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EVALUATING THE EFFECTS OF ELECTRONIC NICOTINE DELIVERY SYSTEMS ON SMOKING REDUCTION, NEGATIVE MOOD, AND STRESS AMONG SMOKERS WITH MENTAL ILLNESS

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EVALUATING THE EFFECTS OF ELECTRONIC NICOTINE DELIVERY SYSTEMS ON
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MENTAL ILLNESS

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by

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Abstract

Introduction: Smokers with mental illness (MI) are disproportionately affected by negative health outcomes. Electronic nicotine delivery systems (ENDS) may represent a harm reduction tool for those who reduce and/or replace their cigarettes with ENDS. Little previous research has examined how smokers with MI respond to ENDS. This analysis aimed to address this research gap using secondary data from a randomized controlled trial of ENDS varying in nicotine delivery among smokers with and without current MI. The aims were to test 1) the effects of MI status, condition, and time on changes in smoking behavior and negative mood and stress measures, 2) whether changes in negative mood and stress mediate condition-related effects on smoking, and 3) whether this mediation was moderated by MI status.

Methods: Smokers (n=520) interested in reduction but not cessation were randomized to receive either a non-nicotine-containing plastic cigarette substitute (CIG SUB) or ENDS differing in liquid nicotine concentration (0, 8, or 36 mg/ml) for 24 weeks. MI status was assessed at baseline. Smoking behavior (cigarettes per day; CPD) and negative mood (depression, psychological distress) and perceived stress measures were assessed at week 0, 4, 8, 16, and 24. Conditions were collapsed by nicotine-containing status (CIG SUB/0 mg/ml vs. 8/36 mg/ml), and participants were categorized by MI status (yes, no). Linear mixed models and mediation models were used. Sensitivity analyses included covariate adjustment.

Results: CPD reduction was significantly greater among smokers without MI at week 16 and 24 for the unadjusted analysis only. Nicotine conditions were associated with significantly greater CPD reduction at all time points, and both condition groupings resulted in significant CPD reduction relative to baseline. Significantly greater depressive symptoms were observed for non-nicotine conditions at week 4; significantly greater psychological distress was observed for non-

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nicotine conditions at week 24. With covariate adjustment, negative mood measures were significantly higher at later study time points for those with MI. Perceived stress differed by MI status but not condition grouping. Changes in negative mood and stress did not mediate CPD reduction, but direct effects of condition as well as changes in negative mood on CPD reduction were observed.

Conclusions: Our findings indicate that smokers with MI may experience greater difficulty reducing CPD, but nicotine conditions had similar effectiveness in reducing CPD relative to non-nicotine conditions among smokers with and without MI. Smokers with MI reported increased negative mood at some time points, but changes in negative mood and stress did not explain the relationship between condition and CPD reduction. Results highlight the need for mood management during smoking reduction and cessation efforts for smokers with MI and support the idea that ENDS may be an effective tool for smoking reduction for this group.

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List of Abbreviations

CES-D	Center for Epidemiologic Studies Depression Scale
CIG SUB	Cigarette substitute
CO	Carbon monoxide
CPD	Cigarettes per day
EM	Expectation maximization
ENDS	Electronic nicotine delivery system(s)
FDA	US Food and Drug Administration
MI	Mental illness
nAChR	Nicotinic acetylcholine receptors
PSCDI	Penn State Cigarette Dependence Index
PSS	Perceived Stress Scale
RCT	Randomized controlled trial
REML	Restricted Maximum Likelihood
RR	Risk ratio
SAMHSA	Substance Abuse and Mental Health Services Administration
SMI	Serious mental illness
US	United States
USDHHS	United States Department of Health and Human Services

Introduction

Overview and Motivation for Study

Smoking causes 480,000 deaths annually in the United States (US; Centers for Disease Control and Prevention, 2014). Smoking-related diseases and death are particularly prominent among populations with mental illness (MI). Relative to smokers without MI, smokers with MI are at an increased risk of suffering from smoking-related cancers and cardiovascular disease (Callaghan et al., 2014). For example, approximately 53% of deaths among individuals with schizophrenia, 48% of deaths among individuals with bipolar disorder, and 50% of deaths among individuals with depressive disorder are attributed to tobacco use (Callaghan et al., 2014). The smoking-related death rates among individuals with MI may be attributed partially to the smoking prevalence and intensity among these populations.

Relative to smoking rates among individuals without MI (15.5%), current smoking rates among individuals with MI are much higher for individuals with lifetime MI (33.4%) and individuals with past-year MI (39.0%; Smith et al., 2014). Moreover, 40% of all cigarettes produced in the US are consumed by smokers with MI (Substance Abuse and Mental Health Services Administration; SAMHSA, 2013). Cessation rates among smokers with MI are lower than rates observed among individuals without MI; for example, smokers with past-month MI reported quitting at significantly lower rates relative to smokers without MI (30.5% vs. 42.5%), with cessation rates observed to be as low as 22.0% for individuals with dysthymia (Lasser et al., 2000) for example.

Potential barriers for successful smoking cessation among smokers with MI include biological factors (Wing et al., 2012), psychosocial factors such as increased stress (Tulloch et

al., 2016), limited access to cessation resources (SAMHSA, 2013) as well as nicotine dependence-related factors (Pomerleau et al., 2005). Innovative and timely approaches to promote cessation as well as harm reduction for those who experience greater barriers are needed to address these MI and tobacco-related disparities. One such tool may be electronic nicotine delivery systems (ENDS). While not harmless, ENDS represent a potential means to deliver nicotine without many of the harmful constituents associated with combusted tobacco use (National Academies of Sciences, 2018). Systematic study of ENDS use among individuals with mental health conditions is limited, but results among general populations indicate that these novel tobacco products may hold promise for some groups of smokers (Gentry et al., 2019).

Cigarette Smoking and MI Status

Significant strides have been made in tobacco prevention efforts, as highlighted by nationally representative survey data collected between 2004 to 2011 that suggest a decrease in smoking rates among individuals without MI from 19.2% to 16.5% during that time (Cook et al., 2014). In contrast, during the same time period, smoking rates among those with any MI only decreased from 25.3% to 24.9% (Cook et al., 2014). The term MI describes a health condition during which the affected individual exhibits changes in cognitive, emotional, and/or behavioral processes that in turn can influence the affected individual's functioning in important areas of their life negatively, including work and social functioning (American Psychiatric Association; APA, 2018). The classification category of any MI may include any mental, emotional, or behavioral disorder regardless of the mild or severe nature of the impairment associated with the disorder (National Institute of Mental Health; NIMH, 2019a). Substance use disorders are considered to be MI as well (NIMH, 2021). The classification of severe MI is limited to illnesses associated with severe limitation in functioning due to a behavioral, mental, or emotional illness

causing impairment in at least one area of life (NIMH, 2019a). Severe MI includes

schizophrenia, bipolar disorder, major depression with symptoms of psychosis, or psychotic

disorder but can involve anxiety, personality disorders, and eating disorders if the affected

individual suffers from severe MI-related impairment due to their disorder (Evans et al., 2016).

Today, smoking prevalence rates among individuals with MI remain disproportionately

high. As of 2018, 16.3% of individuals without MI reported current (past 30-day) cigarette

smoking (SAMHSA, 2019). In comparison, current smoking rates among those with any past-

year MI was 28.1% (SAMHSA, 2019). Individuals suffering from multiple MIs have even higher

smoking rates (Lasser et al., 2000). Particularly high prevalence of smoking is observed among

individuals with severe MI. Among individuals with past-year SMI, 37.2% were current smokers

(SAMHSA, 2019) with some of the highest rates of use observed among individuals with

schizophrenia (59.1%) and bipolar disorder (46.4%; McClave et al., 2010).

Depression and anxiety, both of which fall under the umbrella term of mood or affective

disorders, are among the most prevalent MIs in the US. Depression affects 7.1% of the US adult

population (NIMH, 2019b) and is marked by symptoms such as anhedonia (loss of

interest/pleasure) and/or low affect (APA, 2013). Past two-week presence of anhedonia or low

affect in combination with other symptoms such as loss of energy or excessive feelings of guilt

warrants the diagnosis of major depression episode per the Diagnostic and Statistical Manual of

Mental Disorders (DSM-V; APA, 2013). Within the diagnoses of depression, the severity of

impairment is mirrored in smoking rates. For example, 33.5% of those who experienced a major

depressive episode with severe impairment reported current smoking while among individuals

who experienced a major depressive episode without severe impairment, 30.5% reported current

smoking (SAMHSA, 2019). Anxiety disorders affect 18.1% of the US population, making it the

most prevalent MI in the US (Anxiety and Depression Association of America; ADAA, 2018).

Smoking prevalence among individuals with anxiety disorders is higher than in the general

population; a nationally representative survey (n=5,692) conducted between 2001 and 2003

observed past 12-month daily smoking prevalence to be 33.9% for individuals with social

anxiety disorder, 39.5% for panic disorder, 36.5% for generalized anxiety disorder, and 37.9%

for posttraumatic stress disorder (Cougle et al., 2010), the latter of which was classified as an

anxiety disorder in the DSM-IV (APA, 2000).

These smoking rates highlight the severity of the public health threats associated with

smoking within individuals who meet diagnostic criteria of an MI. However, some research

suggests that lifetime reported depressed mood and anhedonia (separate from holding a clinical

diagnosis) predict smoking cessation failure irrespective of lifetime depressive disorder diagnosis

(Leventhal et al., 2014). Moreover, the link between smoking and depressive symptoms has been

reported among individuals below the threshold for a clinical diagnosis, with greater symptom

severity being linked to greater likelihood of being a current smoker as well as a decreased

likelihood of successful quitting (Anda et al., 1990). Similar findings exist in regards to

nonspecific psychological distress, which describes a dimension of somatic and psychological

symptoms that are not linked to any single specific MI but are prevalent among those with

affective disorders (Dohrenwend et al., 1980). In fact, most individuals with high psychological

distress meet the diagnostic criteria for an MI (Lawrence el al., 2011). Among individuals who

score moderately on a questionnaire measuring psychological distress, 33.9% are current

smokers, and among those who score highly, 41.9% are current smokers (Lawrence et al., 2011).

In addition to having a high smoking prevalence, populations with MI smoke with greater

intensity (i.e., consume more cigarettes) relative to smokers without MI. Past research has

assessed the intensity of smoking among those groups focusing on prevalent MI, including depression and anxiety. A longitudinal study revealed that individuals suffering from major depression smoke significantly more cigarettes per day (CPD) relative to those not reporting major depression at age 17 to 18 (mean CPD 2.1 vs. 1.0) and age 20 to 21 (mean CPD 4.6 vs. 2.6; Fergusson et al., 2003). For example, while only 11.6% of a nationally representative sample reported past 12-month heavy smoking (i.e., at least 20 CPD), prevalence of heavy smoking was higher among those with anxiety, including individuals with social anxiety disorder (19.0%), panic disorder (22.4%), general anxiety disorder (25.5%), and posttraumatic stress disorder (24.0%; Cougle et al., 2010).

Additionally, among a nationally representative sample of 23,635 adults, lifetime diagnosis of posttraumatic stress disorder was observed to be significantly and positively related to lifetime smoking status, nicotine dependence, and CPD (Greenberg et al., 2012). Smoking prevalence and intensity (as indexed by CPD) also are higher among individuals who report clinical depression and/or depressive symptoms (Leventhal et al., 2008). Because depressive symptoms are influenced by various psychopathologic factors, the relationship between depression and smoking is difficult to characterize by investigating the link between smoking-related outcomes and depression associations (Leventhal et al., 2008). However, in regards to depression as well as other MI, several mechanisms have been identified that may help explain the patterns of smoking observed among individuals with MI.

Mechanisms Underlying the Relationship Between Mental Health and Smoking

The rewarding properties of nicotine, the dependence-producing chemical found in tobacco, play a critical role in conditioning processes that contribute to shaping smoking

behaviors. However, other processes specific to smokers with MI also may explain the high smoking prevalence among this population compared to other groups.

Pharmacology of nicotine. Nicotine can be absorbed via the bladder, the gastrointestinal tract, the skin, the buccal cavity, and the lungs (Schievelbein et al., 1973). When inhaling cigarette smoke, nicotine is transported into the lungs via inhaled smoke particles and then travels via the pulmonary veins into the arterial circulation (Benowitz, 2010). Via the bloodstream, nicotine then can cross the blood brain barrier, reaching the brain (Oldendorf, 1974). Located across limbic and cortical brain regions are nicotinic acetylcholine receptors (nAChRs) which consist of ligand-gated ion channels (Benowitz, 2010). A set of proteins, α_{2-10} and β_{2-4} are arranged around the pore of the nAChR channel; receptors comprised of two α_4 proteins and three β_2 proteins play an important role in nicotine's rewarding effects (Benowitz, 2010). Nicotine, acting as an agonist, binds to and stimulates nAChRs, triggering the release of a range of neurotransmitters, including norepinephrine, serotonin, glutamate, beta endorphin, acetylcholine, and dopamine (Benowitz, 1999).

A particular reward pathway plays a critical role in this process; nAChRs located in the ventral tegmental area (VTA) of the midbrain, facilitate release of dopamine into the nucleus accumbens (Dani & De Biasi, 2001). Meanwhile, nicotine triggers the glutamate release from glutamate neurons found in the frontal cortex, onto the neurons of the VTA, which then release dopamine (Mansvelder & McGehee, 2002). Additionally, nicotine desensitizes nAChRs located on γ-aminobutyric acid (GABA) neurons in the VTA (Mansvelder & McGehee, 2000, 2002). This desensitization results in a reduction of GABA release, which in turn leads to decreased VTA inhibition and subsequent increased dopamine release (Mansvelder & McGehee, 2000, 2002). The dopamine surge in the nucleus accumbens resulting from nicotine administration

produces pleasurable and rewarding sensations and is a characteristic shared by all drugs of abuse (Di Chiara & Imperato, 1988). Dopamine increases in the shell of the nucleus accumbens have been shown to be nicotine dose-dependent with higher doses producing a greater concentration of dopamine (Nisell et al., 1997; Pontieri et al., 1996). Dopamine is also released into regions of the brain that are tasked with habit forming, learning, and emotional memory, including the dorsal striatum, the prefrontal cortex, and the amygdala (D'Souza & Markou, 2011; Laviolette, 2007; Schultz, 2007; Seamans & Yang, 2004). Dopamine produces a spectrum of effects that users perceive as desirable, and that reinforce the self-administration of nicotine, which in turn increases the likelihood of continued use and the subsequent development of tolerance and dependence.

Development of tolerance and dependence. Positive and negative reinforcement processes contribute to the establishment and maintenance of nicotine dependence following the administration of nicotine-containing products such as cigarettes or ENDS (Benowitz, 2009; Eissenberg, 2004; Glautier, 2004). Nicotine functions as a positive reinforcer, thus increasing the likelihood of reoccurrence of smoking (Shadel et al., 2000). Positive reinforcement occurs when the nicotine user experiences the pleasant and rewarding sensations resulting from nicotine administration. Dependent on dosage, nicotine also produces mild euphoria and heightened arousal (Watkins et al., 2000) or reduced arousal (Nesbitt, 1973) and increased relaxation (Silverstein, 1982). Moreover, nicotine is linked to improved concentration, learning, and attention (Levin et al., 2006). Positive reinforcement processes are at play especially when someone first begins to smoke (Glautier, 2004). However, as nicotine is administered repeatedly, neuroadaptation occurs, and the number of nicotinic binding sites on nAChRs is upregulated in response to the desensitization of the receptors following nicotine administration (Benowitz,

2010; Wang & Sun, 2005). Regular smokers tend to keep nAChRs in a desensitized state during regular smoking (Benowitz, 2010; Brody et al., 2006).

However, once nicotine is no longer administered, nAChRs become responsive again and nicotine abstinence-related symptoms begin to appear (Tidey et al., 2017; Wang & Sun, 2005). Smokers who undergo nicotine abstinence experience a range of aversive symptoms, including somatic symptoms such as gastrointestinal distress, headaches, and insomnia, and psychological symptoms including, but not limited to, anger, restlessness, concentration difficulties, and anxiety which can be suppressed by nicotine administration (Hughes et al., 1991). However, smoking-related stimuli even when not accompanied by nicotine, can also suppress some withdrawal symptoms; a double-blind, within-subjects study (n=32) revealed that nicotine-containing and denicotinized cigarettes suppressed some withdrawal symptoms, including urges to smoke, to a similar degree, while other withdrawal symptoms, such as difficulty concentrating, could only be suppressed by nicotine-containing cigarettes (Buchhalter et al., 2005).

When nicotine is administered and the aversive symptoms (i.e., the aversive stimulus) are alleviated, negative reinforcement takes place and the likelihood of nicotine self-administration increases (Eissenberg, 2004). The transition from positive reinforcement-motivated nicotine administration to withdrawal avoidance is a pivotal time point in the substance use process, as previous use occurrences constituted non-dependent drug use, while the use in order to terminate aversive withdrawal effects present the beginning of dependent drug use (Eissenberg, 2004). As the use of a substance continues, counteradaptation occurs and neurobiological changes lead to an increase in a user's hedonic setpoint; thus, substances, when administered in the same dosage as pre-dependence, no longer produce desirable effects but rather only alleviate the negative state

that occurs during withdrawal (Koob & Le Moal, 1997). In addition to the dependence-producing effects of nicotine, MI-related factors may contribute to the disproportionate prevalence and intensity of smoking among individuals with MI. A body of literature has aimed to isolate processes that may explain the smoking patterns among this population.

      Bidirectional relationship between smoking and MI. Among the attempts to explain the nature of the relationship between MI and smoking, much attention has focused on the temporal precedence of one factor over the other. Some evidence has suggested that MI symptoms and smoking behavior can precede each other and thus form a reciprocal or bidirectional relationship (e.g., Leung et al., 2011; Ranjit et al., 2019). For example, a longitudinal epidemiologic study aimed to examine the role of smoking in among 1,007 young adults with first-onset major depression, as well as the role of major depression in their later smoking behavior (Breslau et al., 1998). Five-year follow-up data revealed that individuals who reported a lifetime diagnosis of major depression at baseline were three times more likely to report daily smoking at the five-year point; in turn, those who reported daily smoking at baseline were significantly more likely to report major depression at five-year follow-up (Breslau et al., 1998). The notion of a reciprocal relationship between tobacco use and MI symptoms hold true for ENDS as well. For example, longitudinal data from 2,460 adolescents suggested that increased depressive symptoms at baseline served as a predictor of cigarette smoking, ENDS use, and dual use (Lechner et al., 2017). In turn, the same study observed that when compared to non-ENDS users, those who reported ongoing ENDS use across the 12-month duration of the study were significantly more likely to report an increase of depressive symptoms over time as well as significantly higher depression scores at 12-month follow up (Lechner et al., 2017).

While research reviewed here suggests that MI symptoms and tobacco use can influence each other, other results support the precedence of tobacco use over MI symptoms. For example, a longitudinal study using data from a nationally representative sample of 42,862 adults found that age at tobacco use initiation served as a predictor of lifetime major depressive disorder later in life (Hanna & Grant, 1999). Relative to nonsmokers, smokers who reported initiating smoking prior to age 13 were almost twice as likely to report lifetime major depressive disorder and reported significantly more major depressive episodes than late-onset smokers and nonsmokers, suggesting that tobacco may serve as a precipitant of depressive disorders (Hanna & Grant, 1999). Similarly, analyses of data derived from two semi-structured interviews of 1,709 adolescents spaced 12 months apart observed that individuals who reported current smoking at baseline were almost twice as likely to report a major depressive episode during the subsequent 12 months (Brown et al., 1996). Other data suggest a similar pattern related to anxiety symptom development. Analyses of two longitudinal nationally representative epidemiologic studies using samples of 1,007 and 4,411 individuals revealed that daily cigarette smoking was linked to an almost four-fold risk of reporting a panic attack later on, while there was no evidence that the presence of panic attacks predicted daily smoking at a later time point (Breslau & Klein, 1999). However, while this particular study did not find symptoms of MI to predict later tobacco smoking, other findings indicate the opposite. In fact, some research suggests that smoking taking place post-symptom onset may serve a specific purpose for smokers with MI, namely the alleviation of the MI symptom severity.

Self-medication hypothesis. In contrast to the use of nicotine to alleviate negative and/or adverse symptoms associated with nicotine abstinence, the self-medication hypothesis describes a process in which an individual uses a substance in order to manage a set of symptoms

associated with a behavioral illness that preceded exposure to the substance (Goldstein, 1987; Khantzian, 1997). Much work has investigated the effects of smoking on the reduction of symptoms associated with MI, suggesting that nicotine and/or smoking may be effective in producing symptom relief. For example, an in-lab experiment using a within-subjects design recruited six minimally nicotine-deprived smokers to complete three counterbalanced sessions differing in cigarette-delivered nicotine administration, including smoking of an own brand cigarette, not smoking, and smoking a zero-nicotine cigarette (Pomerleau et al., 1984). Anxiety was induced by prompting the participants to solve an unsolvable anagram in a short period of time, thus producing task failure among participants while being observed by the researcher (Pomerleau et al., 1984). Thirty minutes prior to all sessions, participants smoked a cigarette to ensure minimal nicotine deprivation. Anxiety symptoms were assessed immediately before and after the nicotine administration manipulation. The own brand condition resulted in significantly greater decreases in anxiety relative to the zero-nicotine cigarette condition (Pomerleau et al., 1984). However, the potentially symptom-alleviating effects of nicotine are not limited to anxiety. For example, the role of nicotine in the symptom regulation of individuals with attention-deficit/hyperactivity disorder (ADHD) has received attention. A cross-sectional analysis of a small subsample of 23 community youth with ADHD observed that non-medicated individuals were significantly more likely to report lifetime or current cigarette smoking (Whalen et al., 2003). Authors here hypothesized that the higher rate of smoking among non-medicated individuals may have been due to the individuals' attempts to self-medicate with nicotine to improve negative affect, attention, and impulsivity (Whalen et al., 2003).

The construct of smoking expectancies, i.e., the anticipation of smoking-related consequences, such as the belief that smoking can alleviate one's negative affect is critical when

considering the self-medication hypothesis. Smoking expectancies have been suggested to influence intensity of smoking (Brandon & Baker, 1991). This finding may imply that smoking may not indeed produce true symptom alleviation but that increased smoking upon stress occurs solely due to smokers' expectations of subsequent mood improvement. However, while smoking expectancies undoubtedly play a role in the maintenance of smoking behavior, several studies have been conducted that investigate the effects of nicotine specifically on nonsmokers' symptoms of MI (i.e., to understand nicotine's effects among on individuals who do not have established smoking expectancies).

For example, in randomized double blind study aimed to investigate the effects of nicotine administration on ADHD symptoms and continuous performance test outcomes, 40 nonsmoking adults with ADHD were assigned to four conditions including control, methylphenidate (20 mg), nicotine (delivered via patch), and nicotine and methylphenidate (Levin et al., 2001). Nicotine and/or methylphenidate was administered for four weeks, with the nicotine concentration starting with 5 mg daily during week 1, 10 mg daily during week 2 and 3, and 5 mg during week 4 (Levin et al., 2001). On the first day of drug administration, transdermal nicotine was associated with significant decreases in ADHD symptom severity; however, the effects of nicotine on ADHD symptoms was no longer detectable during the chronic administration phase (Levin et al., 2001). Another longitudinal study randomly assigned 24 nonsmokers who met criteria for major depressive episodes and reported insomnia to receive either nicotine patches (17.5 mg) or fluoxetine (20 mg; Haro & Drucker-Colin, 2004a). Dosages and administration frequency were maintained until 6 months post-baseline, then administered less frequently, and eventually replaced with a placebo (Haro & Drucker-Colin, 2004a). Rapid Eye Movement (REM) latency, which is frequently implicated in individuals with depression, as

well as depression scores improved significantly across both groups. For the nicotine group, analyses of polysomnographic recordings suggested improvements in slow wave sleep, sleep efficiency index scores, and overall sleep duration, with small decreases in time spent in REM sleep during nicotine withdrawal (Haro & Drucker-Colin, 2004a). The same authors conducted a single-blind clinical study during which nicotine patches (17.5 mg) were administered to 14 nonsmokers with major depression for six months and then tapered off until the end of the 24-month long study until participants received a placebo patch (Haro & Drucker-Colin, 2004b). Improvements in depression scores were reported; at the end of the study, participants reported a 63.5% decrease in depression scores, with a >50% decrease observed in 78.6% of participants. Moreover, REM latency values approached levels seen in non-depressed populations (Haro & Drucker-Colin, 2004b). Taken together, these three examples support the idea that nicotine administration alone (not nicotine-related expectancies) can improve measures of mental health/cognition among those with MI. However, additional factors, including social and environmental factors exist that may contribute to the prevalence of smoking among individuals with MI.

Social and environmental factors. Social and environmental factors contribute to shaping the smoking patterns among individuals with MI. One of the factors that has been implicated in contributing to the high smoking rates among individuals with MI is proximity and density to tobacco retailers; a study geocoded the addresses of 1061 smokers and assessed the proximity to the nearest tobacco retailer as well as the number of retailers available nearby (Young-Wolff et al., 2014). Findings revealed that smokers with severe MI clustered around neighborhoods in which the tobacco retailer density was twice as high relative to their counterparts without severe MI. After controlling for demographics, poverty level, and MI

diagnosis, greater tobacco retailer density was observed to be significantly related to impaired psychosocial functioning as indexed by reported self-injurious behavior, interpersonal difficulties, and psychosis (Young-Wolff et al., 2014). Additionally, social status influences smoking among individuals with MI. A study with a sample of smokers and nonsmokers with severe MI (n=240) observed that objective social status as indexed by several factors including annual income and education was significantly related to smoking status with those lower in social status having a greater likelihood of being smokers (Langlois et al., 2020). Additionally, social status was also significantly related to nicotine dependence among individuals with severe MI, with lower social status being related to greater nicotine dependence (Langlois et al., 2020). These studies highlight the influence of social and environmental factors on smoking patterns among individuals with MI, suggesting that neighborhood-related factors such as easy access to tobacco products and lower social status may exacerbate smoking among individuals with MI.

Summary. The literature reviewed here describes some mechanisms commonly implicated in the development of nicotine dependence among the general smoking population as well as specific processes hypothesized among individuals with MI. In addition to these factors that may contribute to the maintenance of smoking, barriers may exist that make quitting and harm reduction approaches in this vulnerable subgroup of smokers more challenging.

Smoking Cessation/Harm Reduction Challenges among Smokers with Mental Illness

Due to the highly addictive nature of nicotine delivered via cigarettes, smokers encounter significant difficulties when attempting to stop smoking (Babb et al., 2017) or reduce cigarettes smoked as a method of harm reduction (Begh et al., 2015). However, individuals with MI

experience additional barriers to successful smoking cessation, which are reflected in the low quitting rates among this population.

For example, a population-based cross-sectional survey using 4,411 individuals observed that relative to smokers without MI who reported quit rates of 42.5%, both smokers with past-month MI (30.5%) and smokers with lifetime MI (37.1%) reported significantly lower quit rates (Lasser et al., 2000). Additionally, a large-scale population-based survey using data from 142,000 adults observed that lifetime daily smokers who reported past-year MI were more likely to be current smokers (61.6%) relative to lifetime daily smokers without past-year MI (47.2%; Lipari & Van Horn, 2017). For example, smoking cessation after a 9-year follow up was 17.7% for smokers classified as non-depressed and 9.9% for smokers classified as depressed via self-report measure using a cutoff score at baseline (Anda et al., 1990).

Additionally, a cross-sectional study using population-based data from 3,213 individuals observed that ever smokers who suffered from major depressive disorder were significantly less likely to have quit smoking relative to their counterparts without major depressive disorder (Glassman et al., 1990). Similarly, a smoking cessation treatment study of 1,469 daily smokers identified anhedonia, a symptom of depression, to be linked to significantly lower 7-day quit rates (Leventhal et al., 2014). A large cross-sectional population-based survey using data from 248,800 individuals observed that reports of lifetime diagnosis of depression, anxiety, and dual diagnoses of depression and anxiety were most frequent among smokers who reported failed quit attempts, and lowest among those reporting successful smoking cessation (McClave et al., 2009). Smokers who reported failed quit attempts also reported greater severity of depressive symptoms, while those who quit successfully reported the lowest levels of depression (McClave et al., 2009).

Other psychological factors present barriers as well. For example, a trial involving 732 smokers with and without MI indicated that stress was cited significantly more frequently as a reason for cessation relapse across smokers with anxiety and depression relative to smokers without MI (Tulloch et al., 2016). Negative affect also was reported more frequently as a reason for cessation relapse by participants with anxiety, depression, and bipolar disorder. The same study also investigated cessation-specific concerns; relative to smokers without MI, smokers with anxiety disorders were significantly more likely to report fear of failure, mood, and stress as cessation-related concerns (Tulloch et al., 2016). Moreover, relative to smokers without MI, both smokers with psychotic disorders and smokers with anxiety disorders were significantly more likely to report boredom as a cessation-related concern (Tulloch et al., 2016).

Nicotine dependence-related factors present barriers as well. While no significant between-group differences were observed across MI categories for reported concerns about cravings, the majority (55.6%) of individuals with lifetime psychotic disorders and about one third of individuals with anxiety (31.9%) and depression (27.2%) reported cravings as a cessation-related concern (Tulloch et al., 2016). Also, a four-week smoking cessation study (n=81) comparing contingency management smoking treatment to standard smoking treatment revealed that smokers with high levels of depressive symptoms at baseline reported an increase of withdrawal symptoms and smoking urges during week 1, while smokers with low levels of depressive symptoms reported a decrease in withdrawal symptoms and smoking urges during the first week (Reid & Ledgerwood, 2016). Additionally, relative to smokers who reported low levels of depressive symptoms at baseline, those who reported high levels of depressive symptoms at baseline reported higher levels of nicotine withdrawal throughout the entire study (Reid & Ledgerwood, 2016). Depressed mood has also been linked to relapse; a smoking

cessation treatment study (n=1,469) found smokers with depressed mood as well as those who specifically reported anhedonia to be at a significantly greater risk of relapse relative to their counterparts without depressed mood (Leventhal et al., 2014). Thus, depressive symptoms present a risk factor for cessation complications (e.g., increased nicotine withdrawal at the start of cessation) as well as relapse and should be considered when evaluating the effectiveness of smoking cessation or harm reduction approaches, as they may influence rates of success particularly among smokers with MI.

Social and environmental factors likely contribute to the reduced likelihood of quitting smoking as well. For example, greater tobacco retailer density in one's neighborhood has been found to be significantly related with lower self-efficacy for smoking cessation (Young-Wolff et al., 2014). Moreover, a systematic literature review of qualitative and quantitative studies on barriers among vulnerable populations found that such populations, including smokers with MI, live in environments in which smoking is common and acceptable and that being around other smokers was perceived to be a barrier (Twyman et al., 2014).

An additional factor leading to a discrepancy in cessation rates among smokers with and without MI exists at provider-level in the healthcare system. A survey of all known private and public substance use treatment facilities in the US (n=5,737) identified a lack of access to cessation resources; only 42% of all surveyed facilities provided smoking cessation services (SAMHSA, 2013). Other provider-level barriers include the gross underestimation of healthcare providers' perceptions of smokers' willingness to quit. For example, when 231 smokers with severe MI who were patients at community mental health centers were surveyed about their cessation interest and treatment, interest in taking cessation medication was reported by 44.0%, and only 13.0% reported current use of cessation medication (Chen et al., 2017). Additionally,

while 25.0% reported interest in undergoing cessation counseling, only 5.4% reported current cessation counseling (Chen et al., 2017). Such findings may be linked to a underestimation of interest in smoking cessation among smokers with MI; results from the same survey indicated that while 82.0% of smokers with severe MI reported wanting to quit or reduce their cigarette intake, over 90.0% of the psychiatrists surveyed reported that the perceived lack of interest in smoking cessation among their patients with severe MI presented a barrier to implementing cessation efforts (Chen et al., 2017).

Social and environmental factors as well as MI symptom-related factors, nicotine dependence-related factors, and provider-level factors constitute some of the barriers that prevent smokers with MI from successful cessation, despite several smoking cessation and harm reductions being available for smokers, including smokers with MI.

Smoking Cessation/Harm Reduction Treatment Approaches for Those with Mental Illness

Smoking treatment approaches for individuals with MI typically mirror those implemented among the general smoking population and it remains unclear if smokers with MI derive greater benefits from cessation treatments specifically tailored to MI symptoms relative to traditional treatment (Baker et al., 2004). The US Food and Drug Administration (FDA) has approved seven first-line medications for the treatment of tobacco use (Fiore et al., 2008). While some of the first-line medications contain nicotine, some do not, and all have been deemed to be generally safe (Little & Ebbert, 2016) as well as effective in aiding adult smoking cessation (Fiore et al., 2008). Additionally, counseling delivered across various settings is considered effective. It is critical to provide aid to smokers during cessation attempts, as unaided quit attempts are only successful in 4% to 7% of smokers (Fiore et al., 2008). Ideally, treatment should aim to achieve complete smoking cessation in order to avoid smoking-related harm

altogether. However, in cases where complete abstinence may not be possible, the alternate goal of harm reduction may be pursued (Hughes, 1995; Kozlowski, 1989), meaning that if a behavior such as smoking is continued, harm potential should be reduced to a minimum if possible, which can include nicotine delivery through alternative, less harmful methods (Britton & Edwards, 2008).

Nicotine replacement therapy (NRT) products are administered in order to replace the nicotine in the body typically derived from smoking and subsequently alleviate nicotine withdrawal symptoms and decrease the desire to smoke (Silagy et al., 2004). For this purpose, the FDA has approved multiple NRT products including nicotine gum, lozenge, nasal spray, inhaler, and the transdermal patch (Fiore et al., 2008). NRT products differ in their dose and speed of nicotine delivery over time. For example, relative to the 5-10 minutes that cigarette-derived nicotine takes to be absorbed, nicotine that is delivered via a nicotine gum and absorbed through the buccal mucosa takes about 30 minutes (Russell et al., 1980). Nicotine delivery time is critical as smoking cigarettes allows the user to titrate their plasma nicotine concentrations during the day particularly in response to nicotine cravings that may arise (Sweeney et al., 2001).

To prevent relapse, combination NRT therapy may be offered to smokers in order to address components of nicotine dependence. Benefits of this approach have been noted in a meta-analysis including 63 randomized controlled trials (RCTs; n=41,509) with greater cessation success rates at 6-month follow-up when a slow acting NRT (i.e., patch) was combined with a fast acting NRT (e.g., gum; Lindson et al., 2019). In addition to how quickly nicotine is delivered, the dose of nicotine dose delivered plays a role in cessation success, with higher dosages of nicotine being linked to greater likelihood of long-term cessation; e.g., cessation rates with 4 mg nicotine gum relative to 2 mg nicotine gum (risk ratio=1.43; Lindson et al., 2019).

Two non-nicotine medications are currently FDA-approved and marketed for smoking cessation. Bupropion mimics the stimulant effects typically associated with nicotine, thus promoting suppression of nicotine abstinence-related withdrawal symptoms and subsequently preventing smoking relapse by blocking the reuptake of norepinephrine and dopamine as well via the blocking of nAChRs (Fiore et al., 2008; Warner & Shoaib, 2005). Similarly, varenicline, a partial nAChR agonist, inhibits nicotine from binding to its respective receptors, thus slowing the release of dopamine while decreasing negative symptoms associated with nicotine abstinence (Kaur et al., 2009).

Behavioral treatment has been established as an integral factor in smoking cessation with several approaches deemed effective, including counseling by a professional in a face-to-face setting, group counseling, phone counseling, and self-help programs, the latter of which can consist of printed or electronic materials (Crain & Bhat, 2010). Cognitive behavioral therapy can teach smokers to cope with negative symptoms associated with nicotine abstinence as well as associated mood effects and smoking urges. This method focuses on motivational and behavioral factors associated with smoking (Crain & Bhat, 2010). Intensive smoking cessation support includes residential programs, where severely nicotine dependent individuals suffering from comorbid conditions such as medical conditions and/or substance use disorders can receive behavioral counseling, education, pharmacotherapy, and group therapy (Crain & Bhat, 2010). Newer behavioral treatment approaches make use of mobile technology; relative to a control condition, moderate effectiveness was found for text message cessation programs, regardless of whether such programs included an in-person or online counseling component or consisted solely of text messages (Spohr et al., 2015).

Effectiveness of available treatments in smokers with MI. Smokers with MI
experience a set of psychological stressors that may present barriers to successful smoking
cessation. However, some research describes effective cessation methods for smokers with MI.
For example, a review of results from eight RCTs that included n=10 to n=298 of smokers with
schizophrenia, "psychotic disorder", or schizoaffective disorder, assessed point prevalence
abstinence and/or smoking reduction at different time points for different treatment methods,
using meta-analysis to when treatment and comparisons were deemed similar (Banham &
Gilbody, 2010). Findings revealed that relative to traditional care, NRT in combination with
individual therapy produced significantly greater rates of smoking abstinence among smokers
with severe MI at four-month follow-up (risk ratio; RR=2.74) relative to smokers with severe MI
randomized to receive standard care consisting of access to community mental health teams and
general practitioners (see Baker et al., 2006). However, significant differences were no longer
observed at seven-month follow up (Banham & Gilbody, 2010). Bupropion plus group therapy
was found to be more effective relative to placebo combined with group therapy at trial endpoint
(RR=4.18; Banham & Gilbody, 2010). Moreover, bupropion in combination with group therapy
and NRT produced greater abstinence rates relative to group therapy combined with NRT
(RR=2.34); additionally, bupropion was more effective than placebo in producing smoking
abstinence (RR=2.77). Smoking reduction ($\geq$ 50% reduction of CPD from baseline) could not be
investigated using a meta-analysis given the differences in outcomes and time points across
different studies. The authors of the literature review reported that no significant differences in
smoking reduction rates was found in the RCTs included between NRT and placebo, between
NRT plus group therapy, or group therapy alone (Banham & Gilbody, 2010). However, relative
to usual care, NRT produced greater rates of smoking reduction at four-month follow-up

(RR=2.62), and group therapy in combination with bupropion was more found to be more effective for smoking reduction than group therapy alone at the three-month time point (Banham & Gilbody, 2010).

Smokers with current depression were more likely to be abstinent at 6-month follow-up or longer relative to control when a psychosocial mood management factor (mostly a cognitive behavioral therapy component) was added to cessation treatment (RR=1.47), as suggested by a meta-analysis of 11 RCTs (n=1,844; van der Meer et al., 2013). Similarly, a meta-analysis of the results of 13 RCTs (n=1,496) suggested that adding psychosocial mood management to the standard smoking intervention was helpful for smokers with past depression (RR=1.41; van der Meer et al., 2013). In regards to the effectiveness of bupropion for smokers with current depression, a meta-analysis of eight RCTs (n=517) suggested that bupropion is effective relative to placebo (RR=1.32), as is bupropion in combination with NRT relative to NRT alone (RR=1.93; van der Meer et al., 2013). Similarly, bupropion was effective among smokers with past depression relative to placebo (RR=1.57), as well as when used in conjunction with NRT relative to placebo and NRT (RR=5.46; van der Meer et al., 2013). Lastly, a prospective cohort study aiming to estimate the prevalence of varenicline and NRT prescriptions among more than 13 million primary care patients in the United Kingdom found that smokers with MI who were prescribed varenicline had a 19.0% greater likelihood to have quit smoking at two-year-follow up relative to smokers with MI who were prescribed NRT (Taylor et al., 2020). However, the study also found that smokers with MI were 31.0% less likely to receive a varenicline prescription relative to smokers without MI (Taylor et al., 2020). The FDA has recently removed the black box warning advising individuals of severe side effects, including worsening mood (FDA, 2015), which may encourage medical professionals to prescribe the medication more

frequently in the future. The aforementioned study suggests that while some treatment methods may indeed be effective for smokers with MI, barriers indirectly related to some smokers' MI symptoms (e.g., providers' hesitation to prescribe treatment medications based on the patient's MI status) may in turn render such treatments ineffective due solely to non-administration. Overall, while NRT and other FDA-approved smoking cessation medications and behavioral counseling methods such as cognitive behavioral therapy have been found to be safe and effective among individuals with MI, short and long-term smoking rates among this population remain high, suggesting a need for alternative treatment options or improved treatment for this group of smokers.

ENDS Use, Nicotine Delivery, and Use Among Individuals with MI

The body of evidence regarding the effectiveness of nicotine and non-nicotine smoking cessation treatments suggests there is room for improvement among these approaches, particularly for individuals with MI. Although no ENDS are legally marketed for therapeutic use by US-based manufacturers, public and scientific interest in the ability of ENDS to reduce harm among conventional tobacco users remains high.

What are ENDS? This tobacco product class represents a diverse group of electronic devices that consist of a reservoir designed to hold a liquid solution, a battery or other power source, and a heating element (Hiler et al., 2017). The liquid solution typically contains vegetable glycerin and/or propylene glycol, which act as solvents, and flavorings (e.g., tobacco, menthol; Breland, 2017) and may, but does not always, contain nicotine. Some ENDS are puff-activated, while others are activated through the push of a button located on the device. Upon activation, an electrical current is used to heat the liquid solution and produce an aerosol that

users can inhale (Breland, 2017). Nicotine found in ENDS liquid solution varies in its form (pronated vs. non-pronated) which has implications for nicotine yield and delivery (El-Hellani et al., 2018). The nicotine concentration in most liquid solutions ranges from 0 mg/ml to 36 mg/ml (Breland, 2017) but nicotine concentrations in newer products such as JUUL can range upwards to 69 mg/ml (Talih et al., 2019).

Some ENDS products are about the size of a traditional cigarette and are called "first-generation devices" or "cigalikes" (Malek et al., 2018). Such first-generation ENDS are not designed for the user to refill the liquid once it is has been used (i.e., closed ENDS system) and do not give the user the ability to substitute the initial device-linked heating element or battery with other models. However, other ENDS products (often termed "second-generation devices") exceed the size of a traditional cigarette by far and have a tank to store the liquid and a battery detached from tank or cartridge (Breland et al., 2017). Second-generation devices typically are equipped with rechargeable batteries, refillable tanks, as well as features that can be adjusted by the user, including voltage (Harvanko et al., 2017). In comparison, third-generation ENDS devices are equipped with even more adjustable features relative to second-generation ENDS devices (Harvanko et al., 2017). Across the different device generations, differences in nicotine delivery and potentially harmful exposures have been found due to a spectrum of ENDS device and liquid characteristics (Breland, 2017; Talih et al., 2015). So-called pod mods such as JUUL exceed the nicotine delivery of non-cartridge-based ENDS models and resemble traditional cigarettes in their nicotine delivery profile (Hajek et al., 2020); however, nicotine delivery profile of JUUL relative to traditional cigarettes may be dependent on user experience (Prochaska et al., 2021). Effective nicotine delivery of ENDS and a potential subsequent suppression of symptoms

associated with nicotine abstinence may play a critical role in the promotion of ENDS for smoking cessation and/or reduction.

Nicotine Delivery from ENDS

As previously mentioned, negative reinforcement is one of the mechanisms through which ongoing nicotine self-administration is maintained. Among smokers, if nicotine delivery is ineffective from an alternative nicotine delivery product (e.g., ENDS), symptom suppression is likely to be incomplete, thus potentially increasing the likelihood an individual may relapse to their referred source of nicotine delivery. Among ENDS with nicotine-containing liquid solution, the effectiveness of nicotine delivery differs as a function of various factors including the device itself, liquid (i.e., nicotine concentration), and user history with ENDS.

Early studies of first-generation ENDS suggested that these products were ineffective in delivering nicotine to users. For example, a within-subjects experiment of 32 nicotine-deprived cigarette smokers involved conditions differing by product: own-brand cigarette, unlit cigarette (placebo), and two first-generation ENDS (one with liquid containing a 16 mg/ml and the other with liquid containing 18 mg/ml of nicotine). Unlike own-brand cigarette smoking, neither ENDS condition significantly increased plasma nicotine concentrations or heart rate after two 10-puff bouts of use (Vansickel et al., 2010). Use of own-brand cigarettes and both ENDS led to significant decreases in participants' symptoms of nicotine-related abstinence symptoms while the placebo did not (Vansickel et al., 2010). A similarly designed study indicated that a second-generation ENDS was more effective than a first-generation ENDS in delivering nicotine when loaded with the same nicotine concentration liquid (18 mg/ml; Farsalinos et al., 2014). Using a randomized cross-over design study, 23 experienced ENDS users were asked to take 10

standardized ENDS puffs followed by one hour of ad lib ENDS use. Across all measurement points, the second-generation ENDS produced greater plasma nicotine concentrations relative to first-generation ECIG. These condition-related differences in plasma concentrations were mirrored in self-reported cravings, which were significantly lower among participants in the second-generation ENDS condition relative to the first-generation ENDS condition (Farsalinos et al., 2014). Yet another in-lab experiment sought to compare the nicotine delivery of second-generation devices to those of third-generation devices. Exclusive ENDS users of second-generation devices (n=9) and third-generation devices (n=11) were recruited to complete a standardized 10-puff bout and a subsequent ad lib period using their own brand liquid and ENDS (Wagener et al., 2017). Importantly, mean (SD) nicotine concentrations in the liquid solutions of second-generation ENDS users were found to be 22.3 (7.5) mg/ml, which substantially exceeded the 4.1 (2.9) mg/ml found among third-generation ENDS users (Wagener et al., 2017). Yet, users of the third-generation devices achieved greater plasma nicotine concentrations compared to second-generation users at several time points throughout the session (Wagener et al., 2017). Of note, third-generation ENDS' heating elements had lower resistance relative the second-generation devices and consequently higher power than the second-generation devices used in this study (Wagener et al., 2017). Taken together, these data highlight the influence of ENDS device features on nicotine delivery capability.

Another experimental lab-based study highlights the influence of liquid nicotine concentration and ENDS use history on nicotine delivery and nicotine abstinence-associated effects when ENDS device features are held constant (Hiler et al., 2017). Here 33 ENDS-experienced users and 31 ENDS-naive smokers completed four sessions that differed by the nicotine concentration of liquid placed into the ENDS device (0, 8, 18, and 36 mg/ml). The

device was an "eGo" style with non-adjustable voltage settings similar to those described as second-generation ENDS (Caponnetto et al., 2017). The ENDS consisted of a 3.3 volt battery and a 1.5 Ohm cartomizer. Participants completed two standardized 10-puff bouts with a 30-second interpuff interval separated by 60 minutes. Plasma nicotine concentrations differed by ENDS use history, condition, and time with ENDS-experienced users achieving the dose-related increases in plasma nicotine as well as significantly greater plasma nicotine concentrations during nicotine-containing conditions compared to ENDS-naive users (see Table 1). Effects for nicotine abstinence-related symptoms indicated that greater suppression was observed among ENDS-experienced participants with the higher nicotine concentration liquid conditions (which resulted in the greatest nicotine delivery). One important contributor to these effects were differences in puff topography (i.e., puffing behavior) between user groups with experienced users taking larger (in volume) and longer puffs (even though puff number was held constant). A systematic review of studies measuring ENDS puff topography indicated that average puff duration was significantly longer compared to cigarette smoking and appeared to require "stronger suction" (Evans & Hoffman, 2014). This finding suggests that cigarette smokers may need to adapt their puffing behavior to achieve effective nicotine delivery and associated nicotine abstinence symptom suppression when initiating ENDS use.

Table 1. Nicotine boost from nicotine-containing-ENDS conditions after 10 puffs (30 sec IPI) by user experience (data are in ng/ml)

	8 mg/ml*	18 mg/ml*	36 mg/ml*
ENDS-experienced	8.2 (7.8)	13.0 (6.2)	17.9 (17.2)
ENDS-naive	3.6 (3.9)	6.2 (10.2)	6.8 (7.1)
Total sample	6.0 (6.6)	10.0 (12.2)	13.0 (14.3)

Note: Table adapted from Hiler et al., 2017; * indicates significant difference by ENDS use history (p<0.05; Tukey's HSD).

Variability in ENDS nicotine delivery likely offers one explanation for the varying effectiveness observed among the few published RCTs of ENDS for smoking cessation and/or harm reduction. Findings from the most recent Cochrane review included two RCTs (combined n=662), suggesting that smokers randomized to use nicotine-containing ENDS were 2.29 times as likely to achieve smoking cessation relative to smokers randomized to use non-nicotine-containing ENDS (Hartmann-Boyce et al., 2021). A 2018 systematic review undertaken by the National Academies of Sciences, Engineering, and Medicine concluded that there was "limited evidence" that ENDS are effective for smoking cessation, but their use as a complete substitute for cigarettes had "conclusive evidence" of reductions in toxicant exposure reduction and having "substantial evidence" for reduced short-term adverse health outcomes (National Academies of Sciences, Engineering, and Medicine, 2018). Closer examination of the current evidence regarding ENDS for smoking cessation and harm reduction efforts reflects this ambiguity.

ENDS for Smoking Cessation and Reduction

Among the larger (>200) and longer-term (>3 months) RCTs that have examined the effectiveness of ENDS for smoking behavior change, there has been mixed evidence on the role of nicotine dose/delivery. An RCT performed in New Zealand investigated the effects of a first generation ENDS (10-16 mg/ml nicotine) relative to a placebo ENDS (no nicotine) to nicotine patches (21 mg/24 h nicotine patches) on cessation in smokers (n=657) interested in quitting (Bullen et al., 2013). Overall quitting rates (6 months continuous abstinence) did not significantly differ from one another and were low across the three groups, including for the nicotine ENDS condition (7.3%), the non-nicotine-containing condition (4.1%) and the nicotine patch condition (5.8%); authors highlight a lack of statistical power as a possible reason for the absence of significant differences (Bullen et al., 2013). A 12-month prospective double-blind

RCT performed in Italy assigned smokers (n=300) not wanting to quit to one of three ENDS conditions with different nicotine concentrations (7.2 mg/ml nicotine, 5.4 mg/ml, and 0 mg/ml; Caponnetto et al., 2013). All three groups had significant decreases in CPD at week 52 with no significant between-group differences observed; across all groups, 8.7% were tobacco abstinent at week 52 (Caponnetto et al., 2013). On an intention-to-treat basis and excluding those who quit smoking, 14.5% in the nicotine-containing groups and 12.0% in the non-nicotine-containing groups reported at least a 50% reduction in CPD at 52 weeks (Caponnetto et al., 2013). In another large-scale RCT performed in the United Kingdom, participants (n=886) were assigned randomly to receive either a three-month supply of NRT product(s) of their choice or a second-generation ENDS (liquid nicotine concentration of 18 mg/ml) coupled with behavioral support for both groups (Hajek et al., 2019). One-year sustained abstinence (self-report of smoking <= 5 cigarettes from 2 weeks after the target quit date; CO <8 parts per million [ppm]) was significantly more prevalent in the ENDS condition (18.0%) than in the NRT condition (9.9%; Hajek et al., 2019). Among participants who were not abstinent, significant condition-related differences were found in smoking reduction, with 12.8% of ENDS condition participants reporting a 50% reduction relative to 7.4% of NRT participants (Hajek et al., 2019).

Another pragmatic, randomized trial enrolled ENDS-naive smokers and assigned them to one of three 14-week-long conditions, including nicotine patch only (n=125), nicotine patch plus nicotine-containing ENDS (n=500), and nicotine patch plus an ENDS with no nicotine (n=499). Participants were advised to use the nicotine patch daily and to use the ENDS as needed. Nicotine patches in combination with a nicotine-containing ENDS lead to a modest improvement in smoking cessation (6 months continuous and CO-verified ≤8 ppm) of 7%, which was

significantly higher than the quit rate from using patches plus a nicotine free ENDS (4%) or nicotine patches alone (2%; Walker et al., 2020).

An RCT conducted in Canada randomized adult smokers motivated to quit to conditions using either no ENDS at all, ENDS with 0 mg/ml of nicotine, or ENDS with 15 mg/ml of nicotine (Eisenberg et al., 2020). Individual smoking cessation counseling was provided to all groups. At 90-day follow-up, significantly more participants among those randomized to the nicotine-containing ENDS condition plus counseling reported greater 7-day point prevalence abstinence relative to those who had only received counseling (21.9% vs. 9.1%). However, no significant differences were found between those randomized to the 0 mg/ml of nicotine ENDS plus counseling and those assigned to counseling alone (17.3% vs 9.1%; Eisenberg et al., 2020). No significant differences in reported 7-day point prevalence abstinence between participants using ENDS with and without nicotine were found at 12-week and 24-week follow-up (Eisenberg et al., 2020).

These RCTs and others (Maserio et al., 2019; Halpern et al., 2018) underscore the potential utility of ENDS for smoking cessation and reduction efforts as well as relatively low levels of efficacy for FDA-approved treatments among adult smokers. Considering individuals with MI are at increased risk for smoking and development of nicotine dependence and have barriers to treatment, more information is needed regarding how ENDS could potentially be useful ENDS in this population.

Use behaviors and perceptions of ENDS among individuals with mental illness. Similar to higher rates of smoking among individuals with MI, ENDS also appear to be used to a greater degree among those with MI. Results from 2012 nationally representative cross-sectional

survey of 10,041 adults indicated that the likelihood of having tried ENDS was more than twice as high (14.8%) for individuals with lifetime MI relative to their counterparts without lifetime MI (6.6%; Cummins et al., 2014). Significant differences in ever ENDS use among smokers specifically were also noted with 40.3% of current smokers with MI reporting ever use of ENDS relative to 28.7% of their counterparts without MI (Cummins et al., 2014). More recent reports of ENDS use among populations with MI describe similar patterns. A 2015 nationally representative cross-sectional survey among 6,051 adults indicated that ENDS ever use was significantly higher among individuals with MI (24.4%) relative to those without MI (15.5%; Spears et al., 2017). Moreover, there was a positive relationship between the number of lifetime MI diagnoses reported and ever ENDS use, with 15.5% of individuals reporting no MI, 19.8% of individuals reporting two MI, and 42.3% of individuals reporting three or more MI also reporting ENDS ever use (Spears et al., 2019). Similarly, findings from a large-scale, cross-sectional study performed in 2016/2017 (n=892,394) suggested that current and former ENDS users were more likely to report lifetime depressive disorder and poor mental health relative to never ENDS users (Obisesan et al., 2019).

While the literature suggests that lifetime diagnoses of MI may increase the likelihood of ENDS use, other research suggests that even psychological distress may be linked to increased likelihood of ENDS use. A nationally representative survey of 36,697 adults found that individuals who scored higher on a measure of psychological distress were 3.7 times more likely to have ever used ENDS exclusively (Park et al., 2017). Moreover, those higher in psychological distress were 3.2 times more likely to have ever used ENDS and be a former smoker, 4.6 times more likely to be currently using cigarettes and ENDS, and 2.1 times more likely to be current

exclusive ENDS users, with authors noting an increase in odds ratios mirroring increases in psychological distress (Park et al., 2017).

These ENDS use patterns may also be influenced by ENDS perceptions among smokers with MI. Specifically, past research has suggested that smokers with MI perceive ENDS as socially acceptable, less harmful to others, and an effective tool for smoking cessation (Baltz & Lach, 2019; Hefner et al., 2016). Indeed, a survey of 231 smokers with severe MI who were patients at community mental health centers found that 22.0% reported currently using ENDS to quit smoking, while another 50.0% reported being interested in using ENDS as a smoking cessation tool (Chen et al., 2017). Taken together these data highlight the co-occurrence of ENDS use among smokers with MI and that use patterns may be influenced by the appeal of ENDS as a perceived cessation and/or harm reduction tool. Limited by data collected among the general population of smokers, information specific to the effectiveness of ENDS among smokers with MI is even sparser.

ENDS and Smoking Cessation and Reduction for Smokers with Mental Illness

Some small-scale clinical studies and a secondary analysis of data from a RCT have investigated the effects of ENDS among smoking samples with MI in regards to smoking cessation and reduction. During an unblinded, uncontrolled 4-week longitudinal study conducted among 43 military veteran smokers with MI reporting no intention of quitting smoking in the next month, participants were provided with an 1.8 ohm, 4.2 volts (voltage-adjustable) ENDS with either 12 mg/ml or 24 mg/ml nicotine concentration liquid (participant-selected) to use ad lib for four weeks (Valentine et al., 2018). Significant decreases in CPD and CO levels were noted at weekly study sessions; however, CO levels were not significantly lower than baseline at

the one-month follow-up. Significant decreases in nicotine dependence scores relative to baseline were observed at follow-up (Valentine et al., 2018). A nine-week open trial among 12 methadone-maintained smokers with an opioid use disorder asked participants to use a NJOY-branded ENDS for six weeks (Stein et al., 2016). Significant reductions in CPD were observed across the study period with one person reporting biochemically verified 7-day point prevalence of smoking abstinence week 7 (Stein et al., 2016). A one-year prospective observational study among 14 smokers with schizophrenia asked participants to use the ENDS "Categoria" ad lib while reducing their cigarettes smoked (Caponnetto et al., 2013). At week 52, 50% of participants reported sustained 50% reduction in cigarettes smoked from baseline with 14.3% reported having quit smoking (Caponnetto et al., 2013). A secondary data analysis from a larger-scale RCT comparing ENDS with and without nicotine to a nicotine patch (Bullen et al., 2013) evaluated condition-related effects by MI status (defined as use of medication prescribed for MI; O'Brien et al., 2015). Participants with MI (n=86) did not differ significantly from those without MI (n=571) in regards to biochemically verified cessation at six-month follow-up. Additionally, cessation rates among those with MI did not differ significantly by condition; however, participants with MI randomized to the nicotine-containing ENDS condition reported significantly greater reductions in CPD relative to participants with MI assigned to the nicotine patch (O'Brien et al., 2015). These reports suggest that ENDS may hold promise for smoking cessation and/or reduction among smokers with MI, but larger scale studies with greater methodological control and larger samples of smokers with MI are needed.

Past research suggests that smokers with MI may use nicotine-containing cigarettes to manage their negative mood-related symptoms (e.g., Pomerleau et al., 1984). However, research is needed to investigate if, and to what degree, ENDS with and without nicotine may be able to

serve as a substitute for cigarettes for smokers with MI. Moreover, it is not known whether, and to what degree, ENDS with and without nicotine may impact negative mood and stress-related symptoms that are characteristic of MI as well as nicotine abstinence.

Statement of the Problem

Cigarette smoking remains the single most preventable cause for death and disease across the world. Despite only accounting for 25% of the US population, individuals with MI smoke 40% of all US-manufactured cigarettes, develop nicotine dependence faster and to a more severe degree, and are less likely to quit smoking relative to smokers without MI. The self-medication hypothesis suggests that individuals with MI may smoke cigarettes to manage their symptoms via nicotine delivery. This pattern could be replaced by certain ENDS, which under certain conditions represent a rapid, non-cigarette-derived, nicotine delivery system. ENDS could be used by smokers with MI to alleviate negative mood and stress-related symptoms that increase during smoking cessation and/or reduction attempts. Understanding whether ENDS and their nicotine content operate differently among those with MI compared to those without MI as well as the interaction between ENDS nicotine content, changes in smoking behavior, negative mood and stress symptoms is critical to informing successful harm reduction efforts among this vulnerable population.

The Present Study Aims and Hypotheses

The present study used data from a RCT (NCT02342795) completed in 2018, which investigated the effects of a second-generation ENDS varying in nicotine concentration (0, 8, and 36 mg/ml) relative to a plastic cigarette substitute (CIG SUB) that delivered no nicotine/aerosol over 24 weeks among 520 smokers interested in reduction but not cessation. ENDS conditions

and their associated nicotine delivery were informed by a clinical laboratory study performed by the same team (Hiler et al., 2017), and primary outcomes centered on condition-related changes in tobacco toxicant exposures and smoking behavior over the study intervention period (Cobb et al., 2021). This secondary analysis focused on a subset of measures by current MI status and collapsed conditions by nicotine-containing status (non-nicotine=CIG SUB and 0 mg/ml vs. nicotine=8 mg/ml and 36 mg/ml) to increase statistical power to test nicotine-related effects. The specific aims were to:

Aim 1) Test the effects of current MI status, condition, and time on changes in CPD.

H1a: Relative to smokers without current MI, smokers with current MI were expected to report smaller CPD reduction over 24 weeks because past research suggests that individuals with MI report greater levels of nicotine dependence (Breslau et a, 1993; de Leon et al., 2002), increased symptoms of withdrawal (Reid & Ledgerwood, 2016), and decreased likelihood of quitting smoking (Cook et al., 2014).

H1b: Between-condition differences in CPD reduction as produced by condition-related nicotine content in the assigned study products were expected to differ as a function of current MI status, with greater between-condition differences found for participants with MI than for participants without MI (anticipated results presented in Figure 1 below). This hypothesis is derived from past research suggesting smokers with MI experience more severe withdrawal symptoms when deprived of nicotine (Smith, Homish, et al., 2014) which in turn can be suppressed by administering nicotine (Hughes et al., 1991).
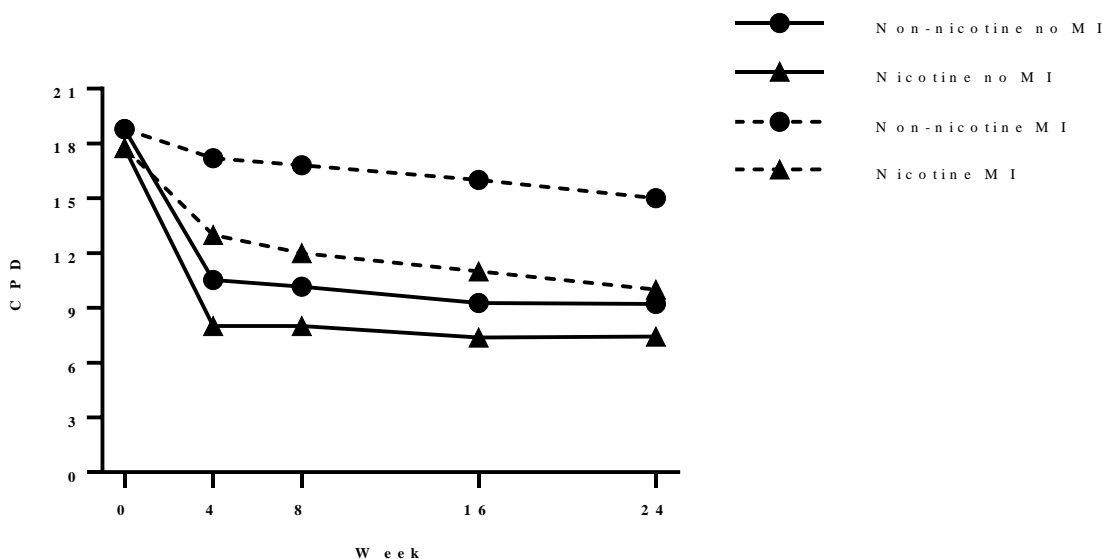
Figure 1. CPD=cigarettes per day. Hypothesized results for *H1b*.

Aim 2) Test the effects of current MI status, condition, and time on changes in negative mood and stress measures.

H2: Relative to the nicotine conditions, the non-nicotine conditions were expected to be associated with greater increases in scores on negative mood and stress measures over time among individuals with current MI relative to those without current MI (see Figure 2). The hypothesis was derived from past literature indicating that presence of an MI is linked to increased symptoms of nicotine abstinence and increased nicotine abstinence-related distress (Smith, Homish, et al., 2014). Past research suggests that smokers use nicotine to alleviate symptoms related to MI (e.g., Haro & Drucker-Colin, 2004a, 2004b); thus, we anticipated that smokers with MI would experience increases in negative mood and stress symptoms when nicotine cannot be obtained via study products.
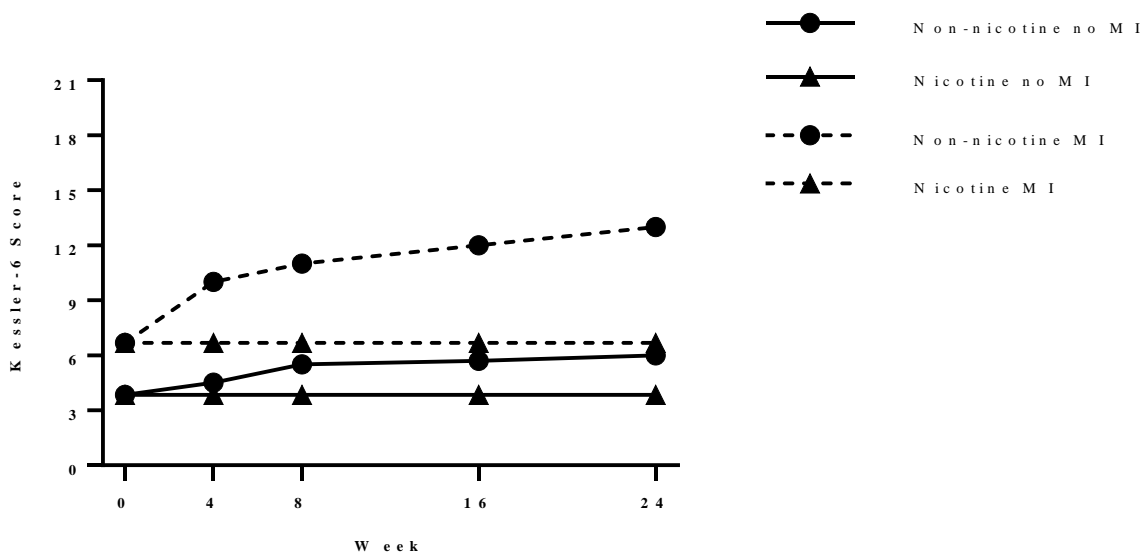
Figure 2. Hypothesized results for *H2*. Figure shows psychological distress (Kessler-6) scores on the y-axis; however, anticipated results of other negative mood and stress measures were expected to follow the same trend.

Aim 3) Test whether changes in negative mood and stress measures mediated condition-related effects on CPD and whether mediation differed by current MI status.

H3a: Changes in negative mood and stress measure scores were expected to mediate condition effects on CPD reduction. Individuals reporting psychological distress smoke greater CPD relative to those reporting no psychological distress (Kulik & Glantz, 2017) and negative affect is linked to increased urges of smoking (Brodbeck et al., 2014). The inability to obtain nicotine from study products in the non-nicotine conditions was expected to lead to smaller CPD changes for individuals reporting negative mood and stress symptoms.

H3b: Mood/stress measure mediation was expected to be stronger among those with current MI. MI is related to increased symptoms of nicotine withdrawal and increased withdrawal-related distress (Smith, Homish, et al., 2014). Additionally, smokers use nicotine to alleviate MI-related

symptoms (Haro & Drucker-Colin, 2004a, 2004b) and negative affect is related to increased

smoking urges (Brodbeck et al., 2014). Thus, smokers with current MI assigned to the non-

nicotine conditions who, in addition to their current MI status reported negative mood and stress,

were expected to report smaller CPD changes relative to smokers without current MI who

reported negative mood and stress symptoms.

Methods

Trial Design

This secondary data analysis used data derived from a two-site, four-arm, double-blind (for all but one condition) RCT consisting of a 24-week intervention period and a follow-up at 36 weeks. The primary site of the trial was Virginia Commonwealth University in Richmond, VA; the secondary site of the trial was Penn State University College of Medicine in Hershey, PA. Site-specific block randomization was used to allocate participants to one of four groups, consisting of a CIG SUB and three ENDS differing in nicotine concentration (0, 8, and 36 mg/ml; see Lopez et al., 2016 for detail).

Previous findings from the parent study of this RCT included significant between-condition differences in CPD at each post-randomization time point (Cobb et al., 2021). Relative to the CIG SUB condition, CPD was significantly lower in the 36 mg/ml condition at all time points, significantly lower for the 0 mg/ml at week 4, 8, and 16, and significantly lower for 8 mg/ml at week 4 (Cobb et al., 2021). Significant within-condition differences also were observed; within all conditions, CPD significantly decreased relative to CPD reported at week 0. Sensitivity analyses revealed similar patterns; except for the 8 mg/ml ENDS condition at week 12, all ENDS conditions resulted in significantly lower CPD relative to CIG SUB at all post-randomization time points (Cobb et al., 2021). Over the intervention period, participants reduced their use of the study product significantly; when using intent-to-treat (missing use data assumed no use), little evidence of between-condition differences in study product use emerged. Study product use rates between week 1 and week 24 dropped from ~87% to ~33% for CIG SUB, from ~85% to ~36% for 0 mg/ml, from ~88% to ~38% for 8 mg/ml, and from ~89% to ~48% for 36 mg/ml. Overall conclusions were that ENDS paired with 36 mg/ml nicotine concentration

liquid, which was representative of cigarette-like nicotine delivery, was the most effective in reducing smoking behavior and associated toxicant exposure. There was some evidence of a dose effect for the other ENDS conditions with 0 mg/ml proving ineffective in reducing biomarkers of tobacco exposure. The CIG SUB condition was associated with the least CPD reduction and no significant changes in biomarkers of tobacco use.

Participants

To be eligible, participants had to be aged 21-65, use more than 9 regular or machine-rolled filtered cigarettes per day for at least the past 12 months, and produce a CO value of at least 9 ppm at baseline. Eligible participants reported interest in smoking reduction but not quitting in the next 6 months. Specifically, eligible participants reported no serious smoking cessation attempts in the past month and no past-month use of any FDA-approved cessation medications. Individuals also had to indicate their ability to read and write in English and be able to provide informed consent.

Exclusion criteria included pregnancy or nursing, inability or unwillingness to have blood samples taken, and known allergic reactions to vegetable glycerin or propylene glycol. Exclusion criteria also included past 12-month severe or unstable medical conditions including but not limited to heart attack and angina accompanied by high blood pressure. Moreover, participants suffering from significant immune system disorders such as uncontrolled HIV or AIDS, respiratory illnesses, or kidney or liver diseases were excluded from the parent study along with participants reporting medical illnesses or use of medication compromising the safety of the participant and/or the biomarker data collected during the trial. Individuals who reported past 6-week surgeries involving general anesthesia were excluded. Participants who reported past-3-month daily, almost daily, and/or weekly use of cannabis, other illicit substances, or prescription

medication for non-medicinal purposes per National Institute on Drug Abuse (NIDA) Quick

Screen, were ineligible. Individuals who self-reported past-6 month inpatient treatment and/or

uncontrolled substance abuse/mental illness were ineligible. Participants reporting hand-rolled

cigarettes were excluded from the study, as were participants who reported past-week use of

non-cigarette nicotine-containing products, including, but not limited to ENDS. Past-month

ENDS use on five or more days led to exclusion as well.

Procedures

All interested participants initially completed a pre-screening over the phone and were, if

deemed potentially eligible, invited to complete an in-person screening session during which

written informed consent was collected. If deemed eligible during the in-person screening,

participants were prompted to engage in their typical cigarette smoking habits while tracking

their CPD consumption for one week via paper diary. After one week, participants returned to

the lab for their baseline visit (week 0). If week 0 was completed successfully, participants were

randomized to one of four conditions (CIG SUB or an ENDS containing liquid with a nicotine

concentration of 0, 8, or 36 mg/ml). Participants were asked to return to the lab for in-person

visits during the 24-week intervention period, specifically at week 2, 4, 8, 12, 16, 20, and 24 (see

Figure 3). Participants were prompted to use their assigned study product ad lib instead of their

cigarettes throughout the 24-week intervention period, after which study products were no longer

provided to participants. Participants were also prompted to reduce their cigarette smoking.

Specifically, participants were asked to reduce their cigarette consumption by 50% during week

0 and 2, and to reduce cigarette consumption by 75% during week 3 and 8. Participants were

asked to continue reducing their cigarette consumption further (without specific quantification of

said reduction) between the remainder of the intervention period, i.e., week 9 to week 24. CPD

and study product use (both of which participants tracked via paper diary during weeks 0-24) were obtained at each visit via timeline follow-back (past 7 days). Upon conclusion of the intervention period and ceasing of study product distribution, participants completed two additional follow-up visits (weeks 28 and 36). Participants who completed all visits were eligible to receive gift cards with a total possible monetary value of $400. Negative mood and stress measures were assessed during week 0, 4, 8, 16, 24, and 36. This secondary analysis focuses on the study intervention period visits (week 0-24) where CPD, negative mood, and stress symptoms were assessed concurrently (see study visits with asterisks in Figure 3).
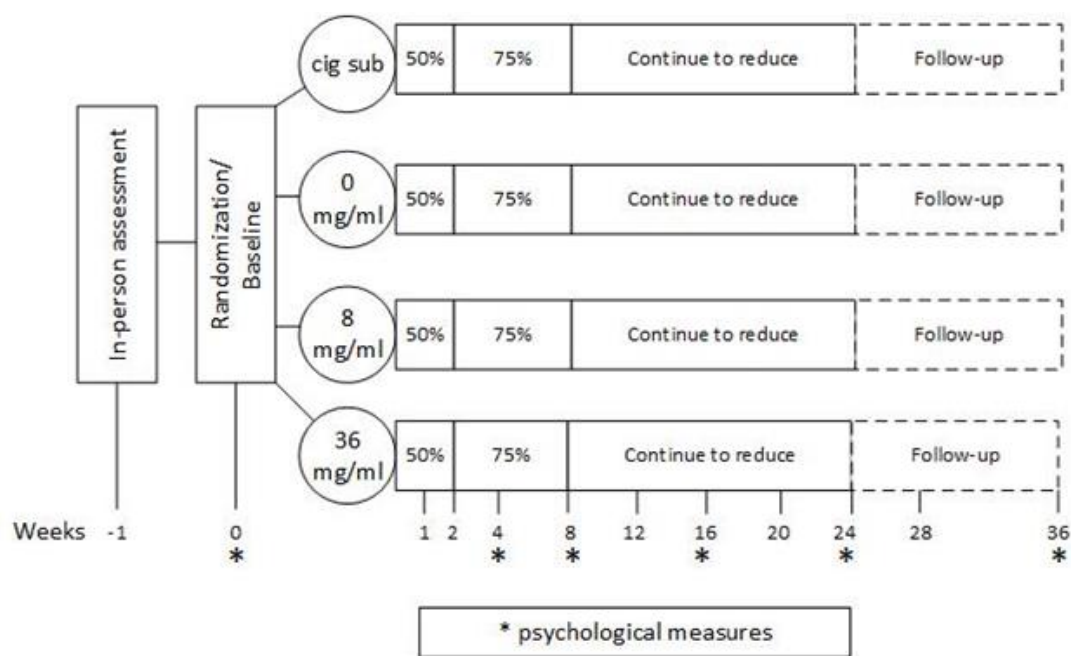
Figure 3. Study design schematic by week and condition with in-person clinic visits indicated. Cigarette smoking instructions that were active during a given week are indicated: 50% reduction (week 0-2), 75% reduction (week 3-8), continue to reduce cigarettes smoked (weeks 9-24; i.e., until the end of the intervention period/randomization phase), and advised to cease all cigarette use (week 25-36; follow-up period). Asterisks (*) indicate that CPD and mood/stress measures were completed during these weeks.

Study Products. Study products are depicted in Figure 4. The ENDS was a 3.3-4.1 V, 1000 mAh battery (SmokTech; Shenzhen, China), that was attached to a 1.5 ohm, dual-coil, 510-style cartomizer (SmokTech; Shenzhen, China) which was purchased free of liquid. AVAIL, an ENDS retailer in Richmond, VA, prepared the liquid solution containing 70% propylene glycol and 30% vegetable glycerin with nicotine concentrations of 0, 8, or 36 mg/ml in menthol and tobacco flavors. The accuracy of the nicotine concentration in the liquid used was confirmed by an independent lab. One ml of liquid was filled into each cartomizer by unblinded study staff. Two CIG SUB devices (QuitSmart, Inc., North Carolina, US) were given to participants in this condition. The CIG SUB consisted of a plastic, patented tube that resembles a tobacco cigarette in size, shape, and color. The plastic tube contains a porous piece of plastic and a small hole where the filter part and the body of the cigarette tube connect, thus creating a draw resistance similar to a cigarette. CIG SUB contained neither nicotine nor tobacco nor aerosol.

Figure 4. Study products. From left to right, cigarette substitute, ENDS battery, and ENDS cartomizer.

Measures

Main outcome measures. Current MI status. During the in-person screening visit, the

participant was handed a comprehensive list of common medical systems by body system. The

list contained a variety of psychiatric disorders that included depression, anxiety, bipolar disorder

I/II, schizophrenia, cognitive/other psychiatric disorders, eating disorders (anorexia nervosa,

bulimia, binge eating disorder, night eating disorder), and alcohol and other substance use

disorders. Participants also had the option to select "other". If "other" was selected, participants

were able to fill in the name of their MI into a blank text field. If a participant selected a

condition, the researcher inquired about and recorded the date of onset and whether the condition

was ongoing . The prevalence of current MI among participants reporting lifetime MI is

displayed in Table 2. When categorizing current MI status, participants who self-reported

lifetime history of a condition and also reported the condition to be ongoing were categorized as

having current MI while all other participants were categorized as having no current MI. The no

current MI category included individuals who reported no lifetime MI, individuals who reported

lifetime MI but the condition to not be ongoing, and individuals who reported lifetime MI but

had missing data for the item assessing whether a condition was ongoing.

Table 2. Current MI among participants previously reporting lifetime MI.

Diagnosis N (%)	Lifetime MI (N=230)	Current MI (N=194)
Depression	142 (100.0)	122 (85.9)
Anxiety	127 (100.0)	110 (86.6)
Bipolar	32 (100.0)	28 (87.5)
Other	26 (100.0)	23 (88.5)
Alcohol or substance use disorder	53 (100.0)	15 (28.3)
Schizophrenia	7 (100.0)	6 (85.7)
Night eating disorder	4 (100.0)	3 (75.0)
Anorexia nervosa	9 (100.0)	3 (33.3)

| **Bulimia** | 8 (100.0) | 0 (0.0) |

Note: No lifetime diagnoses of cognitive disorders or binge eating disorder reported among sample. Current MI was coded as present when participants reported at least one lifetime MI and described at least one lifetime MI condition as ongoing. If participants had reported a lifetime MI and had missing data for the item assessing current MI, they were coded as not having a current MI.

Depressive symptoms. Depressive symptoms were assessed via the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). Instructions stated "Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the past week." Items of this 20-item scale included "I was bothered by things that usually don't bother me", "I felt lonely", "I had crying spells", and "I felt hopeful about the future". Answer options included 0= rarely or none of the time (less than 1 day), 1=some or a little of the time (1-2 days), 2=occasionally or a moderate amount of time (3-4 days), and 3=all of the time (5-7 days). Four items require reverse coding. Higher scores out of the 60 total points possible indicate more severe depression.

Psychological distress. Symptoms of nonspecific psychological distress were measured using the Kessler-6 scale (Kessler et al., 2003). Instructions for participants stated "The following questions ask about how you have been feeling during the past 30 days. For each question, please select the response that best describes how often you had this feeling". The items listed symptoms including "nervous", "hopeless", and "so depressed that nothing could cheer you up". Answer options included 0= none of the time, 1= a little of the time, 2= some of the time, 3= most of the time, and 4= all of the time. Scores across all items are added, totaling up to 24 points, with higher scores indicating greater psychological distress.

Perceived stress. Perceived stress was assessed using the 10-item Perceived Stress Scale (PSS; Cohen et al., 1983). Instructions for participants stated "The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate by marking how often you felt or thought a certain way." Items included "In the last month, how often have you felt that things were going your way?" and "In the last month, how often have you felt confident about your ability to handle your personal problems?". Response options ranged from 0=never to 4=very often, with four items requiring reverse coding. Higher scores out of the 40 total points possible indicate more severe perceived stress.

Cigarettes per day (CPD). CPD was recorded by participants in the Daily Tobacco Use Diary between time points and was assessed via 7-day timeline follow-back at each in-person visit following screening (Sobell & Sobell, 1992). The responses of the 7-day timeline follow-back were averaged to provide a single estimate of CPD for each time point for Aim 1. CPD estimates at week 0 and week 24 were used to create a CPD reduction value for each participant by subtracting CPD recorded at week 24 from CPD recorded at week 0 to be used in the analyses for Aim 3.

Covariates

We examined the influence of demographic variables, baseline characteristics, and selected tobacco dependence-related covariates on our outcomes of interest. Unadjusted models (excluding covariates) constituted our primary analysis method and our sensitivity analyses included the following covariates.

Demographic variables. Demographic variables included age, sex, and race/ethnicity. Age was assessed with the question "What is your current age?" and participants were prompted to type

the corresponding numerical value into a text field. Sex was assessed with the question "Are you male or female?" with participants selecting either male (1) or female (0) from a dropdown list. Race/ethnicity was assessed using the question "What race best describes you?" with dropdown list answer options including Caucasian/White, African American/Black, Asian, American Indian/Alaskan Native, Native Hawaiian or Pacific Islander, and Other. We also asked "Do you consider yourself Hispanic/Latino?" (yes, no). Those who responded with yes were asked "What is your Hispanic ancestry or origin?" and were prompted to select all applicable answers from a list of options, including, but not limited to, Mexican/Mexicano and Mexican American. Race/ethnicity response options were recoded into non-Hispanic White, non-Hispanic Black/African American, while individuals who did not self-identify with neither of the prior categories were classified as Other.

Baseline characteristics. Baseline characteristics assessed included education and income. Education was assessed using the question "What is the highest level of school you have completed or the highest degree you have received?" and included answer options including less than 9th grade, 9th grade, 10th grade, 11th grade, 12th grade/no diploma, high school graduate, GED or equivalent, some college/no degree, associate degree, bachelor's degree, master's degree, professional degree, and doctoral degree. Education-related response options were recoded to reflect "less than college" and "some college or higher" by collapsing the initial answer options. Income was assessed using the question "Which of the following income categories best describes your total household income last year?" with answer options ranging from less than $1,000 to $100,000 and over. Income was not collapsed; instead, we retained the original response options. Additional baseline characteristics were scores of our outcome measures of interest as measured at week 0, including negative mood and stress and CPD.

Tobacco dependence-related measures. Tobacco-dependence-related factors include the Penn State Cigarette Dependence Scale (PSCDI; Foulds et al., 2015) and ever use of other tobacco products in the past. The PSCDI is a 10-item measure used to assess cigarette dependence. Items include "How many cigarettes per day do you usually smoke?" (0-4=0, 5-9=1, 10-14=2, 15-19=3, 20-30=4, 31+=5), "On days that you can smoke freely, how soon after you wake up do you smoke your first cigarette of the day?**"** (within [minutes] 5=5, 6-15=4, 16-30=3, 31-60=2, 61-120=1, 121+=0), and "Do you sometimes awaken at night to have a cigarette?" (yes=1, no=0). Scores range from 0 to 20, with greater scores suggesting greater cigarette-related dependence. Ever use of other tobacco products was assessed using the item "Have you ever used any other types of tobacco?" (yes, no), "What type of tobacco did you use" (cigars, cigarillos, little cigars, pipes, snus, chew/snuff/dip, electronic cigarettes, hookah/water pipe, dissolvable tobacco (lozenge, strips, or sticks)).

Data Analysis

Data Preparation. Our data analyses focused on data collected at five time points which included week 0, week 4, week 8, week 16, and week 24. Data cleaning was conducted. No outliers were found, and no coding errors were detected. While missing data were detected and will be discussed in greater detail below, we did not exclude any cases. The reason for this inclusion was that our analyses were conducted on an intent-to-treat (ITT) basis, meaning that we analyzed participant data based on the condition to which participants were randomized regardless of their adherence to instructions (Detry & Lewis, 2014). The purpose of ITT was to take a "real-world" approach to testing the effect of the intervention, as non-adherence, incorrect administration, and participant characteristics may impact the intervention effect (Detry & Lewis, 2014).

Restricted or residual maximum likelihood (REML) was used for Aim 1 and 2. REML is an approach used in order to estimate the variance components in a dataset and has been deemed particularly helpful when analyzing data from clinical trials which are often associated with unbalanced data due to drop out rates and missing data. REML utilizes all available data to provide a more accurate estimate when a treatment effect is available (Brown & Kempton, 1994). For the proposed analyses of Aim 3, expectation maximization (EM) was used to impute missing data on all continuous outcome variables, including the negative mood and stress measures (Kessler-6, PSS, and CES-D) and CPD. In EM, the available data in the data set is assumed to provide the researcher with information that will help estimate the likely value of missing data points on parameters of interest (Bennett, 2001). Maximum likelihood (ML) methods such as EM, are used to estimate parameters in a probability distribution and to subsequently estimate missing data within a data set (Chen & Gupta, 2010; Myers, 2000).

EM consists of an expectation step (E-step) and a maximization step (M-step). During the E-step, the EM algorithm determines the initial values to impute for missing data based on available data, thus producing the estimate of one's parameter of interest (Bennett, 2001). During the M-step, the algorithm replaces the missing data points with the values estimated in the previous step and then completes maximization of likelihood with the new, complete dataset (Bennett, 2001). Through the M-step, new parameter estimates are obtained which are then used in the subsequent E-step. The repetitive process of E-step and M-step is completed when convergence is reached, meaning that the parameter estimates obtained during EM cycles no longer differ (Bennett, 2001). In EM, the data used to impute missing data should stem from constructs closely related to the missing data. Thus, missing CPD data was imputed using available CPD data from other time points, while missing negative mood and stress measures

scores were obtained separately from available negative mood and stress data, thus creating two datasets that were merged upon completion of EM.

Prior to imputing missing data, the missing data must be deemed to be "missing completely at random" (MCAR) or "missing at random" (MAR; Bennett, 2001). MCAR suggests that no relationship exists between patterns of missing data and any variables or available or missing data (MCAR). MAR suggests that missing data occurs due to available data but not due to the data that is actually missing (Bennett, 2001). NMAR refers to patterns of missing data that can be directly linked to the data collected, e.g., participants missing visits due to side effects associated with the condition to which they were assigned (Bennett, 2001). While both MAR and MCAR are permissible when using REML or EM, the most critical factor here is to determine that the missing data is *not* NMAR. Little's MCAR test, which determines whether data is missing completely at random or not, was conducted.

In Table 2, we outline that no differences were found in missed in-lab visits at the five time points by current MI status. Moreover, no differences in attrition at week 24 were observed by condition (p=0.15). Patterns of missing data that were found were MAR and not MNAR. Prior to completion of REML and EM, assumptions associated with the respective analyses were tested. For the linear mixed models that we used for Aim 1 and 2, the assumptions included a continuous outcome variable (CPD and mood and stress measures) and between-subject factors with more than one independent group. Also, linear mixed models assume a within-subjects factor with more than one group, an assumption that was met as five time points were assessed. Additionally, assumptions for linear mixed models that were assessed included additivity and linearity, absence of collinearity, homoscedasticity, normal distribution of residuals, and homogeneity of variance. For Aim 3, which was assessed using mediation and moderated

mediation analyses, assumptions of the general linear model applied; thus, normality tests, including skewness and kurtosis were assessed. Additionally, linearity, independence of errors, and homogeneity of variance were assessed. We chose not to transform data when violations of normality were found.

Analyses

To maximize power and due to the primary interest in the effect of nicotine relative to no nicotine, all proposed analyses outlined below treated condition, which initially consisted of four levels (CIG SUB and ENDS with varying liquid nicotine concentrations) as two levels differing in nicotine-containing status (non-nicotine-containing conditions and nicotine-containing conditions). Hence, the four conditions were collapsed into two condition groupings. Upon completion of data cleaning, descriptive and bivariate analyses including independent group t-tests and chi-square tests were used to characterize the sample in regards to demographics, cigarette smoking history, baseline CPD, nicotine dependence, current MI status, and mood and stress symptoms across the two collapsed conditions. Clinically relevant cutoff scores for negative mood and stress measures also were used to characterize the sample.

Aim 1 Analysis. For Aim 1 analyses, linear mixed models were used to investigate the relationship of MI status and/or condition and changes in CPD over 24 weeks as indexed by mean differences. For Aim 1a and Aim 1b, subject-specific effects represented the random factor. For Aim 1a and Aim 1b, one mixed linear model was conducted with the fixed factors of current MI (two levels; yes, no), condition (two levels; non-nicotine, nicotine), and time (five levels; week 0, 4, 8, 16, and 24). Main effects and interactions were assessed, with the interaction of MI status x time addressing *H1a* and the interaction of MI status x condition x time addressing

H1b. Significant main effects and/or interactions were explored with t-tests using a Bonferroni correction with which we assessed mean differences between non-nicotine-containing and nicotine-containing conditions and within condition groupings (relative to week 0).

Aim 2 Analysis. Each outcome variable (scores on negative mood and stress measures) was assessed separately using linear mixed models as in Aim 1 with the same fixed and random factors. Main effects and interactions were assessed, with the interaction of MI status (two levels; yes, no) x conditions (two levels; non-nicotine and nicotine) x time (five levels: week 0, 4, 8, 16, 24) addressing *H2*. Significant main effects and/or interactions were explored with t-tests using a Bonferroni correction with which we assessed mean differences between non-nicotine-containing and nicotine-containing conditions and within condition groupings (relative to week 0).

Aim 3 Analysis. The third aim tested whether changes in negative mood and stress scores would mediate condition-related effects on CPD and whether the mediation was moderated by current MI status. After performing EM, we created an average for all three negative mood and stress measures by adding the scores at each of the five time points together and then dividing the total by five. We then z-score transformed the newly created averages for each negative mood and stress measure. After creating the z-scores for each variable, we created two composite score variables. First, we added the CES-D, Kessler-6, and PSS z-scores together and divided the total by three, thus creating the composite variable "negative mood and stress". Second, we added only the CES-D and Kessler-6 z-scores together and divided the total by two, thus creating the composite variable "negative mood". After performing EM, to estimate change in the CPD over the intervention period, we created a difference score for each participant using their week 0 CPD and week 24 CPD and calculating the difference between the two means.

Mediation models also included condition (two levels; non-nicotine, nicotine) and/or current MI status (2 levels; yes, no). All predictor variables were mean-centered except for the already z-score transformed negative mood and stress variables. Categorical predictors were, when applicable, transformed to contain an assigned value of 0 for one of the categories. Despite past research suggesting a correlation between the negative mood and stress variables of interest (Cohen et al., 1983), we ran five separate mediation models in PROCESS macro (Hayes, 2014) to assess direct and indirect effects utilizing 5,000 bootstrap samples. The five mediation models included one mediation model for each of the composite variables and one mediation model for each of the z-score transformed negative mood and stress variables. For each of the five mediation models, we specified that condition would lead to changes in mood and stress symptoms, which in turn would lead to changes in CPD (see Figure 5).
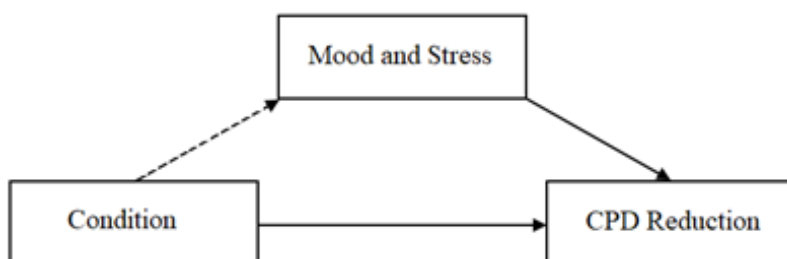
Figure 5. Mediation model. Mood and stress symptoms (scores derived from CES-D, Kessler-6, and PSS) mediating the relationship between condition (non-nicotine-containing, nicotine-containing) and CPD reduction.

The second hypothesis of Aim 3 predicted that the mediation of negative mood and stress measure mediation would be stronger among individuals with current MI (see Figure 6). We planned to use PROCESS Macro model 7 to expand the previously described mediation into moderated mediations, with MI status (yes, no) serving as the moderator between condition (non-nicotine, nicotine conditions) and symptoms of negative mood and stress (see Figure 6).
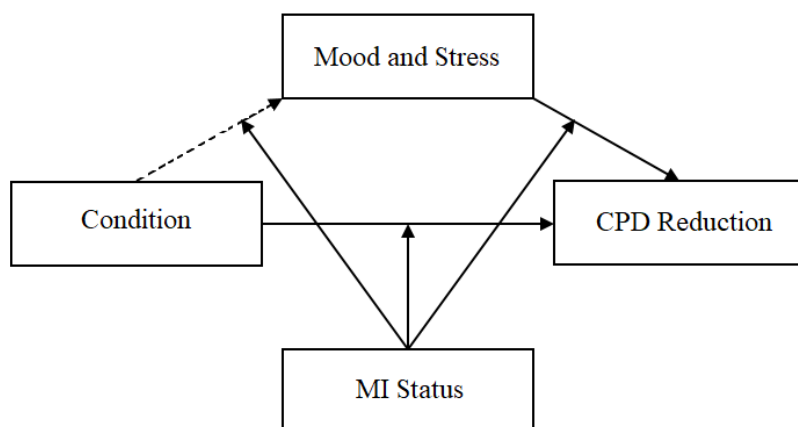
Figure 6. Moderated mediation model. Mood and stress symptoms (as indexed by scores on the CES-D, Kessler-6, and PSS) mediating the relationship between condition (non-nicotine and nicotine) and CPD reduction, with current MI status moderating the direct effects.

Sensitivity Analyses. Sensitivity analyses were conducted in order to determine whether previously unassessed variables would alter the results or whether results would remain robust (Schneeweiss, 2006). Each analysis was run first without controlling for covariates, and then again while controlling for relevant covariates, in order to determine whether outcomes had changed based on potentially confounding variables. For all three Aims, we included demographics (e.g., age, sex, race/ethnicity) and site as well as additional relevant variables that we expected to influence the outcomes, such as the baseline scores of the respective outcome assessed. In the sensitivity analyses for Aim 1 we controlled for baseline Kessler-6 scores but chose not to control for baseline CES-D scores, as CES-D and Kessler-6 correlated highly with one another. Additionally, because the CES-D measures depressive symptoms we anticipated there to be overlap with MI given the high prevalence of depression diagnoses in our sample. For the analyses associated with *H1a, H1b* and *H2*, we controlled for baseline cigarette dependence (Penn State Cigarette Dependence Scale and ever use of other-tobacco products, the latter of which was assessed once at baseline. We chose not to control for current other-tobacco product

use, as all participants who reported past 7-day use of other tobacco products were excluded at baseline. For each of the outcomes assessed in *H2*, we controlled for each measure's respective baseline score. We did not control for Kessler-6 baseline scores when assessing CES-D scores and vice versa due to the reasons outlined above for *H1a* and *H1b*; however, we controlled for PSS scores at baseline for the two negative mood outcomes. When investigating the *H2* outcome PSS, we controlled for Kessler-6 scores at baseline. For *H3a* and *H3b*, we also controlled for baseline CPD.

Aim 1 and 2 Power Analysis. We considered running a power analysis for our proposed linear mixed models with our selected fixed factors, including our within-subjects factor (time) and our between-subjects factors (condition and current MI status) for each of our outcomes (CPD, Kessler-6, CES-D, and PSS). However, the complexity of the proposed models and interactions of interest, challenged this task. As an alternative, we used the available data (untransformed, without covariate adjustment or EM) at week 4 and 24 to estimate the observed power to detect differences by condition and MI status using a between-subjects analysis of variance for each time point separately (see Table 3). Observed power for these differences between conditions varied by time point and by outcome assessed, but overall higher power was noted for main effects of condition and MI status with lower power for the interaction between the two factors (as low as <0.06). These estimates supported approaches to increase power by simplifying the models assessed by collapsing the conditions by nicotine-containing status. Power estimates were expected to be improved by our use of REML/EM to impute missing data. Additionally, a power analysis was conducted using G*Power software (Faul et al., 2009) to determine the necessary sample size for current MI status (2 levels) x condition (2 levels).

Assuming a fairly small effect size of 0.15, 351 participants should be sufficient to detect an

effect (power > 0.8, alpha < 0.05).

Table 3. Observed power for outcomes across week 0 and week 24

	Week 0	Week 24
Variables assessed		
CPD		
MI status	0.054	0.471
Condition	0.912	0.923
MI status*condition	0.075	0.105
CES-D		
MI status	1.000	0.998
Condition	0.734	0.119
MI status*condition	0.100	0.202
PSS		
MI status	0.589	0.790
Condition	0.108	0.072
MI status*condition	0.050	0.066
Kessler-6		
MI status	0.997	1.000
Condition	0.505	0.835
MI status*condition	0.050	0.535

Note. CPD=cigarettes per day; CES-D=Center for Epidemiologic Studies Depression Scale; PSS=Perceived Stress Scale. Asterisks (*) denote an interaction effect between the two factors MI status and condition**.**

Results

Current sample

The present analyses utilize data derived from 520 individuals that were randomized to

four conditions. Across the sample, overall attrition at week 24 was 36% (188/520) and did not

differ significantly by condition (p=0.15): 43% (56/130) for 0 mg/ml, 38% (49/130) for 8 mg/ml,

34% (44/130) for 36 mg/ml and 30% for CS (39/130). Relative to participants who completed

the study, the 188 participants who did not attend the week 24 visit were about four years

younger on average than completers (p=0.0001), less educated (p=0.03), younger at smoking

initiation by about 1 year (p=0.003), and more cigarette dependent (p=0.01). Non-completers had

higher forced vital capacity as measured by PFT at baseline relative to completers (p=0.04). For

the percentage of missed visits across time points by condition, please refer to Table 4. We found

no significant differences between the percentages of missing data between conditions collapsed

by nicotine-containing status (see Table 4). Missing data for the measures of interest (i.e., CPD,

CES-D, Kessler-6, and PSS) are depicted in Table 5.

Table 4. Missed visits by condition grouping

Visit number	Non-nicotine (N=260)	Nicotine (N=260)	Total sample (N=520)	p
Week 0, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Week 4, n (%)	49 (18.8)	38 (14.6)	87 (16.7)	0.196
Week 8, n (%)	81 (31.2)	73 (28.1)	154 (29.6)	0.442
Week 16, n (%)	104 (40.0)	98 (37.7)	202 (38.8)	0.589
Week 24, n (%)	100 (38.5)	106 (40.8)	206 (39.6)	0.591

Note. p-values were calculated using Pearson's chi-square test.

Table 5. Percentage of missing data on mood and stress measures across time points

Measure	Week 0	Week 4	Week 8	Week 16	Week 24
CPD, n (%)	0 (0.0)	88 (16.9)	154 (29.6)	201 (38.7)	206 (39.6)
CES-D, n (%)	0 (0.0)	131 (25.2)	172 (33.1)	221 (42.5)	222 (42.7)
Kessler-6, n (%)	14 (2.7)	102 (19.6)	162 (31.2)	207 (39.8)	212 (40.8)
PSS, n (%)	0 (0.0)	99 (19.0)	163 (31.3)	213 (41.0)	221 (42.5)

Note. CPD=cigarettes per day, CES-D=Center for Epidemiologic Studies Depression Scale, PSS=Perceived Stress Scale.

Baseline characteristics including demographic data and baseline negative mood and

stress scores across the sample and by condition grouping are depicted in Table 6. As was

observed in the main trial analyses which compared a variety of baseline characteristics across

the four randomized conditions (Cobb et al., 2021), no significant differences were observed by condition grouping for any measure examined. Across the sample, participants were about 46 years old on average and were mostly women (58.8%). The majority of participants identified as White (67.3%). Almost 60% reported having completed at least some college education. Participants reported smoking an average CPD of 19. For the CES-D at baseline, the average score fell below the clinical cutoff of 16 (mean; M=12.3, standard deviation; SD=9.8; Weissman et al., 1977). Across the sample, almost one third (27.5%) met or exceeded the CES-D clinical cutoff. For the Kessler-6, the average scores were well below the clinical cutoff (score of ≥13; M=4.9, SD=4.2; Kessler et al., 2003). Across the entire sample, 8.1% had a score that met or exceeded the clinical cutoff for the Kessler-6. Perceived stress at baseline was moderate, with average scores falling below the cutoff for severe perceived stress (scores of ≥27; M=19.9, SD=4.1). Across the sample, 37.3% of participants reported current MI at baseline. The most prevalent conditions were depression (23.5%) and anxiety (21.2%), followed by bipolar disorder (5.4%). No significant differences in the distribution of current MI status or specific MI diagnoses were observed by condition grouping (see Table 7).

Table 6. Baseline characteristics by condition grouping

	Condition			
	Non-nicotine	Nicotine	OVERALL	p
Age				0.537
Available N	260	260	520	
M (SD)	45.9 (11.9)	46.5 (11.4)	46.2 (11.6)	
Site of recruitment				1.000
Available N	260	260	520	
Richmond, VA, n (%)	100 (38.5)	100 (38.5)	200 (38.5)	
Hershey, PA, n (%)	160 (61.5)	160 (61.5)	320 (61.5)	
Sex				0.285
Available N	260	260	520	
Male, n (%)	159 (61.2)	147 (56.5)	214 (41.2)	

Female, n (%)	101 (38.8)	113 (43.5)	306 (58.8)	
Race/ethnicity				0.977
Available N	260	260	520	
White NH, n (%)	175 (67.3)	175 (67.3)	350 (67.3)	
African American/Black NH, n (%)	72 (27.7)	73 (28.1)	145 (27.9)	
Other, n (%)	13 (5.0)	12 (4.6)	25 (4.8)	
Education				0.211
Available N	260	260	520	
Less than college, n (%)	112 (43.1)	98 (37.7)	210 (40.4)	
Some college or higher, n (%)	148 (56.9)	162 (62.3)	310 (59.6)	
Income				0.242
Available N	255	255	510	
Less than $10,000	58 (22.7)	50 (19.6)	108 (21.2)	
$10,000-$39,999	99 (38.8)	94 (36.9)	193 (37.8)	
$40,000-$69,999	47 (18.4)	54 (21.2)	101 (19.8)	
$70,000-$99,999	34 (13.3)	33 (12.9)	67 (13.1)	
$100,000 or more	17 (6.7)	24 (9.4)	41 (8.0)	
CPD (7-day average)				0.970
Available N	260	260	520	
M (SD)	18.6 (7.8)	18.6 (7.7)	18.6 (7.7)	
Penn State Cigarette Dependence Scale				0.165
Available N	247	248	495	
M (SD)	13.6 (2.8)	13.2 (3.1)	13.4 (3.0)	
Ever use of other tobacco product				1.000
Available N	260	260	520	
Never use of other tobacco, n (%)	124 (47.7)	124 (47.7)	248 (47.7)	
Ever use of other tobacco, n (%)	136 (52.3)	136 (52.3)	272 (52.3)	
CES-D				0.265
Available N	233	241	474	
M (SD)	12.9 (9.9)	11.9 (9.7)	12.3 (9.8)	
Kessler-6				0.967
Available N	254	252	506	
M (SD)	4.9 (4.3)	4.9 (4.1)	4.9 (4.2)	
PSS				0.227
Available N	250	255	505	
M (SD)	19.9 (4.4)	19.8 (3.8)	19.9 (4.1)	
Current mental illness (MI)				0.147
Available N	260	260	520	
No current MI, n (%)	155 (59.6)	171 (65.8)	326 (62.7)	
Current MI, n (%)	105 (40.4)	89 (34.2)	194 (37.3)	
Clinical cutoff CES-D				0.492
Available N	260	260	520	
CES-D cutoff not met, N (%)	185 (71.2)	192 (73.8)	377 (72.5)	
CES-D cutoff met, N (%)	75 (28.8)	68 (26.2)	143 (27.5)	

Clinical cutoff Kessler-6				0.748
Available N	260	260	520	
K6 cutoff not met, N (%)	240 (92.3)	238 (91.5)	478 (91.9)	
K6 cutoff met, N (%)	20 (7.7)	22 (8.5)	42 (8.1)	
Clinical cutoff PSS				
Available N				0.648
PSS cutoff not met, N (%)	249 (95.8)	251 (96.5)	500 (96.2)	
PSS cutoff met, N (%)	11 (4.2)	9 (3.5)	20 (3.8)	

Note: M=Mean, SD= standard deviation, NH=non-Hispanic, CPD=cigarettes per day, CES-D=Center for Epidemiologic Studies Depression Scale, PSS=perceived stress scale. *p*-values were calculated using independent samples t-tests for continuous variables and Pearson's chi-square tests for categorical variables.

Table 7. Current mental illness diagnoses by condition grouping

Reported MI diagnosis N (%)	Non-nicotine (N=260)	Nicotine (N=260)	Overall (N=520)	*p*
Any current MI	105 (40.4)	89 (34.2)	194 (37.3)	0.147
Depression	63 (24.2)	59 (22.7)	122 (23.5)	0.679
Anxiety	63 (24.2)	47 (18.1)	110 (21.2)	0.086
Bipolar	14 (5.4)	14 (5.4)	28 (5.4)	1.000
Other	14 (5.4)	9 (3.5)	23 (4.4)	0.286
Alcohol or other substance use disorder	5 (1.9)	10 (3.8)	15 (2.9)	0.190
Schizophrenia	3 (1.2)	3 (1.2)	6 (1.2)	1.000*
Night eating disorder	3 (1.2)	0 (0.0)	3 (0.6)	0.249*
Anorexia nervosa	2 (0.8)	1 (0.4)	3 (0.6)	1.000*

Note: Asterisks (*) indicates that Fisher's exact test was used. All other p-values were calculated using Pearson's chi-square test. While binge eating disorder was assessed, no participants reported current binge eating disorder.

Differences by MI status

Baseline characteristics by current MI status are displayed in Table 8. Participants with MI were significantly more likely to be men (68%) and White NH (80.4%), both *p*=0.001. Participants who reported current MI were more likely to be enrolled in the study at the data collection site in Hershey, PA (75.3%) as opposed to in Richmond, VA (24.7%; *p*<0.001). CES-

D scores were significantly higher among those with current MI (*M*=15.8, *SD*=10.7) compared to

those without (*M*=10.4, *SD*=8.7; *p*=0.001). This same pattern was observed for the Kessler-6

scale (*M*=6.7, *SD*=4.6 vs. *M*=3.9, *SD*=3.5) and the PSS (*M*=20.9, *SD*=3.9 vs. *M*=19.3, *SD*=4.1;

both *p*=0.001). Smokers with MI were also significantly more likely to meet the clinical cutoff

for each of the negative mood and stress measures than participants without MI, with 39.2%

meeting the clinical cutoff score for the CES-D (vs. 20.6%), 14.9% meeting the clinical cutoff

score for the Kessler-6 (vs. 4.0%), and 6.7% meeting the clinical cutoff score of the PSS (vs.

2.1%), all *p*s<0.01. When comparing percentages of missed visits by MI status, there were no

significant differences between those who reported current MI and no current MI (see Table 9),

suggesting that participants in both groups were equally likely to miss visits throughout the

study.

Table 8. Baseline characteristics by current mental illness status

	No MI (N=326)	MI (N=194)	Total (N=520)	*p*
Age				0.622
Available N	326	194	520	
M (SD)	46.4 (12.0)	45.9 (11.1)	46.2 (11.6)	
Sex				**0.001**
Available N	326	194	520	
Male, n (%)	174 (53.4)	132 (68.0)	214 (41.2)	
Female, n (%)	152 (46.6)	62 (32.0)	306 (58.8)	
Race/ethnicity			520	**0.001**
Available N	326	194	520	
White NH, n (%)	194 (59.5)	156 (80.4)	350 (67.3)	
African American/Black NH, n (%)	116 (35.6)	29 (14.9)	145 (27.9)	
Other, n (%)	16 (4.9)	9 (4.6)	25 (4.8)	
Education				0.323
Available N	326	194	520	
Less than college, n (%)	137 (42.0)	73 (37.6)	210 (40.4)	
Some college or higher, n (%)	189 (58.0)	121 (62.4)	310 (59.6)	
Income				0.662
Available N	321	189	510	

Less than $10,000	67 (20.9)	41 (21.7)	108 (21.2)	
$10,000-$39,999	119 (37.1)	74 (39.2)	193 (37.8)	
$40,000-$69,999	65 (20.2)	36 (19.0)	101 (19.8)	
$70,000-$99,999	40 (12.5)	27 (14.3)	67 (13.1)	
$100,000 or more	30 (9.3)	11 (5.8)	41 (8.0)	
Site				**<0.001**
Available N	326	194	520	
Penn State University	174 (53.4)	146 (75.3)	320 (61.5)	
Virginia Commonwealth University	152 (46.6)	48 (24.7)	200 (38.5)	
Cigarettes/day (7-day average)				0.608
Available N	326	194	520	
M (SD)	18.5 (7.7)	18.8 (7.9)	18.6 (7.7)	
Penn State Cigarette Dependence Scale				**0.017**
Available N	313	182	495	
M (SD)	13.2 (2.9)	13.8 (3.0)	13.4 (3.0)	
Ever use of other tobacco products				0.947
Available N	326	194	520	
Never use of other tobacco, n (%)	155 (47.5)	93 (47.9)	248 (47.7)	
Ever use of other tobacco, n (%)	171 (52.5)	101 (52.1)	272 (52.3)	
CES-D				**0.001**
Available N	302	172	474	
M (SD)	10.4 (8.7)	15.8 (10.7)	12.3 (9.8)	
Kessler-6				**0.001**
Available N	316	190	506	
M (SD)	3.9 (3.5)	6.7 (4.6)	4.9 (4.2)	
PSS				**0.001**
Available N	320	185	505	
M (SD)	19.3 (4.1)	20.9 (3.9)	19.9 (4.1)	
Clinical cutoff CES-D				**0.001**
Available N	326	194	520	
CES-D cutoff not met, N (%)	259 (79.4)	118 (60.8)	377 (72.5)	
CES-D cutoff met, N (%)	67 (20.6)	76 (39.2)	143 (27.5)	
Clinical cutoff Kessler-6				**0.001**
Available N	326	194	520	
K6 cutoff not met, N (%)	313 (96.0)	165 (85.1)	478 (91.9)	
K6 cutoff met, N (%)	13 (4.0)	29 (14.9)	42 (8.1)	
Clinical cutoff PSS				**0.009**
Available N	326	194	520	
PSS cutoff not met, N (%)	319 (97.9)	181 (93.3)	500 (96.2)	
PSS cutoff met, N (%)	7 (2.1)	13 (6.7)	20 (3.8)	

Note: **Bold *p*-**values indicate significant differences (*p*<0.05). *p*-values were calculated using independent samples t-tests for continuous variables and Pearson's chi-square tests for categorical variables. NH=non-Hispanic; CPD=cigarettes per day, CES-D=Center for Epidemiologic Studies Depression Scale, PSS=Perceived Stress Scale.

Table 9. Missed visits by current MI status as recorded at each visit

Time point	No MI (N=326)	Current MI (N=194)	Total sample (N=520)	*p*
Week 0, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Week 4, n (%)	51 (15.6)	36 (18.6)	87 (16.7)	0.389
Week 8, n (%)	94 (28.8)	60 (30.9)	154 (29.6)	0.613
Week 16, n (%)	120 (36.8)	82 (42.3)	202 (38.8)	0.217
Week 24, n (%)	126 (38.7)	80 (41.2)	206 (39.6)	0.560

Note: p-values were calculated using Pearson's chi-square test.

Aim 1 and 2

Data from all available data points from the 520 participants were used for the linear

mixed model analyses of Aim 1 and 2. For linear mixed model results unadjusted and adjusted

for covariates, please refer to Table 10. Results for covariates used in the different models are

displayed in Table 11.

Table 10. Statistical results summary for Aim 1 and 2 linear mixed models without and with covariate adjustment.

	MI		Time		Condition		MI x Time		MI x Condition		Time x Condition	
	F	p	F	p	F	p	F	p	F	p	F	p
CPD[a]	2.70	0.101	355.17	**<0.001**	7.64	**0.006**	2.36	0.051	0.03	0.875	5.65	**<0.001**
CPD-adjusted[b]	0.09	0.763	342.18	**<0.001**	20.97	**<0.001**	2.29	0.057	0.10	0.757	5.73	**<0.001**
CES-D[c]	52.71	**<0.001**	1.011	0.400	1.04	0.308	1.93	0.104	0.09	0.761	2.39	**0.049**
CES-D-adjusted[d]	15.66	**<0.001**	0.57	0.688	0.03	0.870	3.08	**0.015**	2.24	0.135	1.78	0.130
Kessler-6[e]	57.72	**<0.001**	3.46	**0.008**	3.64	0.057	1.67	0.154	2.56	0.108	2.19	0.067
Kessler-6-adjusted[f]	13.35	**<0.001**	3.24	**0.012**	5.17	**0.023**	2.64	**0.032**	2.54	0.112	1.82	0.122
PSS[g]	16.84	**<0.001**	10.66	**<0.001**	0.22	0.641	0.70	0.590	0.29	0.588	0.79	0.532
PSS-adjusted[h]	0.11	0.741	9.15	**<0.001**	3.51	0.062	1.25	0.289	0.78	0.377	1.68	0.152

Note. **Bold** *p*-values indicate significance (*p*<0.05). CPD=Cigarettes per day; CES-D=Center for Epidemiologic Studies Depression Scale; PSS=Perceived Stress Scale. Results for MI x Time x Condition are not included due to the lack of significant interactions noted.

[a] df MI = (1, 498.91), df TIME = (4, 1429.68), df CONDITION = (1, 498.91); df MIxTIME= (4, 1429.68); df MIxCONDITION = (1, 498.91); df TIMExCONDITION = (4, 1429.68)

[b] df MI = (1, 493.15), df TIME = (4 ,1411.24), df CONDITION = (1,501.54); df MIxTIME = (4, 1412.37); df MIxCONDITION = (1, 503.35); df TIMExCONDITION = (4, 1412.00)

[c] df MI = (1,521.27), df TIME = (4, 1336.49), df CONDITION = (1,521.27); df MIxTIME= (4,1336.49); df MIxCONDITION = (1,521.27); df TIMExCONDITION = (4,1336.49)

[d] df MI = (1, 464.98), df TIME = (4, 1305.90), df CONDITION = (1,474.10); df MIxTIME = (4, 1307.01); df MIxCONDITION = (1, 472.60); df TIMExCONDITION = (4, 1307.12)

[e] df MI = (1,532.79), df TIME = (4,1463.92), df CONDITION = (1,532.79); df MIxTIME= (4,1463.92); df MIxCONDITION = (1,532.79); df TIMExCONDITION = (4,1463.92)

[f] df MI = (1, 495.23), df TIME = (4, 1442.65), df CONDITION = (1,503.15); df MIxTIME = (4, 1443.19); df MIxCONDITION = (1, 503.60); df TIMExCONDITION = (4, 1443.19)

[g] df MI = (1,530.52), df TIME = (4,1455.20), df CONDITION = (1,530.52); df MIxTIME= (4,1455.20); df MIxCONDITION = (1,530.52); df TIMExCONDITION = (4,1455.20)

[h] df MI = (1, 499.54), df TIME = (4,1417.54), df CONDITION = (1,510.00); df MIxTIME= (4, 1418.37); df MIxCONDITION = (1, 510.79); df TIMExCONDITION = (4, 1418.27)

Table 11. Aim 1 and 2 results for covariates used in adjusted linear mixed models.

	CPD		CES-D		Kessler-6		PSS	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Age[a]	0.09	0.760	3.06	0.081	0.10	0.758	0.03	0.874
Sex[b]	0.43	0.511	0.00	0.983	0.69	0.405	6.42	**0.012**
Race/ethnicity[c]	3.70	**0.025**	0.41	0.661	0.31	0.734	6.90	**0.001**
Site[d]	4.93	**0.027**	0.52	0.472	0.43	0.513	2.39	0.123
CPD at baseline[e]	575.89	**<0.001**	-	-	-	-	-	-
CES-D at baseline[f]	-	-	971.48	**<0.001**	-	-	-	-
Kessler-6 at baseline[g]	1.95	0.163	-	-	542.86	**<0.001**	6.69	**0.010**
PSS at baseline[h]	0.26	0.609	2.97	0.085	11.84	**0.001**	1.73	0.189
PSCDI at baseline[i]	1.04	0.308	0.20	0.655	2.35	0.126	1.33	0.250
Other tobacco use at baseline[j]	0.02	0.903	0.65	0.421	0.23	0.630	1.73	0.189

Note. **Bold** *p*-values indicate significance ($p<0.05$). CPD=cigarettes per day; CES-D=Center for Epidemiologic Studies Depression Scale; PSS=Perceived Stress Scale; PSCDI=Penn State Cigarette Dependence Index. Blank cells indicate that particular covariate was not controlled for in a specific model.

[a] df $_{CPD}$ = (1, 489.92), df $_{CES-D}$ = (1,467.68), df $_{KESSLER-6}$ = (1, 498.98); df $_{PSS}$= (1, 499.53)

[b] df $_{CPD}$ = (1, 491.58), df $_{CES-D}$ = (1, 463.34), df $_{KESSLER-6}$ = (1, 501.24); df $_{PSS}$= (1, 500.16)

[c] df $_{CPD}$ = (2, 491.43), df $_{CES-D}$ = (2, 467.01), df $_{KESSLER-6}$ = (2, 505.39); df $_{PSS}$= (2, 501.50)

[d] df $_{CPD}$ = (1, 479.89), df $_{CES-D}$ = (1, 448.71), df $_{KESSLER-6}$ = (1, 486.88); df $_{PSS}$= (1, 487.33)

[e] df $_{CPD}$ = (1, 545.40), df $_{CES-D}$= not included, df $_{KESSLER-6}$ = not included; df $_{PSS}$= not included

[f] df $_{CPD}$ = not included, df $_{CES-D}$ = (1, 458.53), df $_{KESSLER-6}$ = not included; df $_{PSS}$= not included

[g] df $_{CPD}$ = (1, 504.21), df $_{CES-D}$= not included, df $_{KESSLER-6}$ = (1, 510.79); df $_{PSS}$= (1,510.350)

[h] df $_{CPD}$ = (1, 498.47), df $_{CES-D}$ = (1, 469.71), df $_{KESSLER-6}$ = (1, 500.02); df $_{PSS}$= (1,485.017)

[i] df $_{CPD}$ = (1, 486.67), df $_{CES-D}$ = (1, 445.23), df $_{KESSLER-6}$ = (1,477.08); df $_{PSS}$= (1,479.372)

[j] df $_{CPD}$ = (1, 480.11), df $_{CES-D}$= (1, 448.20), df $_{KESSLER-6}$ = (1, 483.32); df $_{PSS}$= (1,485.017)

Cigarettes per day. The hypothesis that smokers with current MI would report smaller reductions in CPD over 24 weeks than smokers without current MI (*H1a*) was partially supported. The interaction of MI status and time was not significant, $F(4,1429.68)=2.36$, $p=0.051$. However, due to the interaction approaching significance ($p=0.051$), post-hoc tests were performed (see Figure 7). Significant between-group differences were observed at week 16, where smokers without current MI reported significantly fewer CPD (estimated marginal means, *EMM*=8.60, *95%* confidence interval; *95% CI* =7.71,9.50) relative to smokers with current MI (*EMM*=10.48, *95% CI* =9.30,11,67; *p*=0.013). Significant differences were also observed at week 24, where smokers without current MI reported significantly fewer CPD (*EMM*=8.33, *95% CI* =7.43,9.23) relative to smokers with current MI (*EMM*=9.84, *95% CI*=8.65,11.02; *p*=0.047). To test within-condition differences (i.e., relative to week 0), post hoc tests were conducted with a Bonferroni corrected alpha of 0.0125 per test. Relative to week 0 (*EMM*=18.45, *95% CI* =17.65,19.25), smokers without mental illness significantly reduced their reported CPD at week 4 (*EMM*=10.80, *95% CI*=9.96,11.64), week 8 (*EMM*=9.98, *95% CI*=9.11,10.85), week 16 (*EMM*=8.60, *95% CI* =7.71,9.50), and week 24 (*EMM*=8.33, *95% CI*=7.42,9.23; all *p*s<0.001). Similarly for smokers with MI significant reductions in CPD relative to week 0 (*EMM*= 18.82, *95% CI* =17.78,19.85) were observed at week 4 (*EMM*= 11.07, *95% CI*=9.97,12.17), week 8 (*EMM*=10.93, *95% CI*=9.80,12.07), week 16 (*EMM*=10.48, *95% CI*=9.30,11.67) and week 24 (*EMM*=9.84, *95% CI*=8.65,11.02; all *p*s<0.001).

Figure 7. CPD over time by current MI status. CPD=cigarettes per day. Analyses are unadjusted for covariates and represent estimated marginal means with *95%* CI (lower limit, upper limit). Filled symbols indicate a significant difference relative to week 0 within that group (Bonferroni correction α=0.0125; four comparisons with week 0 for each group). One between-group comparison was done at each time point (no Bonferroni correction); asterisks (*) indicate a significant (*p*<0.05) difference between participants without and with current MI at that time point.

The hypothesis that between-condition differences in CPD reduction as produced by condition-related nicotine content in the assigned study products would differ as a function of current MI status, with greater between-condition differences found for participants with MI than for participants without MI (*H1b*) was not supported; the three-way interaction between current MI, time, and condition was not significant, $F(4,1429.68)=0.32$, $p=0.864$.

However, a significant interaction between time and condition was observed, $F(4,1429.7)=5.65$, $p<0.001$. Post hoc analyses (see Figure 8) revealed significant differences between conditions at weeks 4, 8, 16, and 24, with smokers randomized to the non-nicotine conditions reporting significantly greater CPD relative to those in the nicotine conditions (week 24 *EMM*=10.30, *95% CI*=9.30,11.33 vs. *EMM*=7.86, *95% CI*=6.79,8.94; *p*=0.001). Within-condition comparisons for the non-nicotine conditions revealed that relative to CPD at week 0

(*EMM*=18.62, *95% CI*=17.71,19.53), smokers reported significantly fewer CPD at week 4 (*EMM*=11.96, *95% CI*=11.0,12.92), week 8 (*EMM*=11.52, *95% CI*=10.51,12.52), week 16 (*EMM*=10.44, *95% CI*=9.40,11.48), and week 24 (*EMM*=10.30, *95% CI*=9.27,11.33), all *p*s <0.0125. Within the nicotine conditions, relative to CPD at week 0 (*EMM*= 18.65, *95% CI*=17.71,19.59), smokers reported significantly fewer CPD at week 4 (*EMM*=9.91, *95% CI*=8.92,10.90), week 8 (*EMM*=9.40, *95% CI*=8.38,10.42), week 16 (*EMM*=8.64, *95% CI*=7.58,9.71), and week 24 (*EMM*=7.86, *95% CI*=6.79,8.94; all *p*s<0.0125).

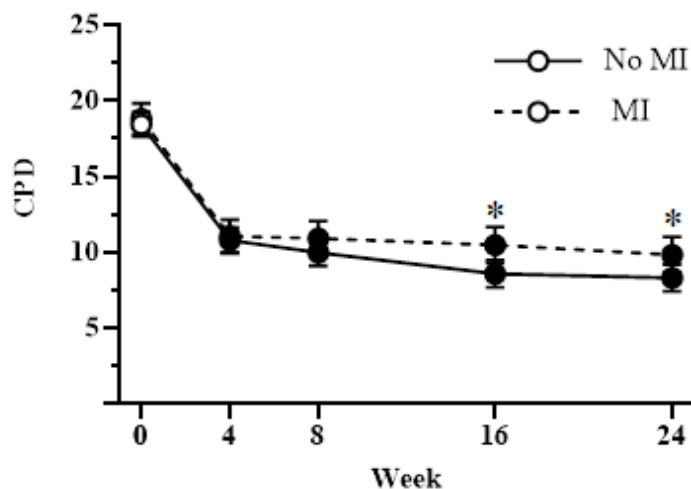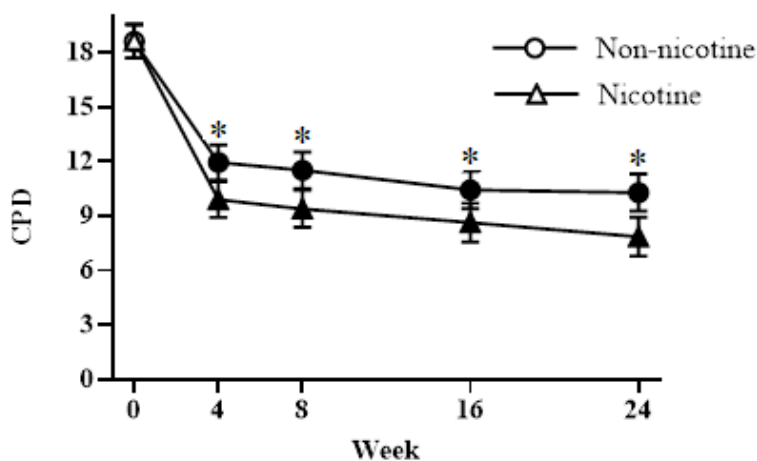*Figure 8.* CPD over time by non-nicotine and nicotine conditions. CPD=Cigarettes per day. Analyses are unadjusted for covariates and represent estimated marginal means with *95%* CI (lower limit, upper limit). Filled symbols indicate a significant difference relative to week 0 within that group (Bonferroni correction *p*=0.0125; four comparisons with week 0 were done for each group). One between-group comparison was done at each time point (no Bonferroni correction); asterisks (*) indicate a significant (*p*<0.05) difference between participants in the non-nicotine and nicotine conditions at that time point.

Cigarettes per day: Sensitivity analysis. When controlling for demographics, site, CPD score at week 0, Kessler-6 score at week 0, PSS at week 0, other tobacco use, and PSCDI at week 0, the hypothesis that smokers with current MI would report smaller CPD reduction over 24 weeks than smokers without current MI (*H1a*) was not supported; the interaction of time and

current MI status was not significant, $F(4,1412.37)=2.29$, $p=0.057$. However, because the

interaction between MI and time was approaching significance, we conducted post hoc tests to

investigate within-group and between-group differences (see Figure 9). No significant between-

group differences were found at any time points (all ps>0.05). As in the unadjusted analysis, we

used a Bonferroni adjusted alpha level of 0.0125 to investigate within-group differences.

Relative to week 0 CPD (*EMM*=17.74, *95% CI*=16.96,18.51), participants without current MI

reported smoking significantly fewer CPD at week 4 (*EMM*=10.34, *95% CI*=9.54,11.15), week 8

(*EMM*=9.45, *95% CI*=8.60,10.29), week 16 (*EMM*=8.00, *95% CI*=7.13,8.87), and week 24

(*EMM*=7.69, *95% CI*=6.82,8.56; all ps<0.001). Similarly, for participants with current MI,

participants reported significantly fewer CPD at week 4 (*EMM*=9.77, *95% CI*=8.74,10.79), week

8 (*EMM*=9.42, *95% CI*=8.35,10.49), week 16 (*EMM*=9.12, *95% CI*=8.00,10.24), and week 24

(*EMM*=8.25, *95% CI*=7.13,9.37) than at week 0 (*EMM*=17.30, *95% CI*=16.33,18.27; all

ps<0.001).
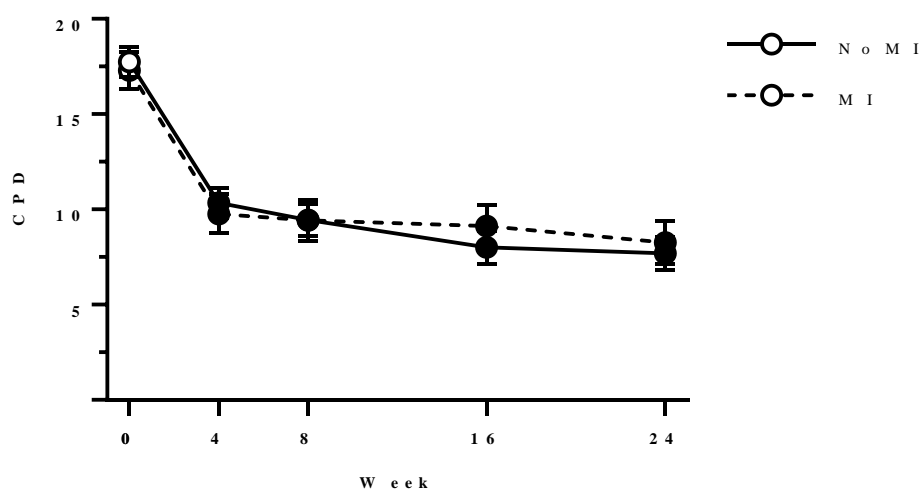
Figure 9. CPD over time by current MI status with covariate adjustment. CPD=cigarettes per
day. Covariates included: sex, age, race/ethnicity, site, week 0 CPD, week 0 Kessler-6 score,
week 0 PSS score, week 0 Penn State Cigarette Dependence Index score. Estimated marginal
means with *95%* CI (lower limit, upper limit) are displayed. Filled symbols indicate a significant

difference relative to week 0 within that group (Bonferroni correction p=0.0125; four comparisons with week 0 were done for each group). No significant between-group comparisons were observed (all ps>0.05).

When controlling for covariates, as was observed in the unadjusted analysis, the three-way interaction between current MI status, time, and condition was not significant, $F(4,1411.67)$= 0.36, p=0.839. However, a significant interaction of time and condition for CPD when adjusted for covariates was observed, $F(4,1412.0)$=5.730, p<0.001 (see Figure 10). At week 4, 8, 16, and 24, smokers in the non-nicotine condition reported significantly greater CPD than the non-nicotine condition (week 24 *EMM*=9.27, *95% CI*=8.30,10.23 vs. *EMM*=6.67, *95% CI*=5.66,7.69; p<0.001). Using the same Bonferroni adjusted alpha as in previous models, for the non-nicotine conditions significant within-groups differences in CPD relative to week 0 CPD (*EMM*=17.54, *95% CI*=16.69,18.38) were observed at week 4 (*EMM*=11.19, *95% CI*=10.30,12.07), week 8 (*EMM*=10.40, *95% CI*=9.46,11.34), week 16 (*EMM*=9.55, *95% CI*=8.58,10.51), and week 24 (*EMM*=9.27, *95% CI*=8.30,10.23), all ps<0.001. For the nicotine condition, significant within-groups differences in CPD relative to week 0 CPD (*EMM*=17.49, *95% CI*=16.62,18.37) were observed at week 4 (*EMM*=8.92, *95% CI*=8.00,9.85), week 8 (*EMM*=8.46, *95% CI*=7.50,9.42), week 16 (*EMM*=7.58, *95% CI*=8.58,10.51), and week 24 (*EMM*=6.67, *95% CI*=5.66,7.69; all ps≤0.001).
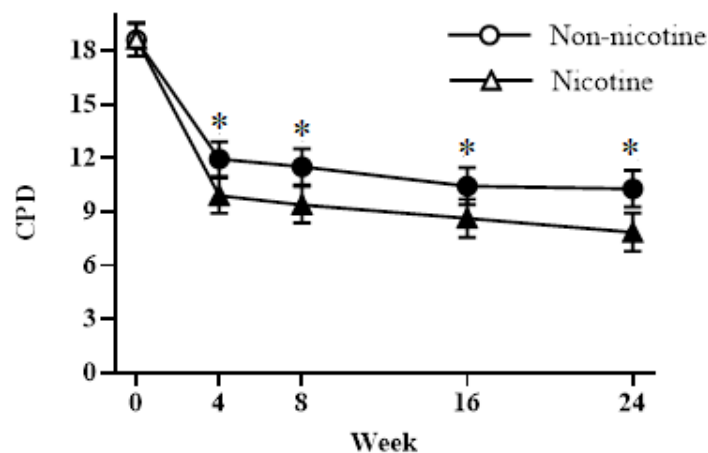
Figure 10. CPD over time by condition grouping. CPD=cigarettes per day. Adjusted model covariates included: sex, age, race/ethnicity, site, week 0 cigarettes per day, week 0 Kessler-6 score, week 0 perceived stress score, week 0 Penn State Cigarette Dependence Index score, and other tobacco use. Estimated marginal means with *95%* CI (lower limit, upper limit) are displayed. Filled symbols indicate a significant difference relative to week 0 within that group (Bonferroni correction *p*=0.0125; four comparisons with week 0 were done for each group). One between-group comparison was done at each time point (no Bonferroni correction); asterisks (*) indicate a significant difference (*p*<0.05) between participants in the non-nicotine and nicotine conditions at that time point.

Depressive symptoms. The hypothesis that relative to nicotine-containing conditions, non-nicotine-containing conditions would be associated with greater increases in CES-D scores over time among individuals with current MI relative to those without a diagnosis (*H2*) was not supported; the three-way interaction between current MI, time, and condition was not significant, $F(4, 1336.49)=1.73$, $p=0.141$.

However, the interaction of time and condition was significant, $F(4,1336.49)=1.729$, $p=0.049$. Post hoc tests (see Figure 11) revealed significant between-group differences at week 4 where participants randomized to non-nicotine conditions reported significantly greater CES-D scores (*EMM*=13.89, *95% CI* =12.53,15.25) relative to participants randomized to the nicotine conditions (*EMM*=11.49, *95% CI* =10.10,12.89; *p*=0.016). No significant within-group

differences were observed within either condition grouping when comparing CES-D scores at week 0 to those reported at other time points (all ps>0.0125; Bonferroni adjusted).
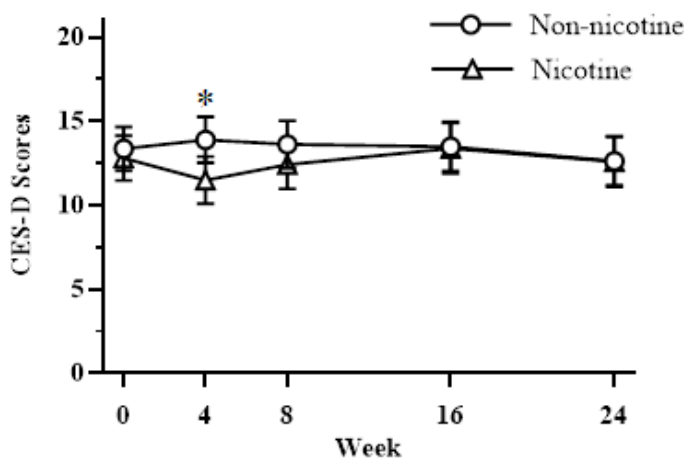
Figure 11. CES-D scores over time by condition grouping. CES-D=Center for Epidemiologic Studies Depression Scale. Analyses are unadjusted for covariates and represent estimated marginal means with *95%* CI (lower limit, upper limit). One between-group comparison was done at each time point (no Bonferroni correction); asterisks (*) indicate a significant difference (p<0.05) between participants in the non-nicotine and nicotine conditions at that time point. No significant within-group differences were found (Bonferroni correction all ps>0.0125).

For CES-D scores, no other two-way interactions were significant. However, the main effect of MI was significant, $F(1, 521.27)=52.71$, p<0.001. Across all time points, CES-D scores of smokers with MI were significantly higher (*EMM*=16.03, *95% CI*=14.71,17.36) than the CES-D scores of smokers without MI (*EMM*=9.90, *95% CI*=8.90,10.90; p<0.001).

Depressive symptoms: Sensitivity analysis. When controlling for demographics, site, CES-D scores at week 0, PSS score at week 0, other tobacco use, and PSCDI at week 0, as was observed in the adjusted model; the three-way interaction between current MI status, time, and condition was not significant, $F(4,1306.64)=1.01$, p=0.404.

However, a significant interaction effect of time and current MI status was observed for CES-D scores, $F(4,1307.01)=3.08$, p=0.015; see Figure 12. Significant differences between the

CES-D scores of smokers without and with MI were observed at three time points. At week 8, smokers without MI reported significantly lower CES-D scores (*EMM*=11.14, *95% CI*=10.08,12.20) than smokers with MI (*EMM*=12.97, *95% CI*=11.56,14.37; *p*=0.020). Similarly, significantly lower CES-D scores were reported at week 16 by smokers without MI (*EMM*=10.91, *95% CI*=9.82,12.01) than by smokers with MI (*EMM*=14.28, *95% CI*=12.80,15.76; *p*<0.001). Smokers without MI had significantly lower CES-D scores at week 24 (*EMM*=10.46, *95% CI*=9.36,11.56), relative to smokers with MI (*EMM*=13.52, *95% CI*=12.04,14.99; *p*<0.001). For the within-group post hoc tests, no significant differences in CES-D scores relative to week 0 CES-D scores were observed for smokers without and with MI (all *p*s>0.0125).
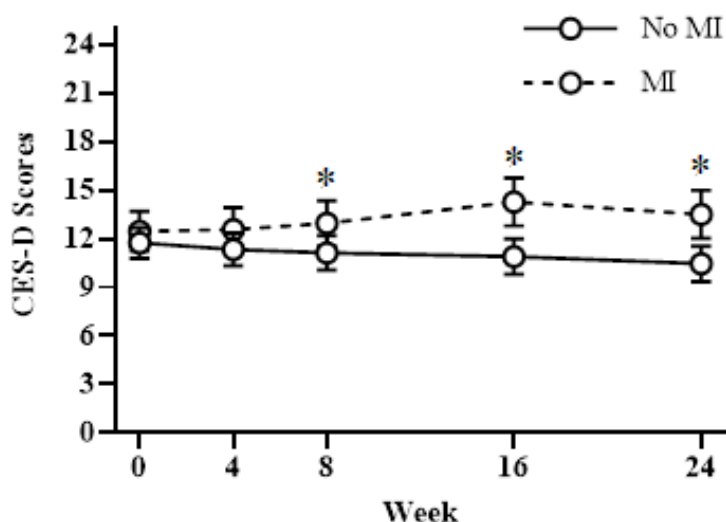
Figure 12. CES-D scores over time by condition grouping adjusted for covariates. CES-D=Center for Epidemiologic Studies Depression Scale. Covariates included: sex, age, race/ethnicity, site, week 0 CES-D scores, week 0 perceived stress score, week 0 Penn State Cigarette Dependence Index score and other tobacco use. Estimated marginal means with *95%* CI (lower limit, upper limit) are displayed. One between-group comparison was done at each time point (no Bonferroni correction); asterisks indicate a significant difference (*p*<0.05) between participants in the non-nicotine and nicotine conditions at that time point.

Psychological distress. The hypothesis that relative to nicotine conditions, non-nicotine conditions would be associated with greater increases in Kessler-6 scores over time among individuals with current MI relative to those without current MI was not supported; the three-way interaction between current MI status, time, and condition was not significant, $F(4,1463.92)=1.96$, $p=0.099$.

No significant two-way interactions were observed for Kessler-6 scores including the interaction of time and condition, $F(4,1463.92)=2.19$, $p=0.067$; however, because this p-value was approaching significance, post hoc tests were conducted to explore between-group and within-group differences (see Figure 13). Post-hoc tests indicated significant differences between the nicotine and non-nicotine conditions at week 24, with smokers in the non-nicotine conditions reporting significantly greater Kessler-6 scores (*EMM*=5.81, *95% CI*=5.09,6.53) relative to smokers in the nicotine conditions (*EMM*=4.48, *95% CI*=3.72,5.23; *p*=0.012). For within-group comparisons (using the same Bonferroni adjustment as previous models), no significant within-group differences between Kessler-6 scores at week 0 and any other time points were observed for the non-nicotine condition (all *p*s>0.0125). Within the nicotine conditions, relative to Kessler-6 scores at week 0 (*EMM*=5.31, *95% CI*=4.68,5.93), scores were significantly lower at week 4 (*EMM*=4.31, *95% CI*=3.63,4.98], *p*=0.004) and week 8 (*EMM*=4.29, *95% CI*=3.58,4.99; *p*=0.005).
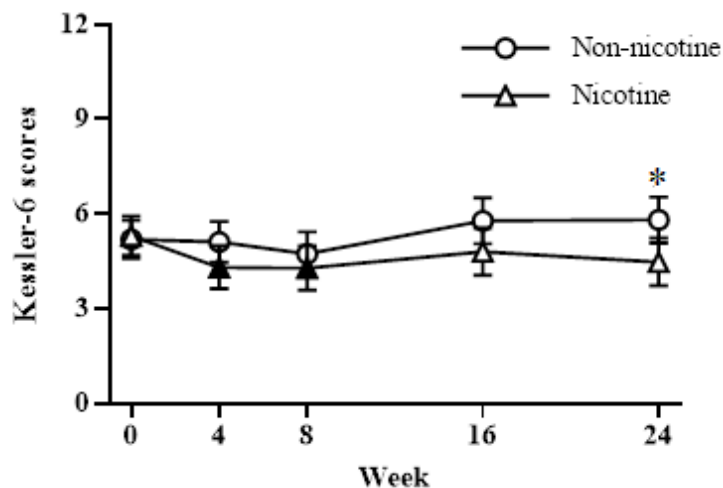
Figure 13. Kessler-6 scores over time by condition grouping. Analyses are unadjusted for covariates and represent estimated marginal means with *95%* CI (lower limit, upper limit). One between-group comparison was done at each time point (no Bonferroni correction). Filled symbols indicate a significant difference relative to week 0 within that group (Bonferroni correction *p*<0.0125; four comparisons with week 0 were done for each group). Asterisks (*) indicate a significant difference (*p*<0.05) between participants in the non-nicotine and nicotine conditions at that time point.

Of note, for Kessler-6 scores, there was a significant main effect of MI, *F*(1,532.79)=57.72, *p*<0.001. Smokers without MI had significantly lower Kessler-6 scores (*EMM*=3.60, *95% CI* =3.17,4.04) than smokers with MI (*EMM*=6.36, *95% CI* =5.76,6.93; *p*<0.001).

Psychological distress: Sensitivity analysis. When controlling for demographics, site, Kessler-6 scores at week 0, PSS scores at week 0, other tobacco use, and PSCDI at week 0, as was observed in the unadjusted model, the three-way interaction of current MI status, time, and condition was not significant, *F*(4, 1443.01)=1.293, *p*=0.274.

However, a significant interaction effect of time and current MI status on Kessler-6 scores was observed, *F*(4,1443.19)=2.64, *p*=0.032. At week 0, smokers without MI had significantly lower Kessler-6 scores (*EMM*=4.54, *95% CI*=4.00,5.08) than smokers with MI

(*EMM*=5.39, *95% CI*=4.71,6.07; *p*=0.024; see Figure 14). Similarly, significantly lower Kessler-6 scores were observed at week 16 for smokers without MI (*EMM*=4.53, *95% CI*=3.90,5.17) compared to smokers with MI (*EMM*=5.62, *95% CI*=4.80,6.43; *p*=0.023). Also, smokers without MI had significantly lower Kessler-6 scores at week 24 (*EMM*=3.91, *95% CI*=3.27,4.55) relative to smokers with MI (*EMM*=6.00, *95% CI*=5.16,6.80; *p*<0.001). For the within-group comparisons relative to week 0, no significant differences in Kessler-6 scores were observed for other time points among smokers without or with MI (all *p*s>0.0125; Bonferroni adjusted).
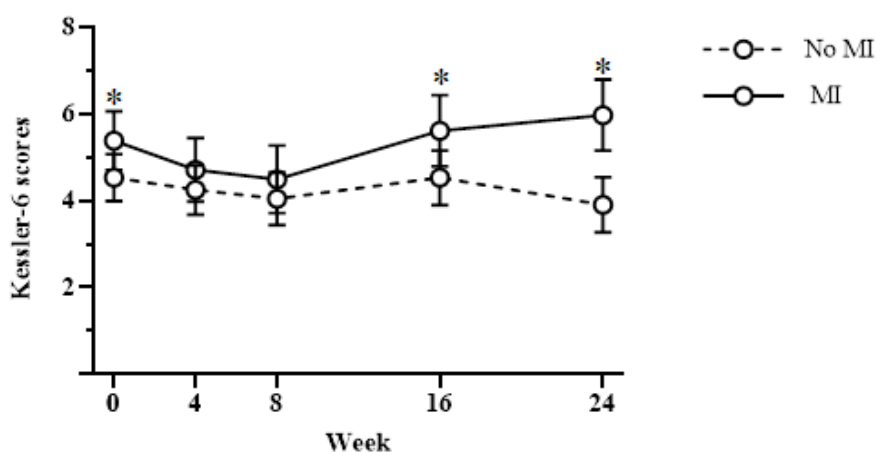
Figure 14. Kessler-6 scores over time by current MI status adjusted for covariates. Covariates include sex, age, race/ethnicity, site, week 0 Kessler-6 scores, week 0 perceived stress score, week 0 Penn State Cigarette Dependence Index score and other tobacco use. Estimated marginal means with *95%* CI (lower limit, upper limit) are displayed. One between-group comparison was done at each time point (no Bonferroni correction); asterisks (*) indicate a significant difference (*p*<0.05) between participants in the non-nicotine and nicotine conditions at that time point. No significant within-group differences were found (Bonferroni correction all *p*s>0.0125).

A significant main effect of condition was observed, $F(1,503.15)=5.10$, *p*=0.023. Post hoc tests revealed that smokers assigned to the nicotine condition had significantly lower

Kessler-6 scores (*EMM*=4.47, *95% CI* =3.98,4.96) relative to smokers in the non-nicotine

conditions (*EMM*=5.03, *95% CI* =4.56,5.50; *p*<0.001).

Perceived stress. The hypothesis that relative to nicotine conditions, non-nicotine

conditions would be associated with greater increases in PSS scores over time among individuals

with current MI relative to those without a diagnosis was not supported; the three-way

interaction of current MI status, time, and condition was not significant, $F(4,1455.20)=0.24$,

p=0.913.

No significant two-way interactions were observed for PSS scores. There was, however,

a significant main effect of MI on PSS scores, $F(1,530.52)=16.84$, *p*<0.001. Smokers with

current MI reported significantly greater PSS scores (*EMM*=19.94, *95% CI* =19.37,20.51)

relative to smokers without MI (*EMM*=18.44, *95% CI*=18.01,18.87, *p*<0.001). A significant

main effect of time on PSS scores was observed as well, $F(4,1455.20)=10.66$, *p*<0.001. Relative

to PSS scores at week 0 (*EMM*=20.08, *95% CI*=19.65,20.52), PSS scores were significantly

lower at week 4 (*EMM*=18.87, *95% CI*=18.40,19.34), week 8 (*EMM*=19.27, *95%*

CI=18.77,19.76), week 16 (*EMM*=19.23, *95% CI*=18.71,19.76), and week 24 (*EMM*=18.49,

95% CI=17.97,19.02; all *p*s<0.0125, Bonferroni-adjusted).

Perceived stress: Sensitivity analysis. When controlling for demographics, site, PSS

scores at week 0, Kessler-6 scores at week 0, other tobacco use, and PSCDI at week 0, as was

observed in the unadjusted model, the three-way interaction of current MI status, time, and

condition was not significant,, $F(4,1417.89)=0.613$, *p*=0.653. No significant two-way

interactions were observed for PSS. However, there was a significant main effect of time on PSS

scores, $F(4,1417.54)=9.15$, *p*<0.001. Relative to week 0 (*EMM*=19.51, *95% CI*=18.99,20.03),

PSS scores were significantly lower at week 4 (*EMM*=18.36, *95% CI*=17.82,18.90), week 8 (*EMM*=18.63, *95% CI*=18.06,19.20), week 16 (*EMM*=18.75, *95% CI*=18.16,19.34), and week 24 (*EMM*=18.13, *95% CI*=17.55,18.72; all *p*s<0.0125, Bonferroni-adjusted).

Aim 3

For Aim 3, following z-score transformation of CES-D scores, Kessler-6 scores, and PSS scores, a composite index of "negative mood and stress" was created. A composite index of "negative mood" using only z-score transformed CES-D scores and Kessler-6 scores was also created. We tested these composite indices and individual negative mood and stress variables into our models as mediators of the relationship between condition (nicotine-containing vs. non-nicotine-containing conditions) and CPD reduction over the course of the trial. The hypothesis that negative mood and stress measure measures would mediate condition effects on CPD reduction (*H3a*) was not supported for "negative mood and stress", "negative mood", depressive symptoms (as indexed by CES-D scores), psychological distress (as indexed by Kessler-6 scores), or perceived stress (as indexed by PSS scores).

Negative mood and stress. In the simple mediation model, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through negative mood and stress indices using 5,000 bootstrap samples (see Figure 15). Please note all following path estimates are represented by *b* (b-weight). Neither the direct path from condition to negative mood and stress (*b*=-0.08, *p*=0.254) nor the direct path from negative mood and stress to CPD reduction was significant (*b*=-0.49, *p*=0.180). The direct path of condition to CPD reduction was significant (*b*=1.94, *p*=0.0014) with the nicotine-containing condition grouping being related to greater CPD reduction. The indirect effect of condition on CPD reduction through negative mood and stress was not statistically significant (*b*=0.04, *95%* CI=-0.04,0.20), indicating that negative

mood and stress neither partially nor fully mediated the relationship between condition and CPD reduction.

Figure 15. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples. Negative mood and stress= composite variable consisting of z-transformed five-visit average CES-D scores, Kessler-6 scores, and PSS scores. *a*=direct path from condition to negative mood and stress; *b*=direct path from negative mood and stress to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for negative mood and stress. Asterisks (*) indicate significance; ** (*p*<0.01).

Negative mood and stress: Sensitivity analysis. We then entered demographics (race/ethnicity, age, and sex), site, and CPD at week 0 as covariates into each of the mediation models (see Figure 16). When controlling for the covariates, the direct path from condition to negative mood and stress was not significant (*b*=-0.08, *p*=0.294); however, the direct path from negative mood and stress to CPD reduction was significant (*b*=-0.73, *p*=0.0097) with greater negative mood and stress being related to smaller CPD reduction. The direct effect of condition on CPD reduction was significant (*b*=1.91, *p*<0.001), with the nicotine-containing condition grouping being related to greater CPD reduction. However, the indirect effect of condition on CPD reduction through negative mood and stress was not statistically significant (*b*=0.06, *95%*

CI =-0.04,0.21), indicating that negative mood and stress neither partially nor fully mediated the

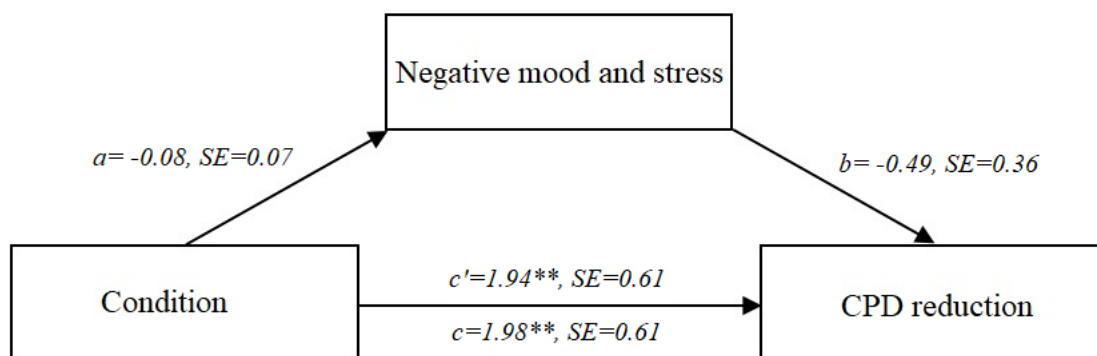relationship between condition and CPD reduction when controlling for covariates.

Figure 16. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples and controlling for covariates. Negative mood and stress=composite variable consisting of z-transformed five-visit average CES-D scores, Kessler-6 scores and PSS scores. *a*=direct path from condition to negative mood and stress; *b*=direct path from negative mood and stress to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for negative mood and stress. Asterisks (*) indicate significance; ** (*p*<0.01), *** (*p*<0.001).

Negative mood. In the next mediation model, condition was specified to have a direct

effect on CPD reduction as well as an indirect effect through negative mood indices alone using

5,000 bootstrap samples (see Figure 17). Neither the direct path from condition to negative mood

(*b*=-0.13, *p*=0.137) nor the direct path from negative mood to CPD reduction was significant

(*b*=-0.41, *p*=0.195). The direct effect of condition on CPD reduction was significant (*b*=1.93,

p=0.0015) with the nicotine-containing condition grouping being related to greater CPD

reduction. The indirect effect of condition on CPD reduction through negative mood was not

significant (*b*=0.05, *95% CI* =-0.03,0.21), indicating that negative mood alone neither partially

nor fully mediated the relationship between condition and CPD reduction.

Figure 17. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples. Negative mood = composite variable consisting of z-transformed five-visit average CES-D scores and Kessler-6 scores; *a*=direct path from condition to negative mood; *b*=direct path from negative mood to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for negative mood. Asterisks (*) indicate significance; ** (*p*<0.01).

Negative mood: Sensitivity analysis. While controlling for the same covariates as in previous models, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through negative mood indices using 5,000 bootstrap samples (see Figure 18). The direct path from condition to negative mood was not significant (*b*=-0.13, *p*=0.139); however, the direct path from negative mood to CPD reduction was significant (*b*=-0.58, *p*=0.016) with greater negative mood being related to smaller CPD reduction. The direct effect of condition on CPD reduction was significant (*b*=1.90, *p*=0.0001) with the nicotine-containing condition grouping being related to greater CPD reduction. The indirect effect of condition on CPD reduction through negative mood was not statistically significant (*b*=0.07, *95% CI* =-0.02,0.24), indicating that negative mood neither partially nor fully mediated the relationship between condition and CPD reduction when controlling for covariates.
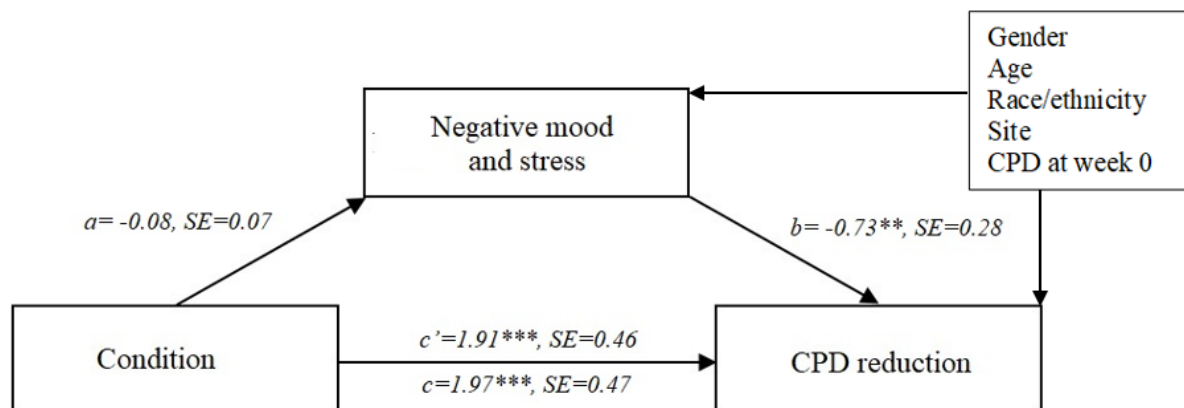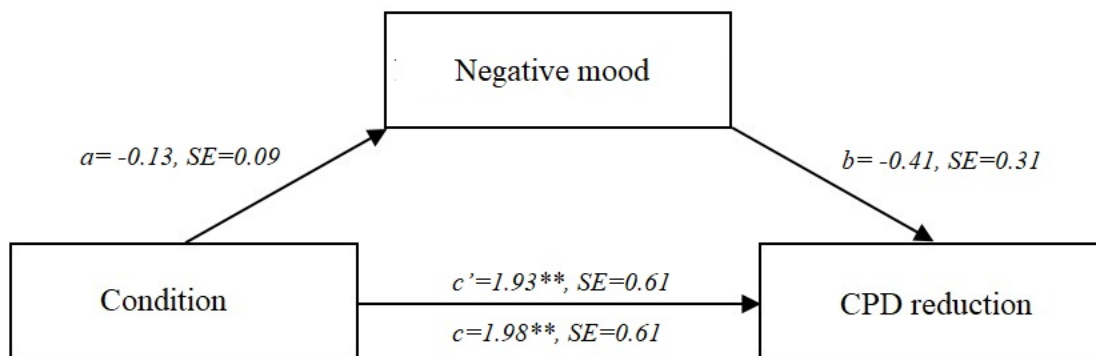
Figure 18. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples and controlling for covariates. Negative mood=composite variable consisting of z-transformed five-visit average CES-D scores and Kessler-6 scores; *a*=direct path from condition to negative mood; *b*=direct path from negative mood to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for negative mood. Asterisks (*) indicate significance; * ($p<0.05$), *** ($p<0.001$).

Depressive symptoms. Since none of the composite variables mediated the relationship between condition and CPD reduction, mean centered CES-D score was entered into the model as a mediator. In the simple mediation model, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through CES-D scores using 5,000 bootstrap samples (see Figure 19). Neither the direct path from condition to CES-D scores (b=-1.0, p=0.212) nor the direct path from CES-D scores to CPD reduction was significant (b=-0.04, p=0.186). The direct effect of condition on CPD reduction was significant (b=1.93, p=0.0014) with the nicotine-containing condition grouping being related to greater CPD reduction. The indirect effect of condition on CPD reduction through CES-D scores was not statistically significant (b=0.04, *95% CI*=-0.03,0.03), indicating that CES-D neither partially nor fully mediated the relationship between condition and CPD reduction.

Figure 19. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples. Depressive symptoms=mean centered five-visit average CES-D scores; *a*=direct path from condition to depressive symptoms; *b*=direct path from depressive symptoms to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for depressive symptoms. Asterisks (*) indicate significance; ** ($p<0.01$).

Depressive symptoms: Sensitivity analysis. While controlling for covariates, the mean transformed variable CES-D was then entered into the model as a mediator. In the mediation model, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through CES-D using 5,000 bootstrap samples (see Figure 20). The direct path from condition to CES-D scores was not significant (b=-0.99, p=0.219). The direct path from CES-D scores to CPD reduction was significant (b=-0.06, p=0.023) with greater CES-D scores being related to smaller CPD reduction. The direct effect of condition on CPD reduction was significant (b=1.91, $p<0.001$) with the nicotine-containing condition grouping being related to greater CPD reduction. The indirect effect of condition on CPD reduction through CES-D scores was not significant (b=0.06, *95% CI*=-0.03,0.21), indicating that CES-D neither partially nor fully mediated the relationship between condition and CPD reduction when controlling for covariates.
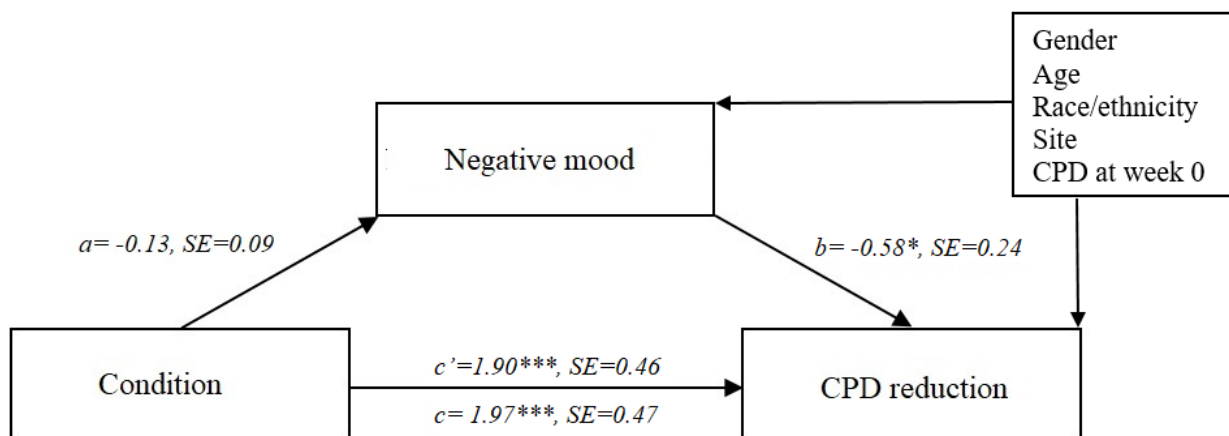
Figure 20. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples and controlling for covariates. Depressive symptoms=mean centered five-visit average CES-D scores; *a*=direct path from condition to depressive symptoms; *b*=direct path from depressive symptoms to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for depressive symptoms. Asterisks (*) indicate significance; * ($p<0.05$), *** ($p<0.001$).

Psychological distress. In the next mediation model, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through Kessler-6 scores using 5,000 bootstrap samples (see Figure 21). Neither the direct path from condition to Kessler-6 scores (b=-0.56, p=0.101) nor the path from Kessler-6 scores to CPD reduction (b=-0.09, p=0.234) was significant. The direct path from condition to CPD reduction was significant (b=1.93, p=0.0015), with the nicotine-containing condition grouping being related to greater CPD reduction. The indirect effect of condition on CPD reduction through Kessler-6 scores was not significant (b=0.05, *95% CI* =-0.03,0.22), indicating that Kessler-6 scores neither partially nor fully mediated the relationship between condition and CPD reduction.
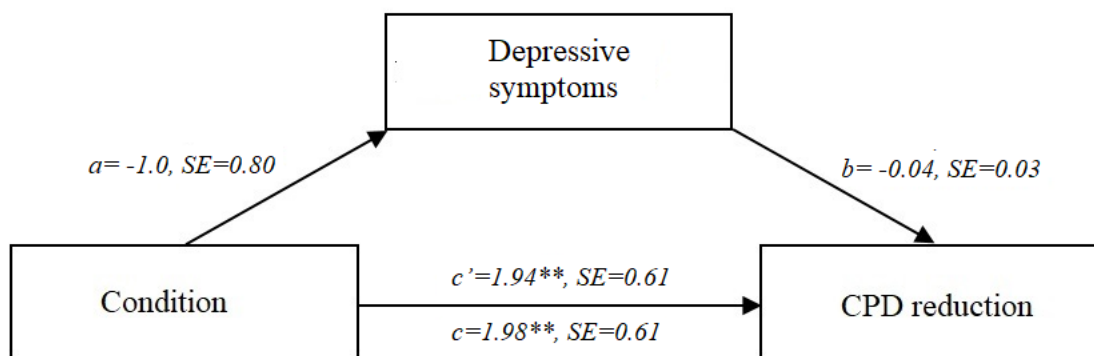
Figure 21. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples. Psychological distress=mean centered five-visit average Kessler-6 scores; *a*=direct path from condition to psychological distress; *b*=direct path from psychological distress to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for psychological distress. Asterisks (*) indicate significance; ** ($p<0.01$).

Psychological distress: sensitivity analysis. While controlling for covariates, the z-transformed variable Kessler-6 was then entered into the model as a mediator. In the mediation model, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through Kessler-6 using 5,000 bootstrap samples (see Figure 22). The direct path from condition to Kessler-6 scores was not significant (b=-0.56, p=0.1004). The direct path from Kessler-6 scores to CPD reduction was significant (b=-0.14, p=0.0169) with greater negative mood and stress being related to smaller CPD reduction. The direct effect of condition on CPD reduction was significant (b=1.89, p=0.0001) with the nicotine-containing condition grouping being related to greater CPD reduction. The indirect effect of condition on CPD reduction through Kessler-6 scores was not statistically significant (b=0.08, *95% CI* =-0.01,0.25), indicating that Kessler-6 scores neither partially nor fully mediated the relationship between condition and CPD reduction when controlling for covariates.
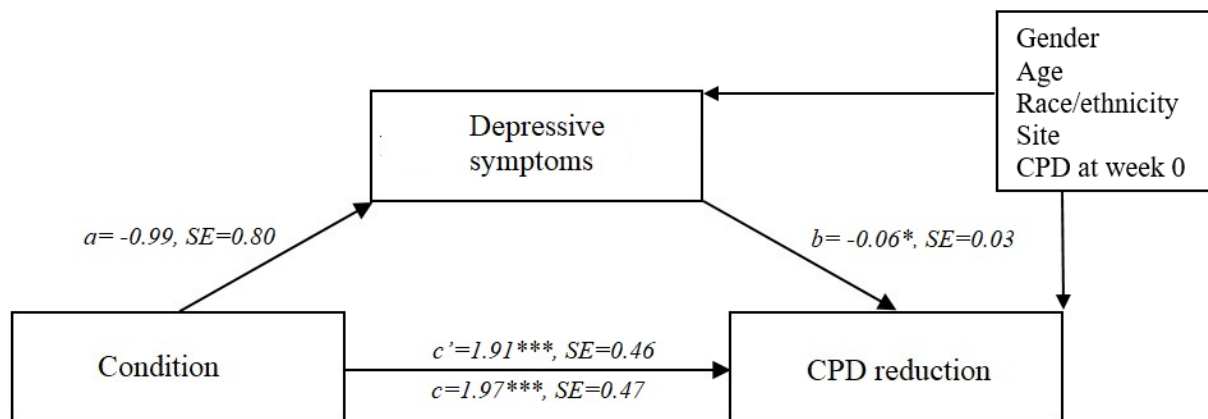
Figure 22. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples and controlling for covariates. Psychological distress=mean centered five-visit average Kessler-6 scores; *a*=direct path from condition to psychological distress; *b*=direct path from psychological distress to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for psychological distress. Asterisks (*) indicate significance; * ($p<0.05$), *** ($p<0.001$).

Perceived stress. We then entered the mean centered variable PSS into the model as a mediator. In the simple mediation model, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through PSS scores using 5,000 bootstrap samples (see Figure 23). Neither the direct path from condition to PSS scores ($b=0.01$, $p=0.965$) nor the direct path from PSS scores to CPD reduction ($b=-0.07$, $p=0.408$) was significant. The direct effect of condition onto CPD reduction was significant ($b=1.98$, $p=0.0011$) with the nicotine-containing condition grouping being related to greater CPD reduction. The indirect effect of condition on CPD reduction through PSS scores was not significant ($b=-0.001$, *95% CI* $=-0.07,0.09$). These results indicate that PSS scores neither partially nor fully mediated the relationship between condition and CPD reduction.
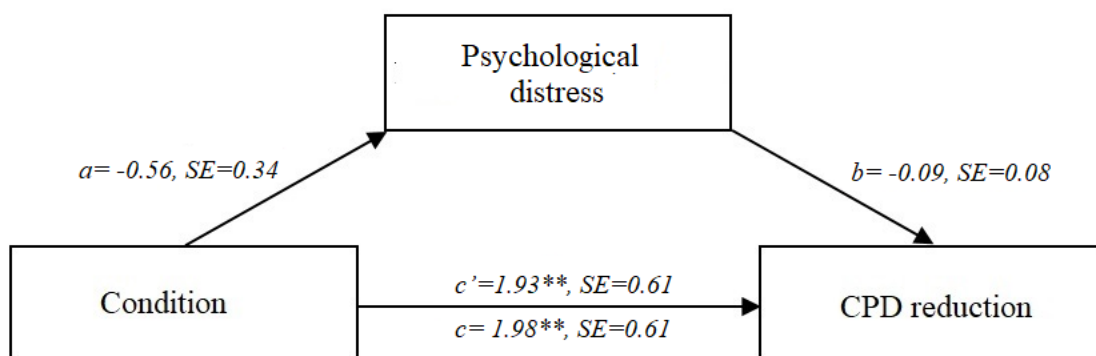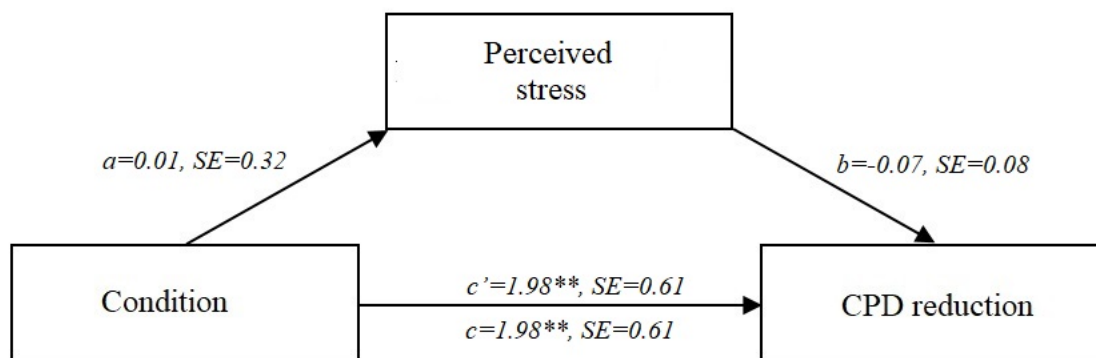
Figure 23. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples. Perceived stress=mean centered five-visit average PSS scores; *a*=direct path from condition to perceived stress; *b*=direct path from psychological distress to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for perceived stress. Asterisks (*) indicate significance; ** ($p<0.01$).

Perceived stress: Sensitivity analysis. While controlling for covariates, the mean centered variable PSS was then entered into the model as a mediator. In the mediation model, condition was specified to have a direct effect on CPD reduction as well as an indirect effect through PSS scores using 5,000 bootstrap samples (see Figure 24). In this model, neither the direct path from condition to PSS scores ($b=0.08$, $p=0.789$), nor the direct path from PSS to CPD reduction was significant ($b=-0.12$, $p=0.074$). The direct effect of condition on CPD reduction was significant ($b=1.98$, $p<0.0001$), with the nicotine-containing condition being related to greater CPD reduction. The indirect effect of condition on CPD reduction through PSS scores was not statistically significant ($b=-0.01$, *95% CI*=-0.10,0.08), indicating that PSS scores neither partially nor fully mediated the relationship between condition and CPD reduction when controlling for covariates.
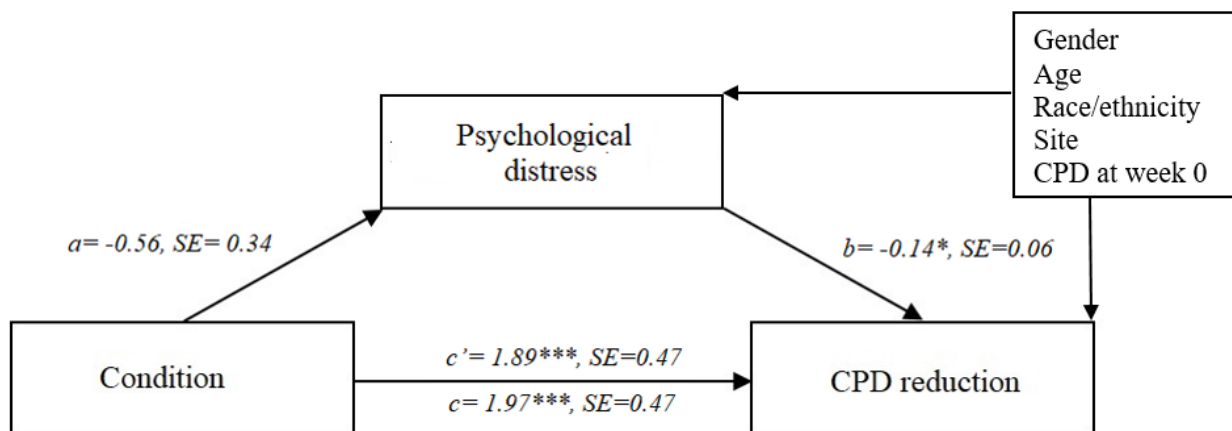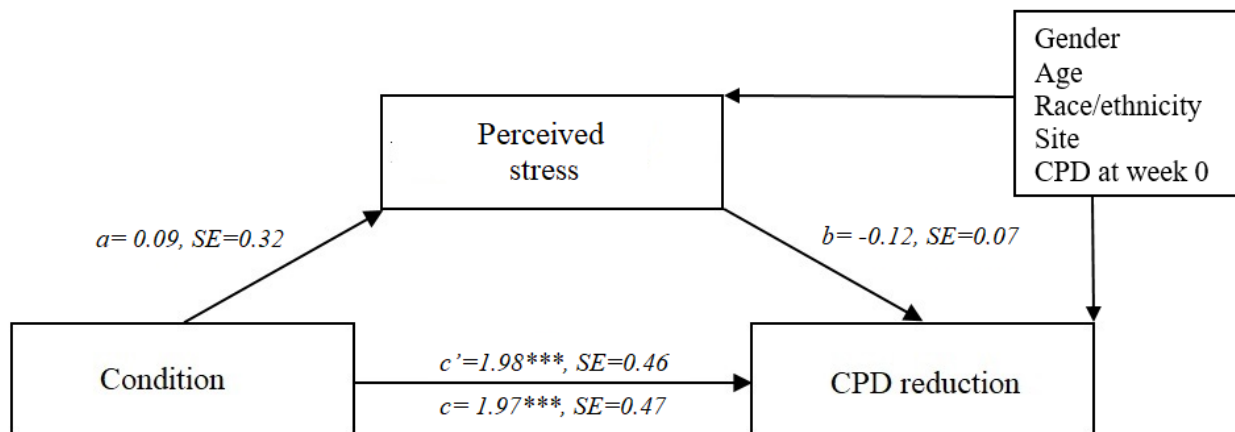
Figure 24. Simple mediation model with unstandardized path loadings and standard errors using 5,000 bootstrap samples and controlling for covariates. Perceived stress=mean centered five-visit average PSS scores; *a*=direct path from condition to perceived stress; *b*=direct path from perceived stress to CPD reduction; *c*=direct path from condition to CPD reduction; *c'*=direct path from condition to CPD reduction controlling for perceived stress. Asterisks (*) indicate significance; *** (*p*<0.001).

We had initially hypothesized (*H3b*) that the mediation effect of "negative mood and stress" would be stronger among individuals with current MI; however, because none of the mediation models were significant, no moderated mediation models were conducted.

Discussion

In order to inform harm mitigation efforts for a vulnerable population of smokers, the present study aimed to investigate whether nicotine-containing ENDS as compared to non-nicotine-containing products produced differential effects on CPD reduction and changes in negative mood and stress indices for smokers without and with current MI (Aim 1 and 2). Related to these aims, the present study also investigated how negative mood and stress measures may influence the effects of ENDS on CPD reduction and whether these effects differed by current MI status (Aim 3). A summary and interpretation of our findings by each aim follow below.

Aim 1: Cigarettes per day

The hypothesis that smokers with current MI would report smaller CPD reduction over 24 weeks than their counterparts without current MI (*H1a*) was partially supported. Participants without and with MI significantly decreased their CPD over time but smokers with current MI did not reduce their CPD to the same extent as those without MI at week 16 and week 24. These differences by MI status were observed prior to including relevant covariates as controls. Of note, the similarity in CPD between participants with and without MI at baseline (week 0) was surprising as smokers with MI tend to smoke more cigarettes relative to smokers without MI (Fergusson et al., 2003; Greenberg et al., 2012). However, effects noted at the later study time points indicated that smokers with current MI had a more difficult time reducing their CPD as the study went on (at least prior to covariate adjustment).

The latter finding may be related to the prevalence of depression and anxiety in our MI sample, with over 20% of participants reporting at least one of the two conditions. Past literature highlights that smokers with depression experience a more difficult time quitting than smokers without depression (Glassman et al., 1990). The differences observed at later time points in the primary analysis also may represent evidence that smokers with MI use cigarette-delivered nicotine to alleviate MI-related symptoms (Goldstein, 1987). For example, nicotine administration has been found to decrease anxiety (Pomerleau et al., 1984) and depressive symptoms (Haro & Drucker-Colin, 2004a). If cigarettes were used to assist with MI symptom management, smokers with current MI may have been reluctant to decrease their smoking past a certain threshold which provided symptom relief regardless of their study product's nicotine content. Of note, smokers with depressive symptoms experience greater nicotine abstinence symptoms than smokers without depressive symptoms when abstaining from nicotine (Reid &

Ledgerwood, 2016). Differences in the severity of nicotine abstinence-related symptoms also may help explain why those with MI had more difficulty reducing their CPD at the last two time points. Brief measures of nicotine abstinence symptoms were assessed during the current study (see Lopez et al., 2016) and could be incorporated into future analyses to understand their relationship to cigarette smoking behavior. However, we did observe the loss of these significant differences by current MI status for CPD after controlling for covariates. The covariates which were significant in this model included race/ethnicity, site, and CPD at week 0 (see Table 11). These associations suggest an overlap of these factors with current MI status which is consistent with the associations observed at the bivariate level for race/ethnicity and site (see Table 8).

Patterns of CPD reduction by condition grouping observed in this study support the idea that ENDS that deliver nicotine are more effective in reducing smoking behavior as compared to a non-nicotine ENDS and/or CIG SUB. Our findings are consistent with the parent study (Cobb et al., 2021). However, the parent study did not collapse conditions, and significant differences in CPD were identified between CIG SUB and the 0, 8 and 36 mg/ml ENDS conditions. It is likely that the differences by condition grouping were driven by the effects previously described by Cobb et al. (2021). These findings also correspond to the acute clinical laboratory study (Hiler et al., 2017) that utilized the same ENDS and liquid solution among smokers. Here the nicotine-containing ENDS conditions resulted in cigarette-like and less than cigarette-like nicotine delivery (see Table 1), and nicotine-containing ENDS resulted in more effective suppression of nicotine abstinence symptoms as compared to 0 mg/ml ENDS. These attributes (among others) may help explain why those assigned to the nicotine-containing ENDS reduced their smoking behavior more effectively.

Regardless of whether we controlled for additional variables or not, the hypothesis that between-condition differences in CPD reduction as produced by condition grouping would differ as a function of current MI status was not supported (*H1b*). Differences in smoking behavior by current MI status and condition grouping over time were too small and/or too variable to be detected. One interpretation of this finding is that current MI status did not interfere with condition-related effects. ENDS with nicotine were effective in smokers with and without MI and non-nicotine conditions did not result in discrepant patterns of CPD reduction between these two groups. Our examination of the two-way interactions observed are consistent with this interpretation, but there are other features of our analysis that may have influenced our ability to detect effects by condition and MI status.

By grouping conditions by nicotine content, rather than comparing the four unique randomized conditions, we may have diluted some effects that may have otherwise been observed. The parent study results (Cobb et al., 2021) revealed that only the 36 mg/ml condition resulted in significant reductions in smoking behavior and the urinary carcinogen biomarker (versus reductions in smoking behavior alone). The 36 mg/ml condition also resulted in the greatest smoking reduction although levels were not significantly different compared to the other ENDS conditions (0 mg/ml and 8 mg/ml). While adding statistical power, collapsing the 36 mg/ml and 8 mg/ml conditions may have made it more difficult to discern differences by nicotine content status. Of note, a lack of significant differences between nicotine and non-nicotine containing ENDS has been observed in other clinical trials for cigarette smoking abstinence outcomes (Bullen et al., 2013; Eisenberg et al., 2020). For example, in a yearlong double-blind RCT among smokers not interested in quitting, no significant differences were observed at 52 weeks between participants randomized to the 7.2 mg/ml, 5.4 mg/ml, and 0

mg/ml ENDS conditions, although all conditions resulted in significant decreases in CPD (Caponnetto et al., 2013).

Another contributing factor to our ability to detect differences by MI status may have been our approach to defining current MI. MI diagnoses are warranted if the participant's daily functioning is strongly and negatively impacted (APA, 2013). However, when symptoms are alleviated and functioning is restored through pharmaceutical and/or behavioral treatment, a smoker's MI, although a valid and current diagnosis, may no longer impact smoking-related behavior to the same degree as the MI of an individual with uncontrolled MI symptoms. Current MI, as defined in this study, did not indicate presence and/or severity of MI-related functional impairment and may therefore have omitted differences in the severity of MI that may have confounded our estimates of interest. The lack of assessment of current MI-related functional impairment also may help explain why no significant differences in baseline CPD were observed between smokers without and with current MI unlike previous work (e.g., Greenberg et al., 2012). Another explanation for the lack of interaction between current MI and condition may be that participants with current MI simply did not experience as many difficulties when assigned to non-nicotine conditions as we had hypothesized. Future work using data from this RCT could probe study product use behavior and acceptibility-related measures of ENDS conditions by current MI status to better understand these effects.

As noted in the methods section, we had sufficiently high power to detect main effects of condition and MI status, but rather low power to detect interactions between those two factors. Future research efforts should consider categorizing MI not based on a self-reported diagnosis through a medical professional, but instead based on symptom prevalence assessed by a questionnaire administered as part of the study. Importantly, this measure should be able to

identify a range of MI; for example, the Mini-International Neuropsychiatric Interview (MINI) presents a brief structured interview that can be effectively used in epidemiological research and multicenter clinical studies (Sheehan et al., 1998). The MINI measures MI that were assessed via self-reported medical diagnoses in the parent study as well as several other MI and has been found to have high sensitivity and specificity (Sheehan et al., 1998). Identifying MI symptom prevalence and severity would have allowed us to categorize those with current symptoms (instead of a current diagnosis alone) as experiencing current MI-related distress. Those with current symptoms would likely be most vulnerable to condition grouping-related presence or absence of nicotine.

Another approach that future trials could use would be to focus recruitment among individuals with current MI which has already been done for clinical trials of reduced nicotine content cigarettes which limited recruitment to smokers with affective disorders or substance use disorders (Higgins et al., 2020). Including only individuals with MI would increase statistical power while simultaneously allowing for some comparisons across MI status (e.g., lifetime MI vs. current MI). Doing so would allow for identification of potential subgroups with enhanced MI-related vulnerability for worse outcomes. To address the next aim, we investigated the influence of current MI status and condition on indices of depressive symptoms, psychological distress, and perceived stress.

Aim 2. Negative mood and stress

Our hypothesis that relative to the nicotine conditions, the non-nicotine conditions would be linked to greater increases in negative mood and stress measures among individuals with current MI relative to those without (*H2*) was not supported. The following paragraphs will focus

on the negative mood measures first and then on perceived stress. Only in the unadjusted models, depressive symptoms and psychological distress scores differed by condition grouping and time with significantly lower scores noted for the nicotine conditions compared to the non-nicotine conditions. When adjusting for covariates, these condition grouping-related effects were less apparent but differences by current MI status over time were noted with significantly greater depressive symptoms and psychological distress scores at later time points for those with current MI.

While condition grouping-related effects on negative mood were only present in unadjusted analyses, these findings highlight the ability of nicotine-containing ENDS to alleviate symptoms of negative affect during smoking reduction in a setting outside the clinical lab. These findings are also in line with past research that suggests tobacco users experience negative psychological symptoms when abstaining from nicotine, including restlessness, nervousness, anxiety, irritability and sadness (Hughes & Hatsukami, 1986; Post et al., 2010). Based on the parent study results (Cobb et al., 2021) and the associated acute clinical lab study (Hiler et al., 2017) participants randomized to the 36 mg/ml condition were likely able to more effectively suppress their nicotine abstinence-associated symptoms (Hiler et al., 2017) including negative mood.

Depressive symptoms did not change over time, but psychological distress for the nicotine-containing conditions decreased significantly at weeks 4 and 8 compared to baseline (week 0). Perhaps not collapsing the conditions by nicotine content would have allowed us to isolate a more pronounced condition-related effect in regards to negative mood and stress. While the parent study analyses did not investigate negative mood among participants, significant condition-related differences across the four conditions were identified in regards to CPD

reduction (Cobb et al., 2021). These CPD-related findings highlight the need to differentiate between the CIG SUB and ENDS with 0 mg/ml. For example, CIG SUB was the least effective of all four study products in regards to CPD reduction (Cobb et al., 2021), and past research suggests that a 0 mg/ml ENDS can suppress some nicotine abstinence symptoms (Caponneto et al., 2012; Hiler et al., 2017). The CIG SUB and 0 mg/ml ENDS condition may have differed in terms of their effects on negative mood. However, the presence and/or lack of these condition-related effects should be interpreted with caution given that after controlling for covariates, the interaction of time and condition was no longer significant for neither depressive symptoms nor psychological distress. When considering the covariate associations observed in these models (see Table 11), baseline levels of negative mood and stress may have contributed to the condition-related effects observed.

After adjusting for covariates, the significant interaction of MI and time revealed that individuals with current MI had significantly higher depressive symptoms and psychological distress at later study time points compared to those without current MI. For psychological distress only, baseline scores also were significantly elevated for those with current MI. The observation that participants with current MI reported significantly greater negative mood at several time points throughout the study is not surprising. Depression was the most frequently reported MI in our sample and it is expected that individuals suffering from depression would score higher on the CES-D given the measure's purpose. Moreover, nonspecific psychological distress is related to affective distress (Dohrenwend et al., 1980), and the majority of our participants with current MI reported depression and anxiety, i.e., affective disorders. While nonspecific psychological distress is not linked to any single specific MI (Dohrenwend et al., 1980), most individuals with high nonspecific psychological distress meet the diagnostic criteria

for an MI (Lawrence et al., 2011). Of note, there were no significant changes in negative mood measures over time for adjusted analyses.

Our hypothesis that relative to the nicotine condition grouping, the non-nicotine condition grouping would be linked to greater increases in negative mood and stress among individuals with current MI relative to those without (*H2*) was not supported for perceived stress. There were no significant two-way interactions either prior to or after controlling for covariates. Some fundamental differences between the negative mood measures and the perceived stress measure may explain the absence of two-way interactions previously identified for the negative mood measures. The CES-D has been designed to assess current depressive symptoms (Radloff, 1997). The Kessler-6 assesses psychological distress (a construct while not indicative of any specific MI) that related to affective distress (Dohrenwend et al., 1980). Psychological distress is usually high among individuals who meet the diagnostic criteria for an MI (Lawrence et al., 2011). While the PSS has also been found to correlate highly with depressive symptoms, the PSS measures an independent and different construct (Cohen, 1983). Past research (not among smokers specifically) has highlighted that individuals with MI report increased perceived stress due to the MI-related stigma they experience (Rüsch et al., 2009) and are more likely to report stressful life events (Silver et al., 2005). The high prevalence of perceived stress and objective stressors among individuals with MI may help explain the main effect of MI observed for perceived stress. However, after controlling for covariates, we were no longer able to identify any significant differences in perceived stress between participants with and without current MI. Covariate associations identified during the sensitivity analyses suggest potential overlap of the current MI construct with demographics and baseline perceived stress and psychological distress measures (see Table 11).

Unlike the main effects of MI for perceived stress, significant declines for PSS relative to baseline were observed in the unadjusted and adjusted analysis. There was no differential effect of condition grouping that may have explained this decrease in perceived stress over time, which is in disagreement with some literature highlighting that smoking serves as a stress management tool (e.g., McEwen et al., 2008). The role of smoking as an effective stress management tool for smokers is disputed; some research indicates that smoking may actually exacerbate negative emotions long-term but that stopping smoking is followed by a reduction of perceived stress (Hajek et al., 2010). Perhaps the significant decreases in perceived stress over time occurred due to the study-related CPD reduction which was present in all conditions.

Surprisingly, no condition-related effects on perceived stress were observed either before or after covariate adjustment. When placing the findings associated with negative mood and stress into context, the bidirectional relationship of negative mood and stress with smoking should be considered. While the self-medication hypothesis assumes the antecedence of symptoms of an MI followed by nicotine self-administration to alleviate those symptoms (Goldstein, 1987), some research suggests that smoking can also occur first and subsequently be followed by an onset of depression later on (Breslau et al., 1998). Similarly, daily smoking has been linked to panic attacks at a later time point without panic attacks predicting initiation of smoking later on (Breslau & Klein, 1999). Through a bidirectional lens, the lack of nicotine in the non-nicotine conditions may not have had an exacerbating effect on symptoms of negative mood and stress for individuals with MI. In fact, reducing nicotine intake may have positively impacted MI-related symptoms. Past research has established that smokers who quit successfully reported significantly fewer days on which they experienced depressive symptoms relative to those who made unsuccessful quit attempts (McClave et al., 2009). While the parent study was

not a smoking cessation study, perhaps successful reduction of CPD in accordance with the researchers' instructions was sufficient to affect negative mood and stress positively. However, the same factors previously implicated in Aim 1 results may have prevented our ability to detect these effects including current MI categorization method. Since we did not assess MI-related functional impairment among our participants, we cannot be certain that they exhibited sensitivity to the absence of nicotine to the degree individuals with MI-related functional impairment might experience. Among individuals reporting current MI, only 39.2% of met the clinical cutoff for the CES-D and only 14.9% met the clinical cutoff for the Kessler-6; therefore, effects may have been not pronounced enough to be detected. Past research supports this possibility. For example, baseline depressive symptoms have been highlighted as critical to how smokers respond to a decrease in nicotine in the past. Findings from a cessation study suggest that while participants with high baseline depressive symptoms experienced an increase of withdrawal symptoms in the first week, participants with low baseline depressive symptoms experienced a decrease in withdrawal symptoms in the first week (Reid & Ledgerwood, 2016).

One particular aspect of the present analysis that could be addressed in future research is the more frequent monitoring of negative mood and stress symptoms. In addition, the Kessler-6 and the PSS assess experiences from the past month versus a more immediate time period. Use of this timeframe may have omitted experiences and symptoms that occurred early in the month or recall error may have impacted those that were less frequent overall. Administering negative mood and stress measures more frequently throughout a longitudinal study may allow researchers to isolate the timeframe after initial smoking reduction when such symptoms may be most pronounced. For example, an ideal design might incorporate past week mood measures or an ecological momentary assessment method to detect changes in mood and stress in real-time.

While we did not identify an interaction between current MI status and condition on negative mood and stress measures, future work that assesses these measures over shorter time intervals may help to isolate factors contributing to the changes in negative mood and stress we observed.

Aim 3. Relationship between condition, CPD reduction, and negative mood and stress

The hypothesis that changes in negative mood and stress would mediate condition effects on CPD reduction was not supported when using the composite variable of depressive symptoms, psychological distress, and perceived stress, the composite variable of depressive symptoms and psychological distress, or depressive symptoms, psychological distress, and perceived stress individually as mediators either prior to or after controlling for covariates. Condition did not serve as a significant predictor of any of the five mediators tested prior to and after controlling for covariates. None of the five mediators significantly predicted CPD reduction prior to controlling for covariates. However, after controlling for covariates, both composite variables and the individual variables, depressive symptoms and psychological distress, significantly predicted CPD reduction, with greater negative mood and stress being related to smaller CPD reduction. Perceived stress alone did not predict CPD reduction. In addition, prior to as well as after controlling for covariates, condition served as a significant predictor of CPD reduction, with the nicotine-containing conditions being linked to greater CPD reduction. The lack of significant direct effects of condition for all mediators tested in Aim 3 mostly aligned with our findings from Aim 2. In Aim 2, there was little evidence of condition-related effects over time for measures of negative mood and stress with the exception of the CES-D in the unadjusted model. Some of these minor differences in condition-related findings between Aim 2 and Aim 3 are likely due to the time points being assessed; while Aim 2 assessed trajectory over time involving data from five time points, Aim 3 only assessed changes between baseline (week

0) and week 24. The direct effects of condition on CPD reduction in Aim 3 also were consistent with patterns observed in Aim 1.

The finding that changes in negative mood and stress were not predicted by condition is surprising because past research suggests that smokers' feelings of stress are influenced by nicotine administration, with greater stress levels being reported prior to smoking than after smoking (Parrott, 1994a; Parrott, 1994b). Importantly, nicotine-deprived smokers experience significantly greater depressive symptoms, irritability, and concentration difficulties as well as significantly lower pleasure relative to non-nicotine-deprived smokers and nonsmokers (Parrott, 1994b). These differences indicate that smoking may not in fact facilitate positive mood but merely produce alleviation of negative mood pre-smoking resulting from nicotine deprivation (Parrott, 1994b). Since baseline nicotine dependence did not differ significantly between the non-nicotine condition grouping and the nicotine condition grouping, we expected that the presence or absence of nicotine in the study product assigned would have been related to negative mood and stress symptoms. Instead, our findings suggest that condition-related effects did not result in differential patterns of negative mood and stress symptoms that in turn influenced CPD reduction. Perhaps, not observing a relationship between condition and negative mood and stress may indicate that smokers, including smokers with MI, may not be as sensitive to a study product-related nicotine content as we had hypothesized. In turn, these results would indicate that ENDS, should they be deemed an effective and safe smoking reduction and cessation tool, may not exacerbate the risk of negative mood and stress symptoms.

A possible reason for the lack of direct condition-related effects on measures of negative mood and stress was how these mediators were calculated. The present study assessed five visits across 24 weeks and used an average score for each measure of all five visits as the mediator. As

observed in the unadjusted analyses, CES-D scores diverged between non-nicotine and nicotine conditions early on in the intervention (week 4; see Figure 11), but these differences dissipated as time went on. Also observed in the unadjusted analyses, Kessler-6 scores diverged between non-nicotine and nicotine conditions at later study time points (week 24; see Figure 13). Our mediation analyses could have been structured to examine relationships between these variables at early versus later time points. Some research suggests that nicotine withdrawal symptoms subside within as little as ten days (Shiffman et al., 2006). Assessing a time span of 24 weeks, however, may have diluted early effects of condition-related nicotine content on negative mood and stress as participants in the non-nicotine containing condition may have adapted to their decreased nicotine intake. Also, because of the timeframe assessed by the measures used (i.e., past week and past month), critical time points during which changes in negative mood and stress may have occurred were not captured. Timeframe differences assessed via negative mood measures may have contributed to discrepancies observed in results from Aims 2 and 3.

Negative mood and stress symptoms significantly predicted CPD reduction after adjusting for covariates. This difference suggests that the included covariates improved our ability to detect this effect in our model. These findings are in line with past research. For example, smokers suffering from psychological distress smoke more CPD relative to smokers not suffering from psychological distress (Kulik & Glantz, 2017), and negative affect is linked to increased smoking urges (Brodbeck et al., 2014). Depressive symptoms are related to poorer cessation outcomes (Leventhal et al., 2008), and negative mood leads to increased relapse risk (Tulloch et al., 2016). Interestingly, even after controlling for covariates, perceived stress did not predict CPD reduction. Given that increased perceived stress is linked to cessation difficulties among smokers (Cohen & Lichtenstein, 1990), we would have expected that perceived stress

would have predicted CPD reduction, with those reporting greater perceived stress experiencing greater smoking reduction difficulties. One possible explanation as to why perceived stress was not a significant predictor of CPD reduction is that across our entire sample, only 3.8% reported severe perceived stress at baseline and mild or moderate levels of perceived stress may not have influenced smoking behaviors sufficiently to detect an effect. Another explanation is that smokers may have either managed or altogether avoided increases in perceived stress by altering their smoking behavior which would explain why such increases were not detected by our analysis. Importantly, prior to and after sensitivity analyses, condition significantly predicted CPD reduction, which is consistent with Aim 1 results as well as the parent study (Cobb et al., 2021). The finding that negative mood and stress did not serve as mediators raises the question of what psychological variables, if any, may help explain the relationship between ENDS-delivered nicotine and the absence thereof on smoking reduction. The investigation of such variables is critical particularly for smokers with MI as past research has shown that negative mood and stress are prevalent among this group (Lawrence et al., 2011; Rüsch et al., 2009).

Effective mood management is a critical factor in ensuring success in smoking reduction and cessation efforts among smokers with MI. More research is needed to evaluate the effectiveness of ENDS on smoking reduction and cessation among this vulnerable group. However, our findings highlight that ENDS-supported reduction among smokers with MI could perhaps be improved by integrating a behavioral treatment component to avoid the interference of negative mood symptoms with reduction or cessation outcomes. Future research should evaluate whether a cognitive behavioral therapy component added to ENDS-supported smoking reduction may help offset the detrimental effect of negative mood on successful reduction or cessation. The question remains unanswered whether a mediation effect of negative mood and

stress or other, unassessed psychological variables on the relationship between condition and CPD reduction would have differed by current MI status. Future research should investigate how, if at all, smokers with MI may exhibit worsening or improvement of psychological variables when undergoing ENDS-supported smoking reduction or cessation, as our findings suggested no interaction effect of current MI and condition on negative mood and stress or CPD reduction. Results derived from such research would provide valuable information on the potential effectiveness of ENDS as smoking reduction and cessation tool among this vulnerable population. Future work that leverages the lessons learned from this study is needed.

Limitations

Several limitations of the present analyses must be considered. Despite collapsing conditions by condition-related nicotine content, our three-way interactions corresponding with our hypotheses likely still were underpowered. We also had a substantial amount of missing data (~40% dropped out by the last study visit). While we applied REML and EM to address this issue, using estimated data presents a limitation, particularly considering that we used intent to treat and did not exclude those with larger amounts of missing data. Estimates based on participants who missed several visits may be less accurate than imputed data for participants who only missed one visit. A supplemental sensitivity analysis used by Cobb et al. (2021) which includes only individuals who had attended visits and provided data at relevant time points may be warranted (i.e., "per-protocol"). Such sensitivity analyses also could include the covariates that were associated with dropout (e.g., age at smoking initiation and education). However, all of the results including those with complex multiple imputation and per-protocol presented in Cobb et al. (2021) did not differ largely from the results obtained by using an intent-to-treat approach

(as in this study) in regards to CPD. We may not find differential effects for the present results by conducting these sensitivity analyses.

As described above, our categorization of MI was likely flawed. Participants who reported that the condition was ongoing may have done so because they continue to receive cognitive behavioral therapy and/or medical treatment for their condition. However, the symptoms of their MI may have been well controlled due to the effects of medication and/or behavioral treatment. In turn, those who reported no ongoing MI may have done so not due to an absence of symptoms but because they assumed their MI to be resolved. By grouping all current MI, our analysis also did not take into consideration between-group differences in smoking intensity and/or nicotine dependence that present among individuals suffering from different MI. For example, participants suffering from schizophrenia and bipolar disorder have the highest smoking rates among individuals with MI (McClave et al., 2010), even exceeding rates found among individuals with depression and anxiety (ADAA, 2018; SAMSHA, 2019). Smokers with greater MI functional impairment and/or more severe MI likely did not participate in this study due to exclusion criteria (uncontrolled mental illness or substance abuse including in-patient treatment within the past six months) and/or the design itself (i.e., number of visits and the use of a potentially unfamiliar study product). Moreover, participants may not have been adequately categorized by self-reported MI status if they lacked access to healthcare or lacked awareness of MI and their presenting symptoms. Similarly, because the data included in the present study stemmed from five in-person visits stretching across 24 weeks, it is possible that individuals were diagnosed with a new MI during this time or experienced an acute onset of a previously non-existent condition that was not captured in the baseline assessment. Thus, our categorization

of current MI may have omitted between-group differences that likely would have contributed to differences in our outcomes.

Another limitation is due to the possible influence of unassessed variables on CPD changes over time. Of note, while participant use of their assigned study product use was assessed, it was not always objectively verified, and participants were not penalized for non-compliance (Cobb et al., 2021). Changes observed in CPD may not be due solely due to condition assignment but also how individuals used their study product and whether they used non-study products to self-administer nicotine. Additionally, two variables that have been identified by past research as influential on smoking cessation were not assessed during the time points on which we focused our analyses. For example, self-efficacy, the belief in one's personal ability to complete actions necessary to reach a goal (Bandura, 1982) has been identified as a significant predictor of smoking cessation (e.g., Stuart et al., 1994). Smokers who maintain long-term smoking abstinence had significantly higher self-efficacy than smokers who relapsed (DiClemente, 1981). In addition, readiness to change, i.e., motivation (DiClemente & Prochaska, 1985), has been identified as a significant predictor of smoking cessation; individuals classified as being in a higher stage of change made increased quit attempts and were significantly more likely to abstain from smoking relative to their counterparts in lower stages of change (DiClemente et al., 1991). While participants in our study reported no interest in smoking cessation at screening, some research suggests that readiness and confidence to quit smoking may have developed during the intervention period. For example, past research involving a sample of smokers who were naive to ENDS and were not interested in quitting, found that after participation in an experimental in-lab phase and a subsequent ad lib phase using ENDS, smokers reported a significant increase in readiness and confidence to quit smoking (Wagener et

al., 2014). Inclusion of these variables at different time points throughout the study could have allowed us to identify an additional critical factor to help explain our findings.

Conclusions

Smokers with MI are at a heightened risk for smoking-related health consequences. ENDS present a possible harm reduction tool for this vulnerable group given their ability to deliver nicotine and their reduced toxicant exposure compared to cigarette smoking. We found some evidence that smokers with MI may experience greater difficulties reducing CPD; however, this effect diminished after controlling for relevant covariates. Overall, condition-related effects did not differ significantly by current MI status meaning that the enhanced ability of the nicotine conditions (ENDS with 8 mg/ml and 36 mg/ml) compared to the non-nicotine conditions (CIG SUB and ENDS with 0 mg/ml) to reduce smoking behavior was not dampened among smokers with MI. There was some evidence that during the intervention smokers with MI experienced higher levels of negative mood and stress, but changes in negative mood and stress did not explain the relationship between condition and CPD reduction. This latter finding suggests that these psychological indices may not be the mechanism by which the nicotine conditions promoted smoking reduction. Future work may benefit from examination of other mood-related indices possibly more closely tied to nicotine withdrawal and dependence in relationship to MI status. The overall effect of negative mood on changes in smoking behavior reinforces intervention efforts that incorporate cognitive behavioral therapy or some other treatment modality that targets mood to improve smoking reduction and/or cessation outcomes. Use of better MI assessments and related measures when testing the effects of ENDS is also needed to deepen our understanding of this product class among smokers with MI. Importantly, there was little evidence of condition-related increases for negative mood and stress symptoms

for smokers with MI in our study. Taken together, the results of this study indicate that ENDS

hold promise for smokers with MI who are interested in smoking behavior change.

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Massey Cancer Center's Cancer Prevention and Control (CPC) Travel Award
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Graduate School Travel Award
Awarded by Virginia Commonwealth University/Graduate School; August 2018 ($300)

Best Student Poster Award
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Research Proposal Development Scholarship
Awarded by the Massey Cancer Center at VCU; May 2017 ($1000)

Outstanding Research Award
Awarded by Central Connecticut State University; May 2015

Foundation for Education and Research in Biofeedback and Related Sciences (FERB) Travel Scholarship for the 46th Annual Scientific Meeting of the Association for Applied Psychophysiology and Biofeedback (AAPB); February 2015 ($300)

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Outstanding Research Award
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Publications (N=12)

Simuzingili, M., **Hoetger, C**., Garner, W., Everhart, R. S., Hood, K. B., Nana-Sinkam, P., Cobb, C. O., & Barnes, A. J. (2021). What influences demand for cigars among African American adult cigar smokers? Results from a hypothetical purchase task. Advance online publication. https://doi.org/10.1037/pha0000491

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Barnes, A. J., Bono, R. S., Rudy, A. K., **Hoetger, C**., Nicksic, N. E., & Cobb, C. O. (2020). Effect of e-cigarette advertisement themes on hypothetical e-cigarette purchasing in price-responsive adolescents. *Addiction*, *115*(12), 2357-2368.

Kheirallah, K. A., Cobb, C. O., Alsulaiman, J. W., Alzoubi, A., **Hoetger, C.**, Kliewer, W., Mzayek, F. (2019). Trauma exposure, mental health and tobacco use among vulnerable Syrian refugee youth in Jordan. *Journal of Public Health*, *42*(3), e343-e351.

Hoetger, C., Bono, R. S., Nicksic, N. E., Barnes, A. J., & Cobb, C. O. (2019). Influence of electronic cigarette characteristics on susceptibility, perceptions, and abuse liability indices among combustible tobacco cigarette smokers and non-smokers. *International Journal of Environmental Research and Public Health*, *16*(10), 1825.

Wall, C.S., Bono, R.S., Lester, R.S., **Hoetger, C.**, Guy, M.C, Eissenberg, T.E., Bickel, W.K., Barnes A.J, & Cobb, C.O. (2018). Triangulating abuse liability for flavored cigar products using physiological, behavioral economic, and subjective assessments: A

within-subjects clinical laboratory trial protocol. *BMJ Open, 8,* e023850. doi: 10.1136/bmjopen-2018-023850.

Conference Presentations (N=34; reverse chronological order)

White, A., Li, D., Snell, L.M., O'Connor, R., **Hoetger, C.**, Croft, D., Lester, R., McIntosh, S., Underwood, M., Schneller, L., Breland, A., Barnes, A., Cobb, C, & Ossip, D. (February 2021). *Perceptions of tobacco product-specific COVID-19 risks and changes in tobacco use behaviors among smokers, e-cigarette users, and dual users.* Poster presented virtually at the annual meeting of the Society for Research on Nicotine and Tobacco, Baltimore, MD.

Hoetger, C., Lester, R.C., Bone, R.S., White, A., Hood, K., Everhart, R.S., Nana-Sinkam, P., Barnes, A.J., & Cobb, C.O. (February 2021). *Social influences and cigar smoking behaviors among African American youth.* Poster presented virtually at the annual meeting of the Society for Research on Nicotine and Tobacco. Baltimore, MD, USA.

Hoetger, C., Lester Scholtes, R., Rudy, A., Barnes, A., & Cobb, C. (March 2020). *Characterizing cigar smoking in African American low-income communities*. Poster presented at the annual meeting of the Society of Research on Nicotine and Tobacco, New Orleans, LA, USA.

Bono, R., Cobb, C., Wall, C., **Hoetger, C.**, Lester Scholtes, R., Rudy, A., Lipato, T., Guy, M., Eissenberg, T., & Barnes, A. (March 2020). *Adult liability for flavored cigars among young adult combustible tobacco cigarette smokers.* Poster presented at the annual meeting of the Society of Research on Nicotine and Tobacco, New Orleans, LA, USA.

Cobb, C., **Hoetger, C.,** Hood, K., Everhart, R., Nana-Sinkam, P., Lester-Scholtes, R., Barnes, A. (June 2019). *Profiling cigar smoking to inform tobacco prevention among lower income African American communities in Richmond, VA.* Poster presented at the Massey Cancer Center Research Retreat, Richmond, VA, USA.

Hoetger, C., Rudy, A., Bono, R., Barnes, A., & Cobb, C. (February 2019). *Youth susceptibility to electronic cigarettes after exposure to electronic cigarette advertisements.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, San Francisco, CA, USA.

Nicksic, N. E., Bono, R. S., Rudy, A. K., **Hoetger, C.,** Cobb, C. O., & Barnes, A. J. (February 2019). *Profiling racial/ethnic disparities in youth exposure to tobacco advertising.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, San Francisco, CA, USA.

Barnes, A. J., Rudy, A. K., **Hoetger, C.**, Nicksic, N. E., Bono, R. S., & Cobb, C. O. (February 2019). *Exposure to tobacco advertisements and abuse liability for e-cigarettes among adolescents.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, San Francisco, CA, USA.

Bono, R. S., Rudy, A. K., **Hoetger, C.**, Nicksic, N. E., Cobb, C. O., Barnes, A. J. (February 2019). *Youth are less sensitive to electronic cigarette prices after exposure to electronic*

cigarette advertisements. Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, San Francisco, CA, USA.

Hoetger, C., Cariello, A., Perrin, P., Barnes, A., & Cobb, C. O. (September 2018). *Tobacco use and associated knowledge and perceptions of risks and benefits among international students at United States mid-Atlantic universities.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco Europe: Munich, Germany.

Hoetger, C., Rudy, A. K., & Cobb, C. O. (September 2018). *Social and environmental correlates of traditional cigarettes and electronic cigarette use in high school students.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco Europe: Munich, Germany.

Hoetger C., Cariello AN, Perrin P, Barnes A, Cobb CO (June 2018). *Tobacco use and associated knowledge and perceptions of risks and benefits among international students at United States Mid-Atlantic universities.* Poster presented at: Massey Cancer Center Research Retreat: Richmond, VA.

Rudy, A. K., **Hoetger, C.**, Barnes, A., Cobb, C. O. (April 2018). *An experimental investigation of cannabis policy environments on cannabis use attitudes, norms, beliefs, and intentions among young adults.* Poster presented at the Institute for Cannabis Research, Pueblo, CO.

Rudy, A. K., **Hoetger, C.**, Barnes, A., Cobb, C. O. (April 2018). *An experimental investigation of cannabis policy environments on cannabis use attitudes, norms, beliefs, and intentions among young adults.* Poster presented at the Annual Virginia Commonwealth University Graduate Research Symposium, Richmond, VA.

Hoetger, C., Cobb, C., Wall, C., Braxton, D., Cogley, J., Khan, M., Sey, N., Bhatt, S., Rudy, A. K., & Barnes, A. (March, 2018). *TV and online electronic cigarette video advertising: Thematic content and spend characteristics.* Presented at the Virginia Youth Tobacco Products Conference, Richmond, VA.

Cobb, C. O., Wall, C. S. J., Braxton, D., Cogley, J., Khan, M., Sey, S., Bhatt, S., **Hoetger, C.**, Rudy, A. K.,Z & Barnes, A. J. (February 2018). *TV and online electronic cigarette video advertising: Thematic content and spend characteristics.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Baltimore, MD.

Wall, C. S. J., **Hoetger, C.**, Lester-Scholtes, R., Bono, R., Rudy, A., Guy, M., Eissenberg, T., Cobb, C. O., & Barnes, A. (February 2018). *Clinical laboratory evaluation of Black & Mild cigar flavors: Puff topography and physiological effects.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Baltimore, MD.

Wall, C. S. J., **Hoetger, C.**, Lester-Scholtes, R., Bono, R., Rudy, A., Guy, M., Eissenberg, T., Cobb, C. O., & Barnes, A. (February, 2018). *Clinical laboratory evaluation of Black & Mild cigar flavors: Puff topography and physiological effects.* Poster presented at the National Institute of Health Tobacco Regulatory Science Meeting, MD.

Bono RS, Wall C, **Hoetger C.**, Lester-Scholtes R, Rudy A, Guy M, Eissenberg T, Barnes AJ, Cobb CO. *Abuse liability of flavored cigars among young adult cigarette smokers.* Poster presented at the NIH Tobacco Regulatory Science Meeting; June 2018; Bethesda, MD.

Hoetger, C., Braxton, D., Cogley, J., Barnes, A., & Cobb, C. O. (June 2017). *Effects of exposure to tobacco product promotions on the susceptibility to electronic cigarette use among smokers and nonsmokers.* Poster presented at the VCU Massey Cancer Research Retreat, Richmond, VA.

Hoetger, C., Rudy, A., Bono, R., Barnes, A., & Cobb, C. O. (November 2017). *Potential tobacco regulations affect electronic cigarette susceptibility, perceptions of harm and simulated purchases among cigarette smokers and nonsmokers.* Poster presented at the annual meeting of the American Public Health Association, Atlanta, GA.

Lester, R. C., Rudy, A. K., **Hoetger, C.**, Montpetit, A., Lipato, T., Graham, A. L., Eissenberg, T., Cobb, C. O. (June 2017). *Tobacco consumption and toxicant exposure associated with dual use of cigarettes and cig-a-like electronic cigarettes.* Poster presented at Virginia Commonwealth University Massey Cancer Research Retreat, Richmond, VA.

Braxton, D., Cogley, J., Bhatt, S., Sey, N., Khan, M., **Hoetger, C.**, Rudy, A., Barnes, A., & Cobb, C. O. (April 2017). *Electronic cigarette TV and online video advertisement.* Poster presented at the Undergraduate Research Symposium at Virginia Commonwealth University, Richmond, VA.

Hoetger, C. , Rudy, A. K., Bono, R. S., Barnes, A. J., & Cobb, C. O. (March 2017). *Potential electronic cigarette regulations affect susceptibility and harm/addiction perceptions among cigarette smokers and nonsmokers.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Florence, IT.

Barnes, A. J., Bono, R. S., **Hoetger, C.**, Rudy, A. K., & Cobb, C. O. (March 2017). *Differential effects of e-cigarette characteristics on a behavioral economic measure of abuse liability across smokers and non-smokers.* Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Florence, IT.

Austad, C., Gendron, M., **Hoetger, C.**, Lehrer, Moss, D., Thompson, L. & Steffen, P. (August 2015). *The future of psychotherapy: Can biofeedback advance the practice of psychotherapy?* In C. Austad & C. Hoetger (CoChairs). Symposium conducted at the annual meeting of the American Psychological Association, Toronto, ON.

Hoetger, C. (May 2015). *Biofeedback may be a useful stress-management tool for immigrants.* Poster presented at the 27th annual convention of the Association for Psychological Science (APS), New York City, NY.

Gendron, M., Austad, C. & **Hoetger, C.** (March 2015). *The biofeedback practitioner's plight.* Presented at the 46th annual meeting of the Association for Applied Psychophysiology and Biofeedback (AAPB), Austin, TX.

Hoetger, C. (October 2014). *Stressed out: Both college students and counseling centers may benefit from biofeedback.* Poster presented at the 54th annual meeting of the New England Psychological Association (NEPA), Lewiston, ME.

Hoetger, C. (October 2014). *The use of psychological interventions in primary care: Biofeedback.* Poster presented at the 28th Annual Convention of the Connecticut Psychological Association, Haddam, CT.

Austad, C., Gendron, M., Geiling, S., **Hoetger, C.**, Paglarillo, D., Green, C. & Shaker, A. (March 2014). *Using biofeedback to interest students in contemplative practice.* Poster presented at the 2014 International Symposium for Contemplative Studies (ISCS), Boston, MA.

Hoetger, C., Lozo, W., Garcia, D., Singleton, O., & Hershberger, R. (April 2012). *Pay it forward: Using benefit triggered gratitude to increase interest and motivation for a gratitude intervention.* Poster presented at the annual AASU Student Research Symposium, Savannah, GA.

Worrell, W., Herring, A., Moore, J., Lozo, W., **Hoetger, C.**, Singleton, O., & Shay, J. (April 2012). *Inducing gratitude intervention.* Presented at the 37th annual Carolinas Psychology Conference, Raleigh, NC.

Worrell, W., Moore, J., Lozo, W., **Hoetger, C.**, Curtis, D., Hill, B. & Shay, J. (October 2011). *Have you left me speechless? It depends…: The effect of personal and general sexual objectification on self-presentation and self-regulation in women.* Poster presented at the annual meeting of the Society for Southeastern Social Psychologists, Johnson City, TN.

Media Mentions

Discussion of **Hoetger et al. (2019)** in NIDA Notes (https://www.drugabuse.gov/news-events/nida-notes/2020/03/e-cigarette-characteristics-may-influence-use-are-potential-targets-regulatory-policy)

Invited Oral Presentations (N=19; reverse chronological order)

White, A., Ossip, D., Snell, L.M., Li, D., **Hoetger, C.**, O'Connor, R., Lester, R., Croft, D., Underwood, M., McIntosh, S., Breland, A., Schneller, L., Cobb, C., & Barnes, A. (February 2021). *Restricted access to tobacco products and smoking cessation therapies influences hypothetical tobacco use behaviors among smokers and e-cigarette users: results from an online experiment.* Oral presentation held virtually at the annual meeting of the Society for Research on Nicotine and Tobacco. Baltimore, MD, USA.

Bono, R.S., Barnes, A.J., Cobb, C.O, Lester, R.C., **Hoetger, C.**, Underwood, M., White, A. M., & Bickel, W. K. (February 2021). *Substitutability of combustible tobacco cigarettes and e-cigarettes in dual users and exclusive e-cigarette users.* Oral presentation held virtually at the annual meeting of the Society for Research on Nicotine and Tobacco. Baltimore, MD, USA.

Barnes, A., Bono, R., Lester, R., **Hoetger, C.,** Underwood, M., White, A., & Cobb, C.O. (February 2021). *Limits on e-cigarette nicotine concentration in markets with open-system devices: The interaction of nicotine concentration and device power on e-cigarette abuse liability.* Oral presentation held virtually at the annual meeting of the Society for Research on Nicotine and Tobacco. Baltimore, MD, USA.

Simuzingili, M., **Hoetger, C.**, Garner, W., Everhart, R., Hood, K., Nana-Sinkam, P., Cobb, C.O., & Barnes, A.J. (February 2021). *What influences demand for cigars among African American adult cigar smokers? Results from a hypothetical purchase task.* Oral

presentation held virtually at the annual meeting of the Society for Research on Nicotine and Tobacco.

Hoetger, C. (November 2020). *Cigarette smoking among individuals with mental health disorders and methods of smoking reduction and cessation.* Virtual presentation given in an undergraduate health psychology class. Armstrong State University, Savannah, GA.

Hoetger, C. & Eversole, A. (September 2020). Presentation *on "Might limiting liquid nicotine concentration result in more toxic electronic cigarette aerosols?"* (article by Talih et al., 2020). Virtual presentation given at the Center for Coordination of Analytics, Science, Enhancement , and Logistics (CASEL) in Tobacco Regulatory Science (CASEL) Journal Club.

Hoetger, C. (February 2019). *Cigar-related perceptions, use patterns, and purchase behavior among a sample of African American adults residing in the Richmond, VA area.* Oral presentation given at the Virginia Commonwealth University Center for the Study of Tobacco Products Scientific Meeting, Richmond, VA/

Hoetger, C. (December 2019). Characterizing adult cigar use in low-income, African American communities in and around Richmond, Virginia. Oral presentation given at the Virginia Commonwealth University Health Psychology Colloquium, Richmond, VA.

Hayes, R., Hunley, R., **Hoetger, C.**, Fugate-Laus, K. (November 2019). I can quit! Information on how to quit smoking. Oral presentation given at VCU Massey Cancer Center at Stony Point, Richmond, VA.

Hoetger, C. (November 2019). *Treatment of eating disorders.* Oral presentation given in an undergraduate abnormal psychology class, Virginia Commonwealth University, Richmond, VA.

Hoetger, C. (November 2019). *Diagnostic criteria of anorexia nervosa, bulimia nervosa, and binge eating disorder.* Oral presentation given in an undergraduate abnormal psychology class, Virginia Commonwealth University, Richmond, VA.

Bradner, M., Hayes, R., Trout, K., **Hoetger, C.,** Ravyts, S., Williams, A. (August 2019). *Motivational Interviewing.* Training administered to medical students at the Virginia Commonwealth University School of Medicine.

Hoetger, C. (July 2019). *The role of biofeedback, mindfulness, and self-compassion in stress management.* Oral presentation given in an undergraduate stress psychology class, Virginia Commonwealth University, Richmond, VA.

Cobb, C. O., **Hoetger, C.,** Hood, K., Everhart, R. Nana-Sinkam, P., Johnson, K., Hackney, J., Barnes, A. (February 2019). *Profiling youth cigar use in low SES communities: A mixed methods approach.* Invited oral presentation to the Virginia Youth Tobacco Project Research Coalition Annual Meeting; Richmond, VA, USA.

Hoetger, C. (January 2019). *Tobacco use during pregnancy.* Oral presentation given in an undergraduate health psychology class, Virginia Commonwealth University, Richmond, VA.

Hoetger, C. (June 2018). *What factors predict combustible cigarette use among pregnant smokers.* Oral presentation given in an undergraduate women's health class, Virginia Commonwealth University, Richmond, VA.

Hoetger, C. (April 2018). *Clinical laboratory evaluation of cigar flavors.* Oral presentation given in an undergraduate social psychology class, Virginia Commonwealth University, Richmond, VA.

Hoetger, C. (January 2018). *Tobacco use and associated perceptions in an international student population.* Oral presentation given at the scientific meeting of the VCU Center for the Study of Tobacco Products, Richmond, VA.

Hoetger, C. , Rudy, A. K., Bono, R. S., Barnes, A. J., & Cobb, C. O. (February 2017). *Susceptibility to electronic cigarette use and perceptions of harm and addiction among cigarette smokers and non-smokers.* Oral presentation given at the annual meeting of the Virginia Youth Tobacco Project Research Coalition Meeting, Richmond, VA.

Teaching Experience

Applications of Statistics (PSYC214)
Lab Instructor
August 2017-May 2018

Health Psychology (PSYC412)
Primary Instructor
June 2018-July 2018

Psychology of the Abnormal (PSYC407)
Teaching Assistant
August 2019-December 2019

Perception (PSYC406)
Teaching Assistant
August 2019-December 2019

Physiological Psychology (PSYC401)
Teaching Assistant
January 2020-May 2020

Memberships

Society for the Research on Nicotine and Tobacco (SRNT)
November 2016-present

Center for the Study of Tobacco Products (CSTP)
August 2016-present