROCESSES UNDERLYING THE EFFECTS OF VLNC CIGARETTES ON ALCOHOL OUTCOMES

It was hypothesized that VLNC cigarettes would impact alcohol outcomes through its effects on nicotine exposure, withdrawal, and cigarettes per day. The present study supported that the effect of VLNC cigarettes on alcohol outcomes was partly explained by reduced nicotine exposure. For alcohol use, the explanatory role of nicotine exposure was supported specifically during the last four weeks of the study. As expected, on average, VLNC cigarette use, relative to NNC cigarette use, was associated with significantly lower levels of nicotine exposure at Week 2 and Week 6. During the last four weeks, lower nicotine exposure was associated with reduced alcohol use. As there were no moderators of the associations between nicotine exposure and alcohol use, in general, reduced nicotine exposure due to VLNC cigarette use appeared to correspond with reduced drinking.

The mechanisms contributing the marginal reduction in alcohol use following VLNC cigarette use during the first two weeks were not clearly identified. The reduced nicotine

exposure at Week 2 was not associated with concurrent changes in alcohol use. Similarly, neither withdrawal nor smoking behavior appeared to mediate the effect. It is possible that was the additive effect of initial changes in nicotine exposure and smoking behavior contributed to the change, which may not have been captured when examining either mediator independently. For instance, when examining both biomarkers and changes in cigarettes per day simultaneously as predictors of change in alcohol use, the marginal relation between VLNC cigarette use and alcohol use became non-significant. This change in significance suggests that the effect of VLNC cigarette use on alcohol use may have been accounted for after considering changes in nicotine exposure and cigarettes per day. Alternatively, it is conceivable that another process contributed to the marginal effect that was not investigated in the present study.

In the context of binge drinking, reduced nicotine exposure had no overall effect in the average participant; however, the lack of overall effect was due to collapsing across subgroups whose binge drinking increased or decreased in response to nicotine reduction. The subgroups were distinguishable based on their baseline nicotine dependence level. In general, reduced nicotine exposure among less nicotine dependent individuals corresponded with reductions in binge drinking. In contrast, more nicotine dependent individuals increased their binge drinking. Thus, nicotine reduction may have opposite effects on an individual's binge drinking depending on their nicotine dependence level.

The positive relation between nicotine exposure and alcohol outcomes among less nicotine dependent individuals is consistent with previous research. As previously described, nicotine exposure and alcohol use have been shown to be positive related, perhaps due to a combination of the effects of nicotine on alcohol metabolism (Johnson et al., 1991; Perkins et al., 1995) and the reinforcing properties of alcohol (McKee & Weinberger, 2013; Zacny, 1989).

While the present study cannot speak to which mechanisms were at play, any combination of these processes would be expected to lead to a reduction in alcohol use, and similarly binge drinking, in response to reduced nicotine exposure.

The increase in binge drinking among highly dependent smokers relative to less dependent smokers was anticipated as a possible response to withdrawal. This hypothesis was based on inconsistent relations seen between nicotine manipulations and alcohol use among daily and non-daily smokers. Specifically, while nicotine deprivation appeared to increase alcohol use in daily smoker (McKee et al., 2008; Palfai et al., 2000), non-daily smokers decreased their alcohol use (Acheson et al., 2006; Barrett et al., 2006). As a fundamental difference between these groups was likely the experience of withdrawal, it was hypothesized that an important explanatory process was the withdrawal itself, which could promote self-medication by alcohol.

However, when the present study tested the role of withdrawal in explaining compensatory drinking, the process was not supported. The present investigation found no differences in withdrawal between the NNC and VLNC cigarette users, suggesting that nicotine reduction in the presence of continued smoking did not impact withdrawal. The lack of withdrawal due to nicotine reduction is consistent with the primary paper that examined the total sample (Donny et al., Under Review), as well as other studies that have found that VLNC cigarettes largely suppress withdrawal symptoms (Benowitz et al., 2007; Buchhalter et al., 2005; Buchhalter, Schrinel, & Eissenberg, 2001; Donny et al., 2007; Hatsukami et al., 2010a). This suggests that VLNC cigarette use may not substantively increase withdrawal, and thus, would not require alternative means of self-medication like drinking.

Moreover, withdrawal did not covary with alcohol use or binge drinking. The lack of association between withdrawal and alcohol use and binge drinking was seen regardless of

nicotine dependence level and other potential individual difference factors (e.g., drinking to cope motives, history of problem drinking). Given the availability of products with normal nicotine content, it is not surprising that withdrawal did not covary with drinking. Non-compliance was likely the most efficient way for participants to mitigate any withdrawal in response to smoking VLNC cigarettes as opposed to resorting to alternative substances like alcohol. In fact, as previously described, non-compliance was widespread among highly nicotine dependent individuals. Nevertheless, highly nicotine dependent individuals who significantly reduced their nicotine exposure demonstrated an increase in binge drinking (see Figure 27). Thus, withdrawal did not appear to be a process linking VLNC cigarette use to drinking outcomes, which may be due to a combination of non-compliance removing the need to self-medicate or a lack of association more generally between nicotine withdrawal and alcohol use.

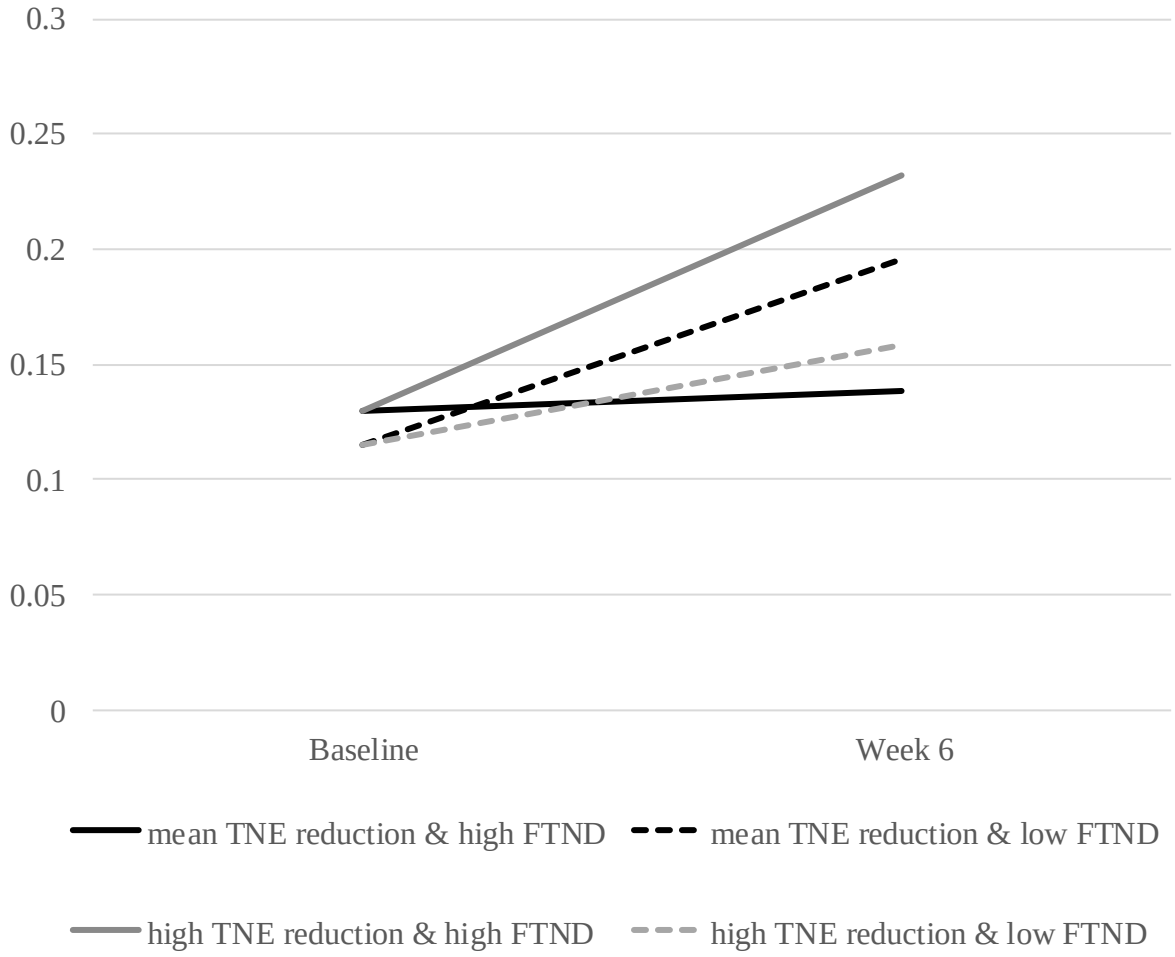


Figure 27. The effect of percent reduction in nicotine biomarkers on binge drinking is moderated by baseline nicotine dependence score (estimated prevalence)

Instead of withdrawal, it appeared that the moderating effect of nicotine dependence was driven by differential response to changes in nicotine exposure. Specifically, while less dependent individuals exhibited reduced alcohol outcomes in response to lower nicotine biomarkers, more nicotine dependent individuals tended to increase binge drinking in response to lower nicotine biomarkers. The pattern of findings among more dependent smokers is consistent with prior research of heavy drinking smokers. Specifically, among heavy drinking smokers, reduced nicotine exposure increased both the intoxicating effects of drinking and alcohol

consumed (McKee et al., 2008). Thus, one possible explanation for the differential relation between nicotine exposure and binge drinking is that nicotine dependence may influence the extent to which nicotine increases or decreases the reinforcing properties of drinking. In other words, in the short term, nicotine reduction among highly dependent smokers may increase the reinforcing effects of alcohol.

It was also hypothesized that cigarettes per day would mediate the effect of VLNC cigarettes on alcohol outcomes. This mediation pathway was supported for alcohol use, but not for binge drinking. Reductions in cigarettes per day in response to VLNC cigarette use corresponded with a concurrent reductions in alcohol use, particularly during the last 4 to 5 weeks of the study. In contrast, cigarettes per day were not associated with changes in binge drinking during the study. The effect seen for alcohol use is consistent with research that has identified cigarettes as a cue for alcohol craving (Drobes, 2002). The differential relation between cigarettes per day and alcohol use and binge drinking was not anticipated. One interpretation of the differential relation is that cigarettes or the act of smoking may cue the onset of alcohol use but may not have a substantial impact on how many beverages are consumed.

It appeared that the association between smoking level and alcohol use was independent from the impact of nicotine exposure on alcohol use. Specifically, additional analyses supported independent effects of changes in cigarettes per day on alcohol use during the last four weeks after controlling for nicotine biomarkers. While this approach may be imperfect as the nicotine biomarkers only captured a snapshot of nicotine exposure (as opposed to exposure over the four weeks), the pattern of findings provides support for the relation of smoking and drinking being partly due to aspects of smoking outside of nicotine exposure per se.

8.0 STRENGTHS AND LIMITATIONS

The present study had several methodological strengths that allowed for examining the processes linking nicotine reduction to alcohol use. VLNC cigarettes provided a unique opportunity to parse out the components of smoking that may impact drinking, particularly the pharmacological effects from the sensory or behavioral effects. Specifically, VLNC cigarettes are believed to largely maintain the sensory aspects of smoking while delivering minimal amounts of nicotine. As a result, it was possible to evaluate how manipulating nicotine, without entirely removing the act of smoking, impacts alcohol outcomes. While VLNC cigarettes still contain small amounts of nicotine, attempts were made to parse out the mechanisms statistically, which allowed for a test of the relative importance of nicotine and changes in smoking behavior in explaining drinking.

Additional methodological strengths included the methods of measurement for cigarette use and alcohol outcomes. Cigarette use and alcohol outcomes were measured daily, by daily IVR calls and weekly TLFB, respectively. While these methods are retrospective, they have been shown to increase reliability and accuracy of reporting, and thus increase confidence in the quality of measurement of these outcomes. Furthermore, the study was a large multisite design consisting of a generally diverse population of daily smokers. The combination of the large sample size and diverse sample allowed for an examination of subgroup differences in response to VLNC cigarettes as well as corresponding mediating processes.

The present investigation also had some limitations. First, non-compliance was prevalent, which likely undermined the extent of nicotine reduction and associated outcomes. The consequence of this non-compliance is that the effect of nicotine reduction on alcohol outcomes may have been underestimated. For instance, alcohol use may have been maintained despite the generally decreased levels of nicotine exposure, particularly if non-compliance tended to occur immediately before or during a drinking episode. More fine-grained data with respect to the timing of non-compliance and alcohol use or a closely controlled study in which non-compliance is greatly limited would be needed to definitively determine the extent to which non-compliance mitigated the effects of VLNC cigarettes on drinking outcomes.

While the present study can make some causal inferences about the main effect of the manipulated study conditions and alcohol use, the same is not true for the relations between the proposed mediators (e.g., cigarettes per day, withdrawal) and alcohol use. The relations between these processes are likely bidirectional. For instance, in laboratory studies, alcohol use has been shown to increase smoking behavior (e.g., Barrett et al., 2013; Mintz et al., 1985). Consequently, it is possible that the supported mediated role of cigarettes per day, was in part, due to the reverse effect of alcohol use on smoking level. Similarly, if non-compliance tends to occur in the context of drinking, this would be expected to lead to a positive association between nicotine exposure and alcohol outcomes. Thus, as the mediating processes were not directly manipulated and relations between these processes and alcohol outcomes were examined concurrently, the directionality of the effect cannot be determined.

The combination of non-compliance and examining concurrent associations may have also masked any effects of withdrawal on alcohol use. Individuals who experienced withdrawal likely mitigated those symptoms by being non-compliant, which would remove any need to self-

medicate the withdrawal using alcohol. Furthermore, while weekly withdrawal did not covary with weekly alcohol outcomes, it is possible that examining the weekly timeframes did not allow for this relation to be captured. The weekly timeframe may not capture self-medication if it tends to occur within a day or drinking episode. Finally, prior research has found that people tend to self-medicate certain types of negative affect, like sadness, and may reduce their drinking in response to other types of negative affect like anxiety (Dermody et al., 2014; Hussong papers). Both sadness and anxiety were both combined in a single withdrawal score, which could have led to a cancelling of effects. Taken together, while there was no direct support for withdrawal as a mediator, dismissing this mechanisms may be premature. Further work is warranted to dissect the withdrawal process (as described below).

While the large multisite design produced a generally diverse population of daily smokers, there were several subgroups of smokers excluded from the present study that limit generalizability of findings. For instance, the present study focused entirely on non-treatment seeking smokers. Responses to VLNC cigarettes between treatment-seeking and non-treatment seeking smokers have not been directly compared; however, research of non-treatment seekers who immediately switch to VLNC cigarettes have detected initial increases in withdrawal (Hatsukami et al., 2013b; Hatsukami et al., 2010a) and significant reductions in cigarettes per day during a 6 week period (Hatsukami et al., 2010a). Based on the present study findings, the greater reduction in cigarettes per day among treatment-seekers may correspond with a larger reduction in alcohol use. Furthermore, heavy and problematic drinkers were screened out of the study. Attempts were made to address this issue by examining if relatively higher levels of baseline drinking and other characteristics consistent with a heavy drinking history may moderate the effects of nicotine reduction. These analyses suggested that individuals with a

history of problem drinking and heavier drinkers may not respond differentially to nicotine reduction with respect to changes in alcohol outcomes. Nonetheless, it would be important to examine the tolerability of VLNC cigarettes among treatment-seekers and individuals with heavier or problematic drinking.

Finally, there are likely other factors that impacted alcohol use in the present study that were not directly investigated. Overall, even in the control conditions, there was a significant increase in alcohol use in the first two weeks of the study. Several factors may have contributed to this overall increase, such as improved monitoring of alcohol use, increased comfort in reporting high levels of use (e.g., due to rapport with research assistant or no longer being concerned about being disqualified from the study), and having more money to buy alcohol (e.g., due to study payments and no longer having to buy cigarettes). It is not anticipated that these factors explain the differences seen between VLNC cigarette and NNC cigarette use, as the statistical methods used effectively control for these effects by using the drinking levels of NNC cigarette condition as the control as opposed to baseline drinking levels.

9.0 POLICY IMPLICATIONS AND FUTURE DIRECTIONS

In the context of these limitations and strengths, the study findings provide important insight into the public health impact of a nicotine reduction policy. Cigarette and alcohol use are closely related health behaviors and FDA regulations reducing the nicotine content of cigarettes could impact alcohol use among smokers. Reductions in nicotine exposure and the cues associated with smoking appear to generally decrease alcohol use over time, with changes in nicotine exposure potentially playing an important role early in the policy change and changes in smoking behavior emerging as an important factor. The culmination of these processes appears to be a small beneficial effect of VLNC cigarettes on alcohol use. On average, by the end of the study, VLNC cigarette users drank 12% less alcohol per day than NNC cigarette users. This conclusion is consistent with the existing literature suggesting that smoke-free legislation and tobacco taxes reduce drinking (McKee & Weinberger, 2013). The beneficial effects of nicotine reduction on alcohol outcomes may be primarily experienced specific subgroups, such as individuals who are relatively less nicotine dependent and individuals who do not mitigate their nicotine exposure by using other sources of nicotine.

Similarly, the present study findings suggest that it is unlikely that most VLNC cigarette users would increase their alcohol use. A primary concern was compensatory drinking in response to withdrawal. Consistent with prior research, for most individuals, switching to VLNC cigarettes did not increase withdrawal. Furthermore, reported withdrawal symptoms were

unrelated to alcohol outcomes. Taken together, this suggests that there may be a positive impact of the intervention at the individual level. Assuming that these findings would be replicated in the general population of smokers, notably including treatment seekers and heavier drinkers who were excluded from the present study, this could correspond with an improvement in public health.

One subgroup of smokers who drink that may exhibit increased problem drinking in response to a nicotine reduction policy is highly nicotine dependent smokers. Specifically, individuals who are more highly nicotine dependent (FTND score greater than 5) reported an increase in binge drinking in response to nicotine reduction. For individuals who substantially reduced their exposure to nicotine, the prevalence of binge drinking for highly dependent smokers increased by 10% and for less dependent smokers binge drinking was reduced by 4%. It is possible that the extent of these differences were underestimated as highly dependent smokers tended to be non-compliant. As a result, in order to mitigate any unintended negative consequences, the implementation of a nicotine reduction policy may need to take into account the differential response to nicotine reduction.

The results of the present study suggest that one way of addressing the potential increase in risky drinking among more highly dependent smokers is by calibrating the nicotine reduction process. Specifically, as the primary mechanism of this effect appears to be driven by changes in nicotine exposure, as opposed to withdrawal or changes in cigarettes per day, it is possible that methods that facilitate a gradual transition to reduced nicotine exposure would be helpful. One way of facilitating this may be supplementing VLNC cigarettes with nicotine replacement therapies. As previously described, nicotine replacement therapy, like the patch, prevented compensatory drinking in laboratory studies of daily smokers (e.g., McKee et al., 2008).

Another approach could involve gradual reduction of the nicotine content of the cigarettes themselves. A gradual nicotine reduction approach would involve progressively reducing the nicotine content of cigarettes available in the market place over a predetermined amount of time (Benowitz et al., 2012; Benowitz et al., 2007). The benefits of this tapering approach is that smokers can adjust to each reduction phase, which has been shown to limit compensatory smoking and withdrawal symptoms (Benowitz et al., 2012; Benowitz et al., 2007). Moreover, this approach corresponds with significant reductions in nicotine dependence assessed by the FTND, which could in turn mitigate some of the undesirable effects of nicotine reduction on alcohol use. Thus, both nicotine replacement therapy and gradual reduction of nicotine intake may prevent unwanted effects of a nicotine reduction strategy on alcohol use.

Additional research is warranted to estimate the public health impact of nicotine reduction regulatory strategies on alcohol outcomes. In addition to evaluating the impact of a gradual nicotine reduction strategy on alcohol outcomes, particularly among highly nicotine dependent smokers, increasing the length of follow-up would be beneficial. While the 6 week window in the present study was likely long enough to capture initial compensatory drinking, it may not have been long enough to capture the long-term beneficial effects of nicotine reduction on alcohol outcomes. For instance, reductions in cigarettes per day, and ultimately cessation, may be an important mechanism through which nicotine reduction would impact alcohol use. As a result, following participants for a long enough period of time in which there are significant reductions in cigarette per day relative to baseline would be informative. Based on prior research evaluating gradual nicotine reduction in non-treatment seeking smokers, a six month follow-up period may be sufficient to begin to see reductions in smoking relative to baseline (Benowitz et al., 2012).

Future research is also needed to evaluate the risk of co-use or product switching to compensate for the reduced nicotine levels of VLNC cigarettes, particularly among subgroups who tend to co-use tobacco products like young, white men (Rath, Villanti, Abrams, & Vallone, 2012). To date, including the present study, examinations of the effects of VLNC cigarettes have been conducted among smokers who do not regularly use other tobacco or nicotine products. Studies that have examined VLNC cigarette use alongside the nicotine patch suggest that cigarette use and nicotine exposure still decrease over time and at a faster rate than VLNC cigarettes alone (Hatsukami et al., 2013b; Donny & Jones, 2009). This suggests that many of the same relations between VLNC cigarette use and alcohol outcomes may hold true for individuals who use some alternative nicotine products, but at a level where overall nicotine exposure is still reduced. Research that imitates a free market place by allowing participants to use other nicotine and tobacco products in tandem with VLNC cigarettes would be valuable when evaluating this outcome.

Additional research is also warranted to determine if VLNC cigarettes similarly impacts other health behaviors outside of smoking. The present study focused on the effects of VLNC cigarettes on alcohol use, given the widespread co-use. However, a similar framework can be applied to estimate potential consequences on the use of other substances and, more broadly, health behaviors. For individuals who frequently smoke cigarettes and use other substances, reductions in cigarettes smoked could produce similar reductions in other substances used through cued-reactivity and reward enhancement mechanisms. As nicotine administration enhances responding to other reinforcers, the effect likely applies to substances outside of alcohol (Chaudhri et al., 2006; Donny et al., 2003). Furthermore, like with alcohol use,

individuals who tend to self-medicate negative affect by engaging in negative health behaviors and other substance use could engage in these behaviors while experiencing withdrawal.

In sum, once a nicotine reduction strategy is enacted, it will be important to evaluate the public health impact not only based on smoking-related outcomes, but also based on closely-related health outcomes like alcohol use.

10.0 CONTRIBUTIONS TO THEORY DEVELOPMENT AND FUTURE DIRECTIONS

Only one study has directly examined, among non-daily smokers, the effects of VLNC cigarettes on drinking (Barrett et al., 2006). The present study adds to this research by demonstrating that reduced nicotine exposure also impacts alcohol use among daily smokers. This relation appears to unfold differently over time as a result of interrelated mechanisms. In particular, among daily smokers, switching to VLNC cigarettes immediately and drastically reduced nicotine exposure and gradually decreased smoking behavior relative to smoking normal nicotine content cigarettes. As expected, both nicotine exposure and smoking level were positively related to drinking. Together, these processes led to a reduction in alcohol use in response to switching to VLNC cigarettes.

The positive relation between nicotine exposure and alcohol use, particularly among less dependent smokers, was consistent with nicotine enhancing the reinforcing properties of alcohol. Additional work is needed to determine specifically how nicotine exerts its effects on alcohol use and binge drinking. VLNC cigarettes provide a unique opportunity to parse between these processes. Specifically, human laboratory research has achieved high internal validity when focusing on this relation by manipulating nicotine via patch, inhaler, or intravenously. However, these delivery devices may differentially impact alcohol outcomes relative to smoking due to different kinetics of nicotine delivery and removing other aspects of smoking that may facilitate

the relation between nicotine and drinking (e.g., behavioral or sensory aspects of smoking, other constituents in cigarettes). Thus, additional laboratory research of the effect of VLNC cigarettes on alcohol outcomes would allow for a relatively more ecologically valid test of the effects of nicotine in cigarettes on alcohol metabolism, reinforcement, and subjective effects.

Based on the findings in the present study, when conducting this laboratory research of the effect of VLNC cigarettes on alcohol outcomes, it will be important to look at varied samples based on nicotine dependence and amounts of alcohol consumed. Specifically, the relation between nicotine exposure and alcohol outcomes differed between nicotine dependent individuals, particularly at high levels of episodic drinking. As prior research examining the effects of nicotine exposure and alcohol use, as well as subjective effects and reinforcement, has focused exclusively on relatively low levels of alcohol use (typically one to two standard drinks), these studies may not be able to adequately explain these individual differences. These individual differences could be clarified by comparing the effect of VLNC cigarettes on the subjective and reinforcing effects of alcohol when consumed at relatively heavier levels.

Furthermore, the positive relation between cigarettes per day and alcohol use (independent from nicotine) was consistent with cigarettes acting as a cue for drinking. It is important to note, however, that while the effect of cigarettes per day on drinking may be independent from nicotine, the present study cannot speak to the extent to which the relation is due to cigarettes acting as a cue per se. The conclusion that the effect in the present study is specifically a cue effect is tentative for several reasons. For instance, prior research that has examined the effect of cigarette cues on alcohol consumption, as opposed to alcohol craving alone, has found no evidence that cigarette cues impacted alcohol use (Palfai et al., 2000). While the present study provides initial evidence that cigarettes may cue alcohol use, the effect of other

constituents in the cigarettes cannot be ruled out. Cigarettes contain thousands of constituents (US Department of Health & Human Services, 2010; Talhout et al., 2011), any number of which could have pharmacological interaction with alcohol. One example is acetaladehyde, which is both a constituent of cigarette smoke as well as a metabolite of alcohol (Salaspuro & Salaspuro, 2004). It is hypothesized that within a narrow range of acetaldehyde concentrations, that increased acetaldehyde from smoking would increase the reinforcing properties of alcohol (Hunt, 1996). Thus, additional research is needed to disaggregate the effects of cigarettes as a cue to drink from other aspects of smoking, such as exposure to constituents of cigarettes apart from nicotine that may impact alcohol use. As the association between cigarette cues and alcohol use has only been examined in one study of highly nicotine dependent social drinkers, investigating the associations in more diverse samples could provide additional insight into the extent to which cigarettes cue drinking in the majority of smokers who drink.

While withdrawal was not supported as a mechanism linking nicotine reduction to alcohol outcomes, additional research is warranted to confirm this finding. For the reasons outlined in the limitations section, the present study may not have been well-suited to capture an effect of withdrawal. Important next steps include examining momentary relations between withdrawal and alcohol outcomes, particularly during the first week of switching to VLNC cigarettes. It is critical that this research take steps to reduce non-compliance as a way of estimating the full effect of a nicotine reduction policy, after which conventional cigarettes would be unavailable, on drinking.

11.0 CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

While the present study focused exclusively on non-treatment seekers, some of the observed relations between smoking and drinking may have implications for intervening with smoking among alcohol users. Overall, the present study supported complementarity between smoking, nicotine exposure, and alcohol outcomes. Together, the present study and existing literature (e.g., McKee & Weinberger, 2013) suggests that interventions designed to reduce smoking behavior or increase cessation may, in turn, reduce alcohol outcomes. While a potential caveat is withdrawal, the present study did not support the role of withdrawal in promoting compensatory drinking.

Given the apparent complementarity between smoking and drinking, intervening with both issues simultaneously may maximize outcomes. For instance, literature reviews suggest that incorporating smoking cessation treatment in problem drinking interventions may improve drinking outcomes (Prochaska, Delucchi, & Hall, 2004; Ziedonis, Guydish, Williams, Steinberg, & Foulds, 2007). The present study adds to this argument by demonstrating that intervening with smoking could have beneficial cascading effects on concurrent drinking. At the same time, not addressing the smoking may allow for continued nicotine exposure that may increase the risk for relapse.

The concurrent intervention approach may be particularly important for individuals who are both highly nicotine dependent smokers and problem drinkers. For this subpopulation, there

was evidence of compensatory drinking in response to nicotine reduction. This suggests that intervening with smoking, without careful attention to drinking levels, could lead to undesirable consequences. Additional research is warranted to determine if nicotine dependence level impacts the relation between smoking interventions on drinking more generally, or if the effect is unique to VLNC cigarettes. For instance, as nicotine dependence appeared to moderate the effect of nicotine exposure specifically, it is possible that interventions that maintain nicotine exposure (e.g., nicotine replacement therapies) may not produce similar effects on problem drinking.

12.0 SUMMARY

An important outcome of making cigarettes less addictive is reducing smoking rates. The present investigation further demonstrated that VLNC cigarettes could impact closely related health behaviors, like alcohol use and binge drinking. The impact on drinking differed over time and between subpopulations. Specifically, among many smokers, it appears that reducing the nicotine content of cigarettes could have a broader positive impact on public health by also decreasing alcohol use and binge drinking. The reduction in alcohol use appeared to be driven by a combination of interrelated processes, notably nicotine exposure and smoking rate. An important subgroup, however, that warrants further study is highly nicotine dependent individuals, who tended to increase their drinking in response to nicotine reduction. In sum, it is necessary to broadly define the public health impact to include unintended health consequences on non-smoking behaviors.

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