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Pain Characteristics and Nicotine Deprivation as Predictors of Performance during a Laboratory Model of Smoking Cessation

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Abstract

Although cigarette smokers with co-occurring pain report experiencing more severe nicotine withdrawal and greater difficulty quitting, limited work has examined the role of pain in smoking cessation-related outcomes. The goal of this study was to examine clinically-relevant pain characteristics (i.e., pain persistence, pain intensity, and pain-related disability) as predictors of withdrawal and smoking lapse/relapse outcomes using an established laboratory model of cessation. Participants (N = 120 daily cigarette smokers; 48% male; M_{Age} = 36.17, SD = 12.16; M_{CPD} = 20.51, SD = 6.99) were randomized to either continued smoking or 12-hour nicotine deprivation conditions prior to an experimental study visit. Upon arrival to the laboratory, participants completed measures of pain characteristics and nicotine withdrawal symptoms. Primary outcomes included nicotine withdrawal scores and analogs of smoking lapse (i.e., latency to initiating smoking) and relapse (i.e., number of cigarettes smoked). Results indicated that persistent pain and nicotine deprivation each predicted more severe nicotine withdrawal. Cox regression analyses further revealed that moderate-to-severe pain-related disability and nicotine deprivation each predicted quicker latency to lapse during the laboratory cessation paradigm. Contrary to expectation, there were no statistically-significant interactions between nicotine deprivation and pain characteristics. Clinical implications include the possibility that smokers with pain would likely benefit from tailored and integrated cessation treatment.

Pain Characteristics and Nicotine Deprivation as Predictors of Performance during a Laboratory Model of Smoking Cessation

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Pain Characteristics and Nicotine Deprivation as Predictors of Performance during a Laboratory Model of Smoking Cessation

Pain and cigarette smoking are highly prevalent and co-occurring, with a combined annual economic burden of more than $800 billion in the United States alone (Gaskin & Richard, 2012; USDHHS, 2014; Xu, Bishop, Kennedy, Simpson, & Pechacek, 2015). Accordingly, there has been increasing empirical focus on the role of pain in the onset and maintenance of tobacco addiction. Initial research suggests that smokers with pain may be less likely to successfully quit smoking. However, limited research has directly examined the role of pain in smoking cessation outcomes. The current study is the first to test whether several clinically-relevant pain characteristics (i.e., pain persistence, pain intensity, and pain-related disability) predicted nicotine withdrawal and lapse/relapse outcomes assessed using a laboratory paradigm of smoking cessation. We also tested whether nicotine deprivation moderated effects of pain characteristics on smoking withdrawal, lapse, and relapse outcomes.

Overview of Pain and Smoking

Pain

Pain is a subjective experience that is inherently unpleasant, interrupts attention and behavior, and compels one to escape its presence (Eccleston & Crombez, 1999; Price, 2000). Approximately half of all U.S. adults endorse past three-month pain, and more than 25 million suffer from pain that occurs every day (Nahin, 2015). Greater severity of pain has been associated with a variety of negative health effects, including major depressive disorder, insomnia, and greater impairment and disability (Finan & Smith, 2013; Goesling, Clauw, & Hassett, 2013; Lee et al., 2015). Pain also represents an enormous public health burden, motivating up to half of all annual physician visits in the United States, and accounting for an

annual economic impact of up to $635 billion in healthcare costs and lost productivity (Gaskin & Richard, 2012; IOM, 2011; Mayo Clinic, 2001; McCarberg, 2011).

Traditional assessments of pain severity focus on duration, such that longer-lasting pain is considered to be more severe (Merskey & Bogduk, 1994). Although duration of pain remains an important factor (e.g., Treede et al., 2015), there is growing recognition that pain is multidimensional, and that approaches to characterizing pain should incorporate indices of persistence, intensity, and disability (Turk & Melzack, 2011).

Persistence. Pain persistence is typically assessed via frequency of symptoms over a specific time period (e.g., number of days having experienced pain over the previous six months; Force, 2010; Merskey & Bogduk, 1994). For example, individuals who report pain on ≥ 90 out of the last 180 days are considered to have a persistent pain condition (Von Korff, Ormel, Keefe, & Dworkin, 1992). Prevalence estimates indicate that up to 19% of adults in the United States general population meet criteria for persistent pain (Kennedy, Roll, Schraudner, Murphy, & McPherson, 2014). Persistent pain has been shown to negatively impact a variety of health-relevant outcomes, including sleep, brain function, cardiovascular activity, and sexual function (Chapman & Gavrin, 1999). Among a nationally representative sample, individuals who met criteria for persistent pain (vs. non-persistent pain) endorsed higher rates of depression, anxiety, and fatigue (Kennedy et al., 2014). Pain persistence has also been uniquely associated with increased odds of substance use after detoxification among adults with substance use disorders (Larson et al., 2007).

Intensity. Valid measures of pain intensity include numerical rating scales, visual analogue scales, and verbal rating scales (Thong, Jensen, Miró, & Tan, 2018). Numerical rating scales tend to be the most commonly utilized (i.e., 0-10, 0-100; Turk & Melzack, 2011) and are

among the least influenced by non-pain intensity factors (e.g. depressive symptoms, catastrophizing; Thong et al., 2018). Researchers have further suggested that composite measures of average pain, pain at its worst, and current pain yield more comprehensive clinical data that can be used to better index characteristic pain intensity (Von Korff et al., 1992). In comparison to pain persistence, pain intensity has been shown to be a stronger predictor of healthcare costs and utilization of medical care among clinical pain patients (Pérez, Navarro, Saldaña, Wilson, & Rejas, 2015). Moderate-to-severe pain intensity has also been associated with lower rates of abstinence, greater substance use, and greater service utilization among individuals in outpatient addiction treatment (Caldeiro et al., 2008). Greater pain intensity has further been shown to predict a higher likelihood of meeting criteria for a substance-related disorder (Higgins et al., 2014).

Disability. Pain-related disability encompasses a variety of domains, including the impact of pain on physical, occupational, recreational, and social functioning. Self-report measures of pain-related disability typically assess degree of interference with work, school, housework, recreational, and social or family activities (Von Korff et al., 1992). Frequency with which pain interferes with functioning is also often assessed. Similar to pain intensity, a composite score can be generated to index pain-related disability. In comparison to either persistence or intensity, pain-related disability has been more strongly associated with likelihood of unemployment, severe anxious/depressive symptoms, and greater utilization of healthcare resources (Bean, Johnson, & Kydd, 2014; Häuser et al., 2014; Ma, Chan, & Carruthers, 2014). There is also growing empirical support for the notion that pain-related disability may play a unique role in the maintenance of substance use (Zale & Ditre, 2015; Zale, Lange, Fields, & Ditre, 2013). For example, greater pain-related disability has been associated with the presence

of alcohol, nicotine, and cannabis use disorders (McDermott, Joyner, Hakes, Okey, & Cougle, 2018).

Measures of pain persistence, pain intensity, and pain-related disability tend to be moderately correlated (Schmidt, Raspe, & Kohlmann, 2010; Von Korff et al., 1992). For example, a recent systematic review found that individuals who endorsed greater pain intensity also reported greater disability, poorer functioning, and greater frequency of pain symptoms (Kooijman et al., 2015). Although measures of pain intensity and pain-related disability are often the most highly correlated (Turk & Melzack, 2011), measures of pain persistence tend to be only slightly-to-moderately correlated with pain intensity and pain-related disability (Von Korff et al., 1992). In summary, persistence, intensity, and disability each represent distinct and clinically-relevant characteristics of the pain experience.

Cigarette Smoking

More than fifty years after the first Surgeon General's report warning on the health hazards of smoking cigarettes (USDHHS, 1964), tobacco use remains the leading preventable cause of mortality worldwide (WHO, 2017), accounting for an annual economic burden of more than $300 billion in the United States alone (USDHHS, 2014). Almost 70% of all smokers report a desire to quit, but only 5% successfully achieve abstinence (CDC, 2011), and most relapse within one week of initiating a quit attempt (Partos, Borland, Yong, Hyland, & Cummings, 2013). Thus, despite substantial empirical progress in the identification of reliable predictors of smoking cessation (e.g., nicotine dependence, withdrawal symptoms, self-efficacy for quitting; Brandon, Drobes, Ditre, & Elibero, 2009), there is a clear need to better understand additional factors that may play a role in the continuation of smoking.

Nicotine withdrawal. Nicotine withdrawal (Koob & Le Moal, 2001; Piper et al., 2011) comprises subjective, cognitive, and physiological symptoms that can emerge within 30 minutes of abstinence (Hendricks, Ditre, Drobes, & Brandon, 2006) and typically last up to four weeks (Leventhal, Waters, Moolchan, Heishman, & Pickworth, 2010; McLaughlin, Dani, & De Biasi, 2015). Withdrawal severity consistently predicts cessation failure (McCarthy, Piasecki, Fiore, & Baker, 2006; Piasecki et al., 2000), and assessing nicotine withdrawal symptoms at the beginning of a quit attempt may facilitate detection of those most at-risk for relapse. Because withdrawal begins almost immediately after finishing a cigarette (Hendricks et al., 2006), there is also increasing focus on assessing incipient withdrawal symptoms among current smokers. Electronic diary studies suggest that daily patterns of withdrawal may be a mechanism that drives continued smoking (Chandra, Scharf, & Shiffman, 2011; Perkins, Briski, Fonte, Scott, & Lerman, 2009). In fact, greater reported withdrawal severity among current smokers has been shown to predict lower likelihood of reducing smoking and initiating a quit attempt in the future (Weinberger, Desai, & McKee, 2010; Weinberger, Platt, Shuter, & Goodwin, 2016). Therefore, assessment of withdrawal both among current smokers and recent quitters provides a useful metric in predicting the likelihood of current or future cessation success.

Translational paradigms of smoking cessation. Large-scale clinical trials that identify predictors of smoking lapse (i.e., time between initial abstinence and smoking again) and relapse (i.e., transition from lapse to continued smoking) require substantial time, effort, and expense. Laboratory paradigms of smoking cessation are useful and efficient methods of examining precipitants of cessation milestones in a controlled, experimental setting. McKee and colleagues developed a laboratory paradigm of smoking cessation that is widely used to assess lapse and relapse behavior during a single session by providing financial incentives for abstinence from

cigarettes (McKee, 2009; McKee, Weinberger, Shi, Tetrault, & Coppola, 2012). In this paradigm, lapse behavior is assessed via the number of minutes participants maintain smoking abstinence during a 50-minute period, and relapse behavior is assessed via the number of cigarettes smoked during a 60-minute period following the initial lapse.

Studies using this laboratory paradigm have verified antecedents to lapse and relapse commonly observed in treatment outcome research, such as acute nicotine deprivation (Leeman, O'Malley, White, & McKee, 2010; Leventhal et al., 2014), cigarette craving (Roche et al., 2014), anhedonia (Leventhal et al., 2014), negative affect/stress (Leventhal et al., 2014; McKee et al., 2011), alcohol consumption (McKee, Krishnan-Sarin, Shi, Mase, & O'Malley, 2006), and gender (Pang & Leventhal, 2013). Furthermore, this paradigm has been used to identify and screen potential cessation pharmacotherapies (Verplaetse et al., 2017) and behavioral interventions (Moody, Poe, & Bickel, 2017).

Prevalence of Pain and Smoking

There has been increasing empirical interest in pain and tobacco cigarette smoking, as both are highly prevalent and co-occurring conditions (Ditre, Brandon, Zale, & Meagher, 2011; Martel, Shir, & Ware, 2017; Parkerson, Zvolensky, & Asmundson, 2013). Rates of smoking among persons with pain are two to three times that observed in the general population, with even higher rates among treatment-seeking pain patients (Michna et al., 2004; Zvolensky, McMillan, Gonzalez, & Asmundson, 2009). Accumulating research further suggests that cigarette smokers experience greater prevalence and intensity of pain than nonsmokers. For example, when compared to individuals who have never smoked cigarettes, both current and former smokers evince a greater risk of lifetime pain (e.g., Palmer, Syddall, Cooper, & Coggon, 2003). In addition, a recent study among daily smokers found that approximately 40% met

criteria for chronic pain (Bakhshaie et al., 2016), compared to approximately 30% in the general population (Johannes, Le, Zhou, Johnston, & Dworkin, 2010).

Interrelations Between Pain and Tobacco Smoking

An evolving reciprocal model posits that tobacco use and pain interact in the manner of a positive feedback loop, resulting in greater pain and maintenance of tobacco dependence (Ditre et al., 2011; Ditre, Zale, & LaRowe, 2019; Zale, Maisto, & Ditre, 2016). The reciprocal model can be broken down into the effects of smoking on pain (e.g., tobacco smoking as a risk factor in the onset of painful conditions), and the effects of pain on smoking (e.g., pain as a proximal antecedent of smoking behavior). Consistent with the first line of empirical inquiry, cigarette smoking has been identified as a unique risk factor in the onset and progression of several painful conditions (e.g., Aho & Heliovaara, 2004; Shiri, Karppinen, Leino-Arjas, Solovieva, & Viikari-Juntura, 2010). A recent meta-analysis further showed that nicotine produces acute analgesic effects (Ditre, Heckman, Zale, Kosiba, & Maisto, 2016), and chronic pain patients have reliably endorsed the use of cigarettes to cope with pain (e.g., Jamison, Stetson, & Parris, 1991; Patterson et al., 2012). Emerging research further suggests that nicotine deprivation is associated with greater self-reported pain intensity (LaRowe, Kosiba, Zale, & Ditre, 2018) and increased sensitivity to experimental pain induction (Ditre, Zale, LaRowe, Kosiba, & De Vita, 2018; Nakajima & Al'Absi, 2014).

When examining the second direction of the reciprocal model (i.e., the effects of pain on smoking), converging research indicates that pain can be a potent motivator of tobacco smoking (Dhingra et al., 2014; Ditre & Brandon, 2008; Ditre, Heckman, Butts, & Brandon, 2010; Kosiba, Zale, & Ditre, 2018). Smokers undergoing experimental pain induction (vs. no pain induction) have reported greater urge for cigarettes (Ditre & Brandon, 2008), and exposure to painful

stimuli has been associated with increased tobacco craving and withdrawal symptoms (Kotlyar et al., 2011; Parkerson & Asmundson, 2016). Ecological momentary assessment research has further shown that painful episodes often precede bouts of smoking (Dhingra et al., 2014). Finally, cross-sectional studies provide evidence that more intense daily pain is associated with greater number of cigarettes smoked per day (Aigner et al., 2015), and that smokers in pain (vs. without pain) tend to endorse more central features of tobacco dependence (e.g., craving, tolerance, automaticity, loss of control; Ditre, Kosiba, Zale, Zvolensky, & Maisto, 2016).

Pain and smoking cessation. Given established effects of pain on smoking behavior, an important next step is to examine the role of pain in the context of quitting. Although preliminary, the extant literature suggests that pain may influence various cessation-related outcomes, including pre-cessation processes (e.g., self-efficacy, expectancies for quitting), the subjective quality of quit attempts (e.g., perceived difficulty, withdrawal), and lapse/relapse to smoking. For example, smokers with pain have reported lower confidence in their ability to stay quit (Zale, Ditre, Dorfman, Heckman, & Brandon, 2014), and a greater number of unsuccessful past attempts to quit smoking (Waldie, McGee, Reeder, & Poulton, 2008). Chronic pain status has been associated with expectations for experiencing more severe withdrawal during future cessation attempts (Ditre et al., 2016), and smokers with co-occurring pain (vs. no pain) are nearly 3.5 times more likely to identify pain as a barrier to cessation (Ditre, Zale, Heckman, & Hendricks, 2017).

Despite emerging evidence that pain may influence smoking cessation, no research has directly examined pain as a predictor of nicotine withdrawal, and only three studies have examined associations between pain- and smoking abstinence-related outcomes. First, in a single experimental study, individuals who smoked at least 10 cigarettes per day ($N = 71$) completed a

baseline assessment of pain perception using a cold pressor test (CPT) prior to initiating a quit attempt (Nakajima & al'Absi, 2011). Within the first four weeks of cessation, individuals with greater pre-quit sensitivity to CPT at baseline were more likely to relapse to smoking. A second study examined pain-related anxiety (i.e., the tendency to respond to pain with anxiety or fear) as a predictor of lapse (i.e., the first act of smoking after a quit attempt) and relapse (i.e., return to regular smoking) among 55 daily cigarette smokers who attempted to quit without pychosocial or pharmacological cessation aids (LaRowe, Langdon, Zvolensky, Zale, & Ditre, 2017). Results indicated that higher pain-related anxiety predicted both greater likelihood and faster trajectory to lapse and relapse during the 90-day follow-up period. Finally, a sample of daily smokers with human immunodeficiency virus (HIV; $N = 474$; $M_{CPD} = 19.15$) completed either usual care or usual care plus 11 sessions of cell phone-delivered smoking cessation treatment (Aigner et al., 2017). Usual care included meeting briefly with a clinician, self-help written materials, and information about nicotine replacement therapy. During the 12-month follow-up period, participants with more intense pain were found to be less likely to achieve 24-hour point prevalence smoking abstinence, regardless of treatment condition assignment.

These initial findings suggest that pain and related constructs are associated with poorer cessation outcomes. However, these studies are limited in that they examine only narrow constructs of pain (i.e., pain-related anxiety, sensitivity to laboratory pain induction) or specific populations (i.e., smokers with HIV). Further examining established pain characteristics (i.e., pain persistence, pain intensity, and pain-related disability) in relation to smoking cessation outcomes may help address this gap in the literature, as they are often assessed in both clinical research and practice, and have been shown to differentially predict substance use and health outcomes. For example, greater average pain intensity among smokers has been negatively

associated with likelihood of initiating a quit attempt, and positively associated with greater number of cigarettes smoked per day (Aigner et al., 2015). Pain patients who smoke also report more intense pain and pain-related disability, compared to their nonsmoking counterparts (Hooten, Shi, Gazelka, & Warner, 2011; Weingarten et al., 2008).

Pain Characteristics and Theoretical Frameworks of Addiction

The current study will be the first to assess whether several clinically-important pain characteristics (i.e., persistent pain, pain intensity, and pain-related disability) predict smoking cessation-relevant outcomes. Allostatic load and negative reinforcement theoretical perspectives are commonly applied to the study of both pain and substance use, and directly informed the current study.

Allostatic Load Models

Allostasis refers to the process by which physiological systems maintain stability in the face of change (McEwen & Wingfield, 2003). Through opponent-processes, continued cycles of substance use result in physiological imbalances that can dysregulate reward processing and drive further substance use (Elman & Borsook, 2016). The accumulation of these maladaptive imbalances is referred to as allostatic load. Although allostatic load conceptualizations are commonly used to explain substance use, research has also implicated pain as another stressor that contributes to allostatic load (Simons, Elman, & Borsook, 2014). In this context, repeated bouts of pain and substance use can dysregulate overlapping neural systems responsible for both pain and reward processing, which in turn may engender a pathological state that favors more intense pain and drug-seeking behavior. Thus, greater persistence of pain and continued smoking may both serve as risk factors that contribute to the maintenance of tobacco addiction and the worsening of pain.

Negative Reinforcement Models

Associations between tobacco smoking and pain intensity/disability may be explained, in part, by negative reinforcement conceptualizations of addiction. Negative reinforcement frameworks posit that substance use is largely motivated by the desire to alleviate or avoid aversive internal states, and it has been hypothesized that using substances to cope with negative affect plays a central role in the development of substance use disorders (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). Given the acute analgesic properties of nicotine (Ditre et al., 2016), smokers experiencing increased negative affect due to pain intensity/interference may be more prone to using cigarettes for acute self-medication. However, regular cigarette smoking is also associated with the onset and progression of several chronically painful conditions, which in turn may motivate continued use of nicotine (Ditre et al., 2011). For example, chronic pain patients who reported using smoking as a pain-coping strategy were found to score significantly worse on measures of pain intensity, pain-related disability, and fear of pain, relative to nonsmokers or smokers who denied using cigarettes to cope with pain (Patterson et al., 2012). Although no previous work has examined pain intensity and pain-related disability in relation to smoking cessation-relevant outcomes, negative reinforcement models suggest that these characteristics may play an important role in the experience of withdrawal and relapse to smoking.

The Current Study

The goal of current was to test whether several clinically-relevant pain characteristics (i.e., persistent pain, pain intensity, and pain-related disability) predict severity of self-reported nicotine withdrawal and performance during a laboratory paradigm of smoking cessation. These data were collected as part of a primary study examining the role of self-control depletion and

nicotine deprivation on lapse and relapse outcomes (Heckman et al., 2017). In the nicotine deprivation manipulation, participants were randomized to either deprived (12 hours of nicotine deprivation) or non-deprived groups prior to completing all experimental activities. Thus, we also tested an interaction between nicotine deprivation condition assignment and pain characteristics to determine if nicotine deprivation confers a moderating effect on nicotine withdrawal and lapse/relapse outcomes.

We hypothesized that participants with persistent pain, high pain intensity, or moderate-to-severe pain-related disability would score higher on a measure of nicotine withdrawal and evince poorer performance during a laboratory paradigm of cessation (i.e., quicker latency to smoking, and smoking a greater number of cigarettes after initiating smoking). In a secondary aim, we also examined whether nicotine deprivation moderated these outcomes. Specifically, we hypothesized that participants with persistent pain, high pain intensity, or moderate-to-severe pain-related disability, who were also deprived of cigarettes for 12 hours prior to the baseline session, would score higher on a measure of nicotine withdrawal symptoms, would demonstrate the fastest latency to first cigarette (i.e., lapse), and would smoke a greater number of cigarettes (i.e., relapse) during the laboratory paradigm, relative to non-deprived participants.

Method

Participants

Adult smokers were recruited from the Tampa, FL, area via print and internet advertisements for an experimental study examining nicotine deprivation and self-control processes (Heckman et al., 2017). Prospective participants completed a telephone screener to determine eligibility. Inclusion criteria comprised: English-speaking; age 18-65; smoke at least 15 cigarettes per day for at least 1 year; able to provide a valid, stable mailing address and phone

number. Exclusion criteria included: concurrent use of other nicotine or tobacco products; actively attempting to quit smoking; currently pregnant; hearing or visual impairment that would interfere with study procedures. A total of 120 participants attended the baseline assessment and completed the laboratory paradigm of smoking cessation (Figure 1).

Measures

Smoking and sociodemographic characteristics. Participants completed a smoking history form that assessed daily cigarette consumption and smoking duration. The smoking history form also included an index of cessation self-efficacy that aggregated confidence in the ability to quit smoking for a week, month, and year ($\alpha = .79$), and the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), which is a widely used and valid measure of nicotine dependence. Finally, participants self-reported information about sociodemographic characteristics (e.g., gender, race, education).

Nicotine deprivation manipulation check. Compliance with the deprivation manipulation was verified via self-reported time since last cigarette and pre-session expired carbon monoxide (CO) concentration levels. Participants randomized to the deprivation condition (vs. non-deprived condition) were required to have a CO of $\leq$ 11ppm (Leventhal et al., 2010). Non-deprived participants were required to have a CO level greater than 11ppm.

Nicotine withdrawal. The Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986) was used to assess the severity of nine prototypical nicotine withdrawal symptoms over the past 12 hours (e.g., desire or craving to smoke) on a scale from 0 (*none*) to 4 (*severe*). Individual items were averaged to generate a total withdrawal severity score ($\alpha = .82$).

Pain Characteristics. The Graded Chronic Pain Scale (GCPS; Von Korff, Ormel, Keefe, & Dworkin, 1992) was used to assess pain persistence, pain intensity, and pain-related disability.

The GCPS has frequently been used to assess pain among both clinical and nonclinical samples (Turk & Melzack, 2011). The persistence classification score was based on a single item. Specifically, participants reported the number of days they had experienced pain in the past 180 days, and responses ranging from 90-180 days were classified as persistent pain (≤ 89 days = no persistent pain) per scoring recommendations (Von Korff et al., 1992). The characteristic pain intensity score included summed responses to three questions where participants rated their pain "right now," "on average," and the "worst" pain they had experienced in the past three months on an 11-point scale (0 = *no pain* to 10 = *pain as bad as it could be*). Total scores ranged from 0-30. Participants were then grouped according to their characteristic pain intensity (none-to-low intensity vs. high intensity; Adams et al., 2018; Urquhart, Shortreed, Davis, Cicuttini, & Bell, 2009). The disability score was based on the sum of responses from three items assessing interference of pain with daily functioning over the past 3 months on an 11-point scale (0 = *no interference* to 10 = *unable to carry on any activities*) and one item measuring the number of days pain interfered with usual activities on an 11-point scale (0 = *none* to 10 = *76-90 days*). Total disability scores ranged from 0-40. Consistent with previous work (Ozdemir-Karatas, Peker, Balık, Uysal, & Tuncer, 2013), pain-related disability status was dichotomized (moderate-to-severe vs. none-to-low).

Lapse and relapse behavior. The smoking cessation laboratory paradigm was developed by McKee and colleagues (McKee, 2009; McKee et al., 2012) to assess lapse and relapse behavior in a single experimental session. See Figure 3 for a timeline of the paradigm. Participants are first provided a tray containing eight preferred brand cigarettes, an ashtray, and a lighter with instructions that they can begin smoking at any point over the next 50 minutes. They are also informed that they could earn $1 for every 5 minutes they delayed smoking, with a

maximum payment of $10 over the 50-minute period. *Lapse behavior* is assessed via time to initiating smoking during the 50-minute delay period. After the participant lighted their first cigarette or at the ending of the 50-minute period, a 60-minute self-administration smoking period began where participants were instructed to "smoke as little or as much as you wish." In this paradigm, *relapse behavior* is assessed through the number of cigarettes smoked during the ad libitum smoking period. Primary outcomes included (a) time to first cigarette in minutes (i.e., lapse behavior) and (b) number of cigarettes smoked (i.e., relapse behavior) during the ad libitum smoking period.

Procedure

Following telephone screening, eligible participants were scheduled for a laboratory experimental session and randomized to either a continued smoking condition or a 12-hour nicotine deprivation condition. Participants randomized to the continued smoking condition were instructed to smoke normally prior to their appointment and to smoke their last cigarette five minutes before arriving for their session. Participants randomized to the deprivation condition were instructed not to smoke or use any other nicotine products for 12 hours prior to their appointment. Upon arrival to the laboratory experimental session, participants provided informed consent, and compliance with smoking instructions was verified via self-report and exhaled CO (continued smoking > 11ppm; deprivation ≤ 11ppm; Leventhal et al., 2010). Twenty-eight participants randomized to the deprivation condition and four participants assigned to the non-deprived conditions were excluded due to failure to meet pre-session expired CO concentration levels (see Figure 1). Participants who were compliant with the smoking instructions then completed baseline measures.

Participants were then randomized to either a self-control depletion manipulation or no self-control depletion (Heckman et al., 2017). The self-control depletion manipulation involved watching a six minute emotionally-evocative video clip depicting mutations and death of sea life, and instructions to "Remain completely neutral on the inside and out. Please try your best not to let any feelings or responses you may have show on your face, and to the best of your ability, try to keep all of your internal reactions suppressed" (Baumeister, Bratslavsky, Muraven, & Tice, 1998; Heckman, Ditre, & Brandon, 2012). Participants in the no self-control depletion condition were instructed to "Be as natural as possible, both on the inside and out. If you have any feelings or reactions to the movie, let them flow naturally." All participants were informed that they would be video-recorded while watching the clip. The primary study found no significant interaction between deprivation and self-control depletion on performance during the laboratory paradigm of smoking cessation. However, participants in the self-control depletion condition demonstrated a quicker latency to smoking their first cigarette (relative to controls). There was also no main effect of depletion on the relapse outcome (i.e., number of cigarettes smoked; *p*s > .05).

Data Analytic Plan

All analyses were conducted using SPSS Statistics 21 (IBM Corp, 2013). First, we ran a series of bivariate correlations to test zero-order associations between sociodemographic factors, FTND scores (nicotine dependence), MNWS scores (nicotine withdrawal), nicotine deprivation condition, pain characteristics (persistent pain, pain intensity, and pain-related disability), time to first cigarette (lapse), and number of cigarettes smoked (relapse). Variables that were associated with dependent variables (MNWS total score, minutes to lapse, and cigarettes smoked) were retained as covariates. Nicotine dependence (FTND scores) and cessation self-efficacy were also

included as covariates, given that the primary study found these variables differed as a function of deprivation condition (Heckman et al., 2017), and because they have previously been associated with nicotine withdrawal and cessation outcomes (e.g. Roche et al., 2014; Schnoll et al., 2011; Vangeli, Stapleton, Smit, Borland, & West, 2011). Self-control depletion condition was also included as a covariate in all models examining lapse and relapse, as the manipulation was completed immediately before the laboratory paradigm and predicted greater lapse behavior.

Given that moderate-to-high correlations between predictor variables could indicate issues with multicollinearity, the variance inflation factor (VIF) for each predictor was also assessed. Multicollinearity occurs when two or more predictor variables are highly inter-correlated, which can result in reduced statistical power. The VIF is commonly used to provide an index of the amount of variance that increases due to multicollinearity in an estimated regression coefficient, and a VIF of 10 or greater indicates issues with multicollinearity (Myers, 1990). After assessing the VIF for each of the pain characteristics, there was no indication of multicollinearity for pain persistence (VIF = 1.42), pain intensity (VIF = 1.90), or pain-related disability (VIF = 1.56). These findings are consistent with existing evidence that pain persistence, pain intensity, and pain-related disability represent related, but unique dimensions of the pain experience (Schmidt, Raspe, & Kohlmann, 2010; Von Korff et al., 1992).

Participants were then grouped using GCPS cut-offs for persistent pain (yes/no), high pain intensity (yes/no), and moderate-to-severe pain-related disability (yes/no). Descriptive statistics were computed to characterize the three groupings with regard to demographic and smoking characteristics.

Distributions of all outcome variables were then examined for normality. Skewness and kurtosis fell within acceptable ranges for MNWS scores (nicotine withdrawal) and number of

cigarettes smoked (relapse behavior; George & Mallery, 2003). However, examination of the distribution of the latency to smoke (lapse behavior) variable revealed both floor and ceiling effects, where 11% of participants initiated smoking immediately (n = 14) and almost 46% of participants abstained from smoking for the full 50-minute delay period (n = 55). Non-normality of the latency to smoke variable has been observed in previous research utilizing the laboratory paradigm (Reitzel & Leventhal, 2014; Roche et al., 2014). Therefore, we employed a nonparametric approach to analyzing the lapse outcome (i.e., survival analysis).

First, we examined differences in withdrawal severity (MNWS scores) as a function of persistent pain, pain intensity, and pain-related disability using three separate analysis of covariance (ANCOVA) models. In each model, we included a deprivation condition x pain characteristic interaction term. Significant interactions were probed using the PROCESS Macros for SPSS (Preacher & Hayes, 2008).

Second, we used the Cox proportional hazards model to estimate risk of lapse behavior as a function of persistent pain, pain intensity, and pain-related disability. The Cox model is frequently used to examine predictors of lapse to cigarette smoking (e.g., Lemieux, Nakajima, Hatsukami, Allen, & al'Absi, 2015; Messer et al., 2015; Nakajima & al'Absi, 2011; Schepis, Tapscott, & Krishnan-Sarin, 2016; Zvolensky et al., 2008) and this model has also been used to identify predictors of lapse outcomes during the laboratory paradigm of smoking cessation (Roche et al., 2014). This semiparametric model estimates hazard ratios by examining the pattern of covariation of predictor variables with the event of interest (e.g., lapse; Christensen, 1987; Cox & Oakes, 1984). Unlike ordinary regression models, the Cox proportional hazards model incorporates both 'censored' observations (cases are 'censored' if the exact survival time is unknown; Christensen, 1987) and uncensored observations when estimating model parameters.

Consistent with previous research, individuals who did not smoke during the 50-minute delay period were censored (Roche et al., 2014). Established procedures for the Cox proportional hazards model indicate that a minimum of 5 events should be included per predictor variable to increase confidence interval coverage, and decrease relative bias and type I error (Vittinghoff & McCulloch, 2007). After ensuring that our models were consistent with this recommendation, covariates were entered into the first step. Three separate models were then conducted with pain characteristics (i.e., persistent pain, pain intensity, and pain-related disability) and nicotine deprivation condition entered at the second step, and a pain characteristic x nicotine deprivation interaction term entered at the third step.

Kaplan Meier survival curves were then used to compare trajectories to lapse as a function of persistent pain (yes/no), high pain intensity (yes/no), and moderate-to-severe pain-related disability (yes/no). The Kaplan Meier survival curve represents the probability of maintaining smoking abstinence for a given length of time while considering time in many small intervals (Goel, Khanna, & Kishore, 2010; Kaplan & Meier, 1958). Two survival curves can be compared statistically using a log-rank test to challenge the null hypothesis that the survival curves do not differ by group (Goel et al., 2010). If a significant log-rank result is observed ($p <$ .05), then it can be concluded that the trajectory to lapse behavior differs based on group status. These procedures are well-established and have been previously used to examine the latency to smoke outcome (Roche et al., 2014).

Finally, consistent with previous work, relapse behavior (i.e., number of cigarettes smoked during laboratory paradigm) as a function of pain variables and deprivation was assessed using ANCOVA (Langdon & Leventhal, 2014; McKee et al., 2012; Moody et al., 2017; Oberleitner et al., 2018; Stevenson et al., 2017; Verplaetse et al., 2017; Wilson et al., 2014).

Three separate ANCOVAs examined main effects of persistent pain, pain intensity, and pain-related disability. All models included nicotine deprivation and a pain variable x nicotine deprivation interaction term. Significant interactions were probed using the PROCESS Macro for SPSS (Preacher & Hayes, 2008). For all ANCOVA models examining withdrawal scores and relapse behavior, the magnitude of group differences was examined using partial eta squared (η_p^2), with values of 0.01, 0.09, and 0.25 characterizing effects as small, medium, or large (Richardson, 2011).

Results

Participant Characteristics

Participants included 120 current daily tobacco smokers (48% male; M_{age} = 36.2, *SD* = 12.2) who reported smoking approximately 20 cigarettes per day (*SD* = 7.0) for an average of 17 years (*SD* = 10.9). The mean FTND score was 5.7 (*SD* = 1.9), indicating a moderate level of tobacco dependence (Heatherton et al., 1991). The sample was predominantly white (75%), single (59%), and approximately 33% had completed some college. Almost half of all participants (44%) reported earning less than $10,000 per year.

In terms of pain, participants reported a mean of 47.67 pain days in the past 6 months (*SD* = 64.63). Characteristic pain intensity scores ranged from 0 to 29 (*M* = 11.54, *SD* = 7.84) and pain-related disability scores ranged from 0 to 40 (*M* = 9.70, *SD* = 11.57). Approximately 25% of the sample met criteria for persistent pain (*n* = 31), almost 40% reported high pain intensity (*n* = 47), and approximately 26% of the sample endorsed moderate-to-severe pain-related disability (*n* = 31). Participants with persistent pain (vs. no persistent pain) were more likely to be White (90% vs. 70%; *p* = .029). A greater number of participants with high pain intensity (vs. none-to-low pain intensity) and moderate-to-severe pain-related disability (vs. none-to-low pain-related

disability reported earning an income of less than $30,000 in the past year (90% vs. 70%; p = .014 and 93% vs. 71%, p = .035, respectively). There were no other statistically-significant sociodemographic differences as a function of persistent pain, pain intensity, or pain-related disability.

As expected, the nicotine deprivation manipulation check revealed that deprived participants had significantly lower levels of expired CO (M = 5.31, SD = 2.11) than non-deprived participants (M = 38.74, SD = 21.13; p < .001). Sociodemographic and smoking history data are presented in Table 1.

Bivariate Correlations

All bivariate correlations are presented in Table 2. A negative correlation was observed between gender and number of cigarettes smoked during the laboratory paradigm (r = -.21, p = .019), and a positive correlation was observed between gender and MNWS scores (r = .20, p = .028). Specifically, females had higher MNWS scores (M = 2.27, SD = .84) than males (M = 1.93, SD = .85; p < .05). In comparison, males smoked a greater number of cigarettes (M = 3.31, SD = 1.26) than females (M = 2.77, SD = 1.20; p < .05) during the laboratory paradigm. Thus, gender was included with FTND scores and cessation self-efficacy as covariates in subsequent analyses. No additional covariates were identified via bivariate analyses.

Nicotine Withdrawal Reporting

As expected, and consistent with findings observed in the primary study, there was a main effect of nicotine deprivation in all three models (Heckman et al., 2017), such that deprived participants reported more severe withdrawal (M = 2.27, SD = .82) than non-deprived participants (M = 1.92, SD = .86; p < .05). There was also a main effect of persistent pain on severity of withdrawal symptoms (F [1, 120] = 7.100; p = .009; η_p^2 = .059), such that participants

with persistent pain reported experiencing more severe withdrawal (M = 2.43, SE = .14; Figure 4), relative to those with no persistent pain (M = 1.98, SE = .09). There was no difference in withdrawal reporting as a function of pain intensity (F [1, 120] = 2.627; p = .108) or pain-related disability (F [1, 120] = .489; p = .486). We also observed no interactions between deprivation condition and either persistent pain (F [1, 120] = .178; p = .674), pain intensity (F [1, 120] = .926; p = .338), or pain-related disability (F [1, 120] = .430; p = .513). Given that interaction terms were not statistically-significant, only the main effects were interpreted (see Table 3). Unadjusted and adjusted withdrawal statistics are presented in Table 6.

Laboratory Smoking Cessation Outcomes

Lapse. Mean time to smoking the first cigarette (i.e., lapse) was approximately 20 minutes (SD = 20.34) for the entire sample. Consistent with the primary study, Cox regression analysis showed that nicotine deprivation increased the likelihood of lapse behavior ($p < .05$; Table 4). Examination of the means revealed that participants deprived of nicotine smoked their first cigarette faster (M = 27.26, SD = 21.33) than those who were not deprived (M = 34.03, SD = 18.80). As hypothesized, Cox regression analysis further revealed that pain-related disability predicted faster latency to lapse (HR = 2.702, p = .014; see Table 4), such that participants with moderate-to-severe pain-related disability were at almost three times greater risk of initiating smoking. These effects were evident above and beyond the variance accounted for by gender, cessation self-efficacy, nicotine dependence, self-control depletion condition, and nicotine deprivation condition. Neither persistent pain (HR = 1.652, p = .190) nor pain intensity (HR = 1.610, p = .063) predicted lapse behavior after including covariates. We observed no significant interactions between nicotine deprivation condition and either persistent pain, pain intensity, or pain-related disability (ps > .05). Kaplan Meier survival analysis indicated that the presence of

moderate-to-severe pain related disability predicted a more rapid trajectory to initiating smoking (p = .029; Figure 5). Examination of the adjusted mean survival time revealed that participants with moderate-to-severe pain-related disability smoked approximately 8 minutes faster (M = 24.58, SE = 3.57) than participants with none-to-low pain-related disability (M = 32.61, SE = 2.12). No statistically-significant differences in lapse trajectories were observed as a function of persistence or intensity (ps > .05).

Relapse. On average, participants smoked 3 cigarettes (SD = 1.26) after initiating smoking. There was no main effect of deprivation on number of cigarettes smoked in any model. Similarly, there was no effect of persistent pain (F [1, 120] = .002; p = .964), pain intensity (F [1, 120] = 1.340; p = .249), or pain-related disability (F [1, 120] = .071; p = .791) on the relapse outcome. There were also no significant interactions between nicotine deprivation and either persistent pain (F [1, 120] = .973; p = .326), pain intensity (F [1, 120] = .416; p = .520), or pain-related disability (F [1, 120] = .014; p = .905). Unadjusted and adjusted means for the relapse outcome are presented in Table 6.

Discussion

The current study is the first to examine clinically-relevant pain characteristics (i.e., pain persistence, intensity, and disability) as prospective predictors of nicotine withdrawal and cessation-relevant outcomes. Lapse and relapse behavior was assessed using a validated laboratory paradigm of smoking cessation. Results indicated that smokers with persistent pain (vs. no persistent pain) scored higher on a measure of nicotine withdrawal prior to completing the laboratory paradigm, regardless of deprivation condition assignment. Examination of the partial eta squared values further supported the presence of a small-to-moderate effect of persistent pain on nicotine withdrawal. Results also indicated that smokers with moderate-to-

severe levels of pain-related disability initiated smoking (i.e., lapse behavior) 8 minutes faster than smokers with none-to-low levels of pain-related disability. Importantly, these effects were evident above and beyond the variance accounted for by nicotine dependence, cessation self-efficacy, gender, nicotine deprivation condition, and self-control depletion condition. Although nicotine deprivation predicted both greater severity of withdrawal and increased lapse behavior during the laboratory paradigm, we observed no interaction between deprivation condition and either persistent pain or pain-related disability. We also observed no main effect of either deprivation condition or pain characteristics on number of cigarettes smoked (i.e., relapse behavior) during the experimental paradigm.

This study advances prior work documenting that smokers with pain (vs. no pain) tend to experience greater difficulty (Zale et al., 2014) and more severe withdrawal when attempting to quit smoking (Ditre et al., 2016). Importantly, this is the first study to directly examine pain as a predictor of nicotine withdrawal severity. Laboratory studies have shown that some withdrawal symptoms emerge almost immediately after finishing a cigarette (Hendricks et al., 2006), and there has been interest in examining fluctuations in withdrawal reporting among continued smokers (Chandra et al., 2011; Perkins et al., 2009). In fact, greater withdrawal severity among current, non-treatment-seeking smokers has been shown to predict decreased odds of reducing smoking and initiating future quit attempts (Weinberger et al., 2010; Weinberger et al., 2016). That smokers with persistent pain reported more severe withdrawal, regardless of deprivation condition assignment, suggests these individuals may be less likely to successfully quit smoking, relative to smokers without persistent pain. Additionally, these findings also suggest that pain persistence may differentially predict greater nicotine withdrawal, compared to pain intensity and pain-related disability. Given the preliminary nature of these findings, future work is needed to

examine changes in withdrawal reporting among both smokers and recent quitters as a function of pain characteristics.

These results also indicated that participants with moderate-to-severe pain-related disability (vs. none-to-low pain-related disability) were almost 3 times more likely to initiate smoking and smoked their first cigarette approximately 8 minutes faster during the laboratory paradigm of smoking cessation. In comparison, neither pain persistence nor pain intensity predicted lapse behavior. There was also no evidence of an interaction between nicotine deprivation and pain characteristics. Our finding that smokers with moderate-to-severe pain-related disability (vs. none-to-low pain-related disability) initiated smoking faster during the experimental paradigm is consistent with a growing empirical literature suggesting pain is implicated in lapse/relapse to smoking (Aigner et al., 2017; LaRowe et al., 2017; Nakajima & al'Absi, 2011) and that pain-related disability may confer unique predictive utility (i.e., beyond pain status or intensity) in the prediction of substance-related outcomes (e.g., Zale & Ditre, 2015; Zale, Lange, Fields, & Ditre, 2013). For example, smokers tend to endorse higher levels of pain-related disability than nonsmokers (Hooten et al., 2011; Patterson et al., 2012), and among chronic pain patients, individuals with higher pain-related disability are more likely to report using cigarettes as a pain-coping strategy (Patterson et al., 2012). Contrary to our hypothesis, there was no effect of pain persistence or pain intensity on lapse during the experimental paradigm. Although these findings suggest that pain-related disability may uniquely predict greater likelihood of lapse to smoking compared to either pain persistence or intensity, this is the first study to examine pain characteristics as a predictors of lapse/relapse outcomes. Additional work is needed to replicate these findings and further establish the predictive utility of pain-related disability, relative to other pain characteristics, in the context of smoking cessation.

Strengths of the current study include its rigorous experimental design, and use of reliable and valid measures of pain, nicotine dependence, and smoking withdrawal. Several limitations also bear noting. First, participants were not recruited based on the presence of chronic pain. Thus, the current sample may not be representative of all smokers with chronic pain, and these findings should be replicated among those with varying levels of clinical pain. Nonetheless, the high prevalence of pain among in the current sample (e.g., approximately 40% of the sample endorsed high pain intensity) is consistent with other prevalence data (Bakhshaie et al., 2016), and supports the utility of assessing pain among all smokers, regardless of chronic pain status. Second, the sample was comprised of heavy smokers who were participating in an artificial quit attempt. Thus, the extent to which these results may generalize to lighter smokers, treatment-seeking smokers, or smokers who are actively attempting to quit remains unclear. Third, lapse and relapse outcomes were assessed using a laboratory model of smoking cessation. Although this approach enhances internal validity (e.g., Leeman et al., 2010; Leventhal et al., 2014), external validity is inherently limited as these data do not reflect 'real-world' lapse or relapse processes. An important next step would be to test pain characteristics in the prediction of withdrawal and established cessation milestones among individuals who are actively attempting to quit smoking (i.e., initial abstinence, lapse, relapse; Shiffman et al., 2006). A follow-up period of at least two weeks has been suggested for smoking cessation research (Baker et al., 2011), as initial smoking lapses are most likely to occur during this timeframe (Garvey, Bliss, Hitchcock, Heinold, & Rosner, 1992; Hughes, Keely, & Naud, 2004). Finally, although we observed no significant effect of any pain characteristic on the relapse outcome (i.e., number of cigarettes smoked), it is common for factors that predict lapse behavior to not also predict relapse behavior (and vice versa) in the experimental cessation paradigm (Langdon & Leventhal, 2014; Leventhal

et al., 2014; Pang & Leventhal, 2013; Reitzel & Leventhal, 2014; Roche et al., 2014). For example, Roche and colleagues (2014) found that only 2 of 11 established risk factors (withdrawal and craving to relieve the discomfort of withdrawal) predicted both latency and number of cigarettes smoked. Collectively, these findings suggest that the laboratory paradigm provides distinct indices of lapse and relapse processes, and that smokers with pain-related disability may be more sensitive to initiating smoking.

A growing body of evidence indicates that pain is linked to smoking behavior and the maintenance of tobacco dependence, and these data contribute to an emerging literature indicating that smokers with pain are at risk for poorer cessation outcomes. In the current study, persistent pain and pain-related disability independently predicted greater nicotine withdrawal and lapse behavior. Thus, smokers who experience persistent pain and pain-related functional impairment would likely benefit from tailored treatment approaches. In addition, it may be advisable to incorporate assessment of clinically-relevant pain characteristics among smokers who are preparing to quit. Cessation interventions have been successfully administered to smokers with chronic pain (Saragiotto et al., 2018), and integrated treatments for pain and smoking have been shown to increase knowledge of pain-smoking interrelations, and confidence/intention to quit smoking (Ditre, LaRowe, Vanable, De Vita, & Zvolensky, 2018; Hooten, LaRowe, Ditre, & Warner, 2018).

In summary, this is the first study to test the role of clinically-relevant pain characteristics as predictors of withdrawal reporting and smoking lapse/relapse behavior. These experimental findings suggest that pain persistence and pain-related disability may be associated with more severe nicotine withdrawal and early lapse to smoking. Limited research has examined the effects of pain on smoking cessation, and these findings represent an initial, yet important step

towards better understanding the role of pain characteristics in the maintenance of tobacco dependence. This and future work has the potential to inform the development of tailored treatments, including relapse-prevention interventions (e.g, Meltzer et al., 2018), for smokers with co-occurring pain.

Table 1

Sociodemographic, Smoking, and Pain Characteristics

	Total Sample	Pain Persistence		Pain Intensity		Pain –Related Disability	
		No Persistent Pain	Persistent Pain	None-to-Low	High	None-to-Low	Moderate-to-Severe
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Gender							
Male	58 (48.3%)	44 (49.4%)	14 (45.2%)	38 (52.1%)	20 (42.6%)	47 (52.8%)	11 (35.5%)
Race							
White	90 (75.0%)	62 (69.7%)*	28 (90.3%)*	55 (75.3%)	35 (74.5%)	65 (73.0%)	25 (80.6%)
Non-White	30 (25.0%)	27 (30.3%)*	3 (9.7%)*	18 (24.7%)	12 (25.5%)	24 (27.0%)	6 (19.4%)
Marital Status							
Single	71 (59.2%)	53 (59.6%)	18 (58.1%)	44 (60.3%)	27 (57.4%)	55 (61.8%)	16 (51.6%)
Married	18 (15.0%)	14 (15.7%)	4 (12.9%)	11 (15.1%)	7 (14.9%)	11 (12.4%)	7 (22.6%)
Separated/Divorced/Widowed	21 (25.8%)	22 (24.7%)	9 (29.0%)	18 (24.7%)	13 (27.7%)	23 (25.8%)	8 (25.8%)
Education							
Did Not Graduate High School	21 (17.5%)	19 (21.3%)	2 (6.5%)	13 (17.8%)	8 (17.0%)	16 (180.0%)	5 (16.1%)
High School Graduate	38 (31.7%)	27 (30.3%)	11 (35.5%)	24 (32.9%)	14 (29.8%)	25 (28.1%)	13 (41.9%)
Some College or Greater	61 (50.8%)	43 (48.3%)	18 (58.0%)	36 (49.3%)	25 (53.2%)	48 (53.9%)	13 (42%)
Income							
<$10,000 Per Year	53 (44.2%)	40 (44.9%)	13 (41.9%)	30 (41.1%)*	23 (48.9%)*	38 (42.7%)*	15 (48.4%)*
$10,000 - $30,000 Per Year	40 (33.3%)	27 (30.3%)	13 (41.9%)	21 (28.8%)*	19 (40.4%)*	26 (29.2%)*	14 (45.2%)*
>$30,000 Per Year	27 (22.5%)	22 (24.7%)	5 (16.1%)	22 (30.1%)*	5 (10.6%)*	25 (28.1%)*	2 (6.5%)*
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Age	36.17 (12.16)	36.36 (11.98)	35.64 (12.86)	34.68 (12.35)	38.50 (11.61)	35.51 (12.46)	38.06 (11.24)
Cigarettes per Day	20.51 (6.99)	20.54 (7.36)	20.43 (5.90)	20.50 (6.43)	20.52 (7.85)	20.12 (6.20)	21.62 (8.90)
Years of Smoking	16.77 (10.94)	17.37 (11.26)	15.06 (9.96)	15.37 (10.90)	18.96 (10.76)	15.68 (10.56)	19.90 (11.58)
FTND [a]	5.75 (1.85)	5.71 (1.80)	5.87 (2.03)	5.61 (1.80)	5.95 (1.93)	5.66 (1.81)	6.00 (1.96)
Cessation Self-Efficacy	.88 (.98)	.88 (.98)	.85 (.99)	.83 (.96)	.95 (1.01)	.84 (.98)	.97 (.97)
Expired Carbon Monoxide	21.47 (22.31)	21.46 (23.43)	21.48 (19.05)	21.08 (24.90)	22.06 (17.80)	21.92 (23.74)	20.16 (17.85)

Note. [a] FTND - Fagerström Test for Nicotine Dependence; * $p < .05$; ** $p < .01$.

Table 2

Bivariate Correlations Between Sociodemographic, Smoking History, Primary Predictor, and Primary Outcome Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Age	-	.07	-.04	.08	-.14	.45**	-.11	-.11	. 00	-.17	.02	.12	.15	.04	-.09
2 Gender		-	.10	.16	-.08	.19*	.00	.20*	.09	.00	.02	.15	.20*	.07	-.21*
3 Race			-	-.30**	-.13	.18*	.14	.10	-.02	.14	-.20*	.05	-.06	-.03	-.08
4 Education Level				-	.19*	.19*	-.20*	.05	.10	-.06	.12	.02	.00	.15	.10
5 Income					-	-.02	-.16	-.13	.08	.11	-.08	-.14	-.15	-.07	.02
6 Marital Status						-	-.06	-.12	-.08	-.15	.00	.00	.11	.06	-.10
7 FTND [a]							-	.11	-.18*	-.20*	.00	.12	.09	.05	.04
8 MNWS [b]								-	-.04	.21*	.20*	.20*	.19*	-.07	.23*
9 Cessation Self-Efficacy									-	.25**	-.04	.05	.04	.13	-.14
10 Nicotine Deprivation Condition										-	-.09	-.04	-.03	-.17	.07
11 Pain Persistence											-	.70**	.60**	-.06	.00
12 Pain Intensity												-	.80**	-.08	.03
13 Pain-Related Disability													-	-.14	-.03
14 Time to First Cigarette [c]														-	.05
15 Number of Cigarettes Smoked [c]															-

Note. [a] FTND - Fagerström Test for Nicotine Dependence; [b] MNWS - Minnesota Nicotine Withdrawal Scale; [c] Outcomes (i.e., lapse and relapse) from Laboratory Paradigm of Smoking Cessation; * $p < .05$; ** $p < .01$.

Table 3

Pain Characteristics and Nicotine Deprivation Predicting Nicotine Withdrawal Reporting

	df	F	*p*	η_p^2
Persistent Pain				
FTND [a]	1	2.685	.104	.023
Gender	1	5.540	.020*	.046
Cessation Self-Efficacy	1	1.328	.252	.012
Nicotine Deprivation	1	9.917	.002**	.080
Persistent Pain	1	7.100	.009**	.059
Persistent Pain x Nicotine Deprivation	1	.178	.674	.002
Pain Intensity				
FTND [a]	1	2.375	.126	.020
Gender	1	5.119	.026*	.043
Cessation Self-Efficacy	1	1.653	.201	.014
Nicotine Deprivation	1	9.788	.002**	.079
Pain Intensity	1	2.627	.108	.023
Pain Intensity x Nicotine Deprivation	1	.926	.338	.008
Pain-Related Disability				
FTND [a]	1	2.534	.114	.022
Gender	1	5.100	.026*	.043
Cessation Self-Efficacy	1	1.332	.251	.012
Nicotine Deprivation	1	8.485	.004**	.069
Pain-Related Disability	1	.489	.486	.004
Pain-Related Disability x Nicotine Deprivation	1	.430	.513	.004

Note. [a] FTND - Fagerström Test for Nicotine Dependence; * $p < .05$; ** $p < .01$.

Table 4

Cox Proportional Hazards Regressions Examining Minutes to First Cigarette (i.e., Lapse) during the Laboratory Paradigm of Smoking Cessation

	Adjusted Hazard Ratio 95% Confidence Interval	***p***
Persistent Pain		
FTND [a]	.965 (.841-1.106)	.607
Gender	.791 (.482-1.297)	.353
Cessation Self-Efficacy	.757 (.563-1.019)	.066
Self-Control Depletion	1.712 (1.029-2.846)	.038*
Nicotine Deprivation	1.763 (.958-3.244)	.068
Persistent Pain	1.652 (.780-3.502)	.190
Persistent Pain x Nicotine Deprivation	.768 (.263-2.243)	.629
Pain Intensity		
FTND [a]	.963 (.839-1.106)	.596
Gender	.798 (.487-1.306)	.369
Cessation Self-Efficacy	.728 (.538-.984)	.039*
Self-Control Depletion	1.759 (1.053-2.938)	.031*
Nicotine Deprivation	1.681 (1.003-2.818)	.049*
Pain Intensity	1.610 (.975-2.659)	.063
Pain Intensity x Nicotine Deprivation	.559 (.195-1.599)	.278
Pain-Related Disability		
FTND [a]	.952 (.832-1.090)	.476
Gender	.699 (.418-1.168)	.171
Cessation Self-Efficacy	.746 (.555-1.002)	.052
Self-Control Depletion	1.815 (1.066-3.092)	.028*
Nicotine Deprivation	1.877 (1.003-3.513)	.049*
Pain-Related Disability	2.702 (1.218-5.993)	.014*
Pain-Related Disability x Nicotine Deprivation	.549 (.184-1.638)	.282

Note. [a] FTND - Fagerström Test for Nicotine Dependence. Indicator Groups for Categorical Variables: Gender (Female), Self-Control Depletion (Not Depleted), Nicotine Deprivation (Not Deprived), Pain (No Pain); * $p < .05$; ** $p < .01$.

Table 5

Pain Characteristics and Nicotine Deprivation Predicting Number of Cigarettes Smoked (i.e., Relapse) during the Laboratory Paradigm of Smoking Cessation

	df	F	*p*	η_p^2
Persistent Pain				
FTND [a]	1	.167	.683	.001
Gender	1	4.869	.029*	.041
Cessation Self-Efficacy	1	2.341	.129	.020
Self-Control Depletion	1	.159	.691	.001
Nicotine Deprivation	1	1.363	.245	.012
Persistent Pain	1	.002	.964	.000
Persistent Pain x Nicotine Deprivation	1	.973	.326	.009
Pain Intensity				
FTND [a]	1	.101	.751	.001
Gender	1	5.348	.023*	.045
Cessation Self-Efficacy	1	2.748	.100	.024
Self-Control Depletion	1	.198	.657	.002
Nicotine Deprivation	1	1.809	.181	.016
Pain Intensity	1	1.340	.249	.012
Pain Intensity x Nicotine Deprivation	1	.416	.520	.004
Pain-Related Disability				
FTND [a]	1	.148	.701	.001
Gender	1	4.953	.028*	.042
Cessation Self-Efficacy	1	2.386	.125	.021
Self-Control Depletion	1	.156	.693	.001
Nicotine Deprivation	1	1.399	.239	.012
Pain-Related Disability	1	.071	.791	.001
Pain-Related Disability x Nicotine Deprivation	1	.014	.905	.000

Note. [a] FTND - Fagerström Test for Nicotine Dependence; * $p < .05$; ** $p < .01$.

Table 6

Unadjusted and Adjusted Means of Primary Outcomes as a Function of Pain Characteristics

	Pain Persistence		Pain Intensity		Pain–Related Disability	
	No Persistent Pain	Persistent Pain	None-to-Low	High	None-to-Low	Moderate-to-Severe
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Unadjusted						
Nicotine Withdrawal [a]	1.99 (.84)*	2.42 (.81)*	2.02 (.88)	2.23 (.81)	2.06 (.83)	2.23 (.93)
Time to First Cigarette [b]	31.09 (20.58)	28.95 (19.91)	31.54 (20.90)	28.97 (19.55)	32.61 (20.01)*	24.58 (20.21)*
# of Cigarettes Smoked [b]	3.05 (1.29)	3.00 (1.15)	2.97 (1.34)	3.13 (1.11)	3.04 (1.28)	3.00 (1.21)
	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)
Adjusted						
Nicotine Withdrawal [a c]	1.98 (.09)*	2.43 (.14)*	2.00 (.10)	2.25 (.12)	2.07 (.09)	2.20 (.15)
# of Cigarettes Smoked [b d]	3.03 (.13)	3.02 (.22)	2.92 (.15)	3.19 (.18)	2.91 (.18)	3.19 (.18)

Note. [a] Minnesota Nicotine Withdrawal Scale; [b] Outcomes (i.e., Lapse and Relapse) from Laboratory Paradigm of Smoking Cessation; [c] Adjusted for the effects of nicotine dependence (FTND scores), cessation-self efficacy, gender, and nicotine deprivation condition; [d] Adjusted for the effects of nicotine dependence (FTND scores), cessation-self efficacy, gender, nicotine deprivation condition, and self-control depletion condition; * $p < .05$; ** $p < .01$.

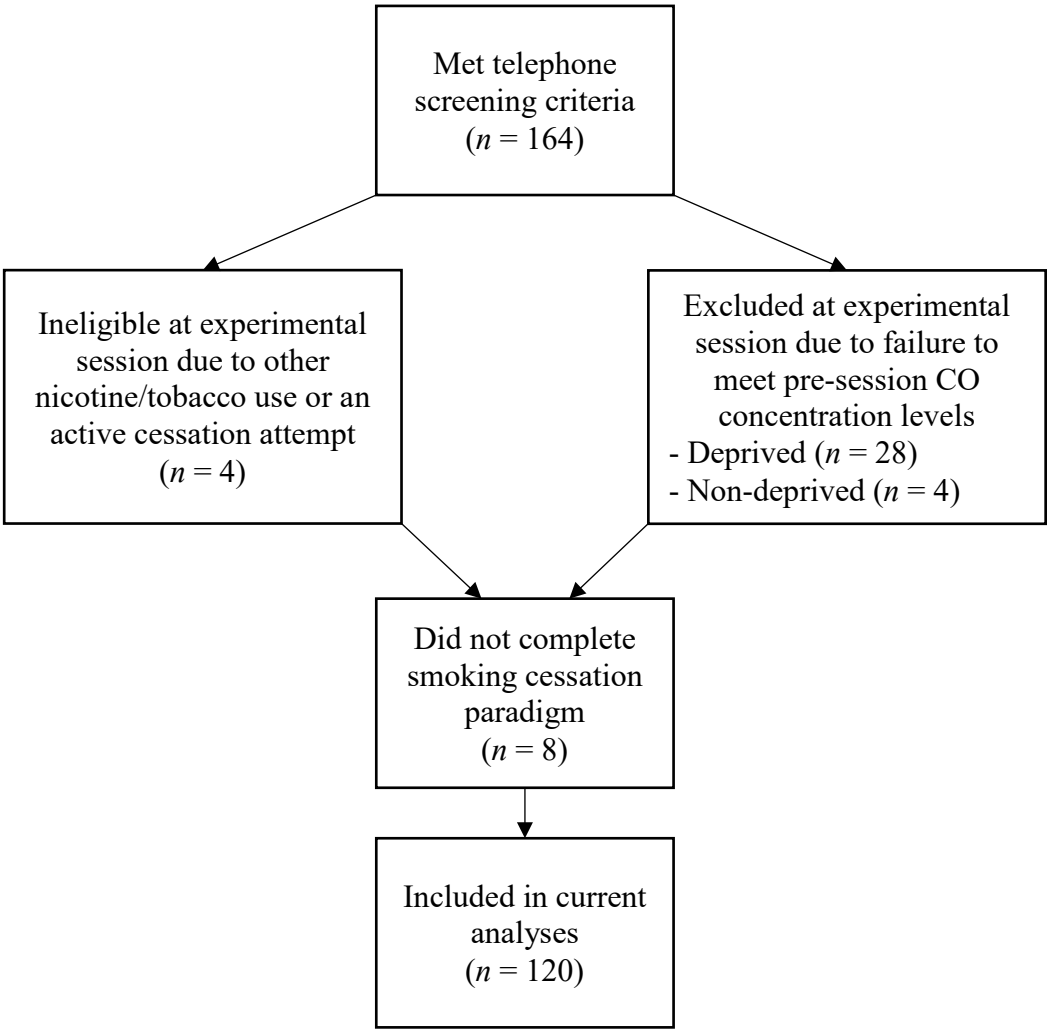

Figure 1. Inclusion of Participants.

Recruitment	Telephone Screening	Eligible Participants: Scheduled and randomized to deprivation condition.	Nicotine Deprivation Manipulation	In-Person Experimental Session	Baseline Measures	Self-Control Depletion Manipulation	Smoking Cessation Paradigm
Responded to an ad for a study testing nicotine deprivation and smoking on self-control processes.	Screened for inclusion and exclusion criteria		Abstain from using any nicotine/tobacco product for 12 hours prior to session Smoke 1 cigarette 5 minutes prior to session	Complete informed consent, verify compliance with CO	Sociodemographic, smoking history, pain characteristics, nicotine withdrawal symptoms		Time to first cigarette, number of cigarettes smoked

Figure 2. Timeline of Study Procedures.

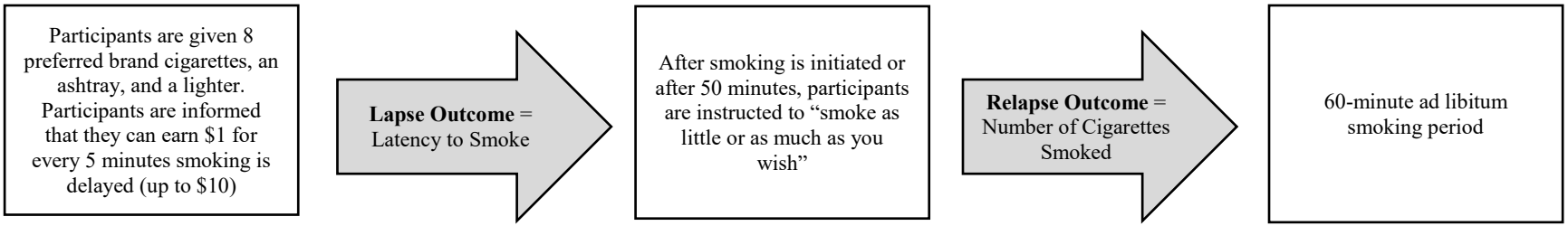

Figure 3. Procedure and Primary Outcomes from the Laboratory Paradigm of Smoking Cessation.

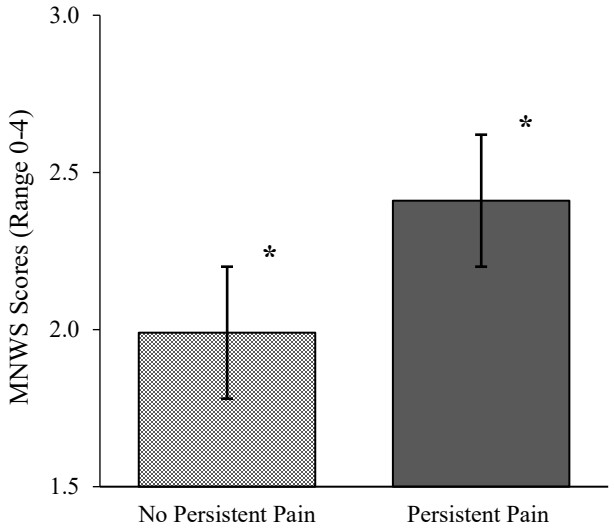

Figure 4. Minnesota Nicotine Withdrawal Scale (MNWS) Scores as a Function of No Persistent Pain versus Persistent Pain. *Note:* Means statistically adjusted for nicotine dependence (FTND scores), gender, cessation self-efficacy, and nicotine deprivation condition; * $p < .05$.

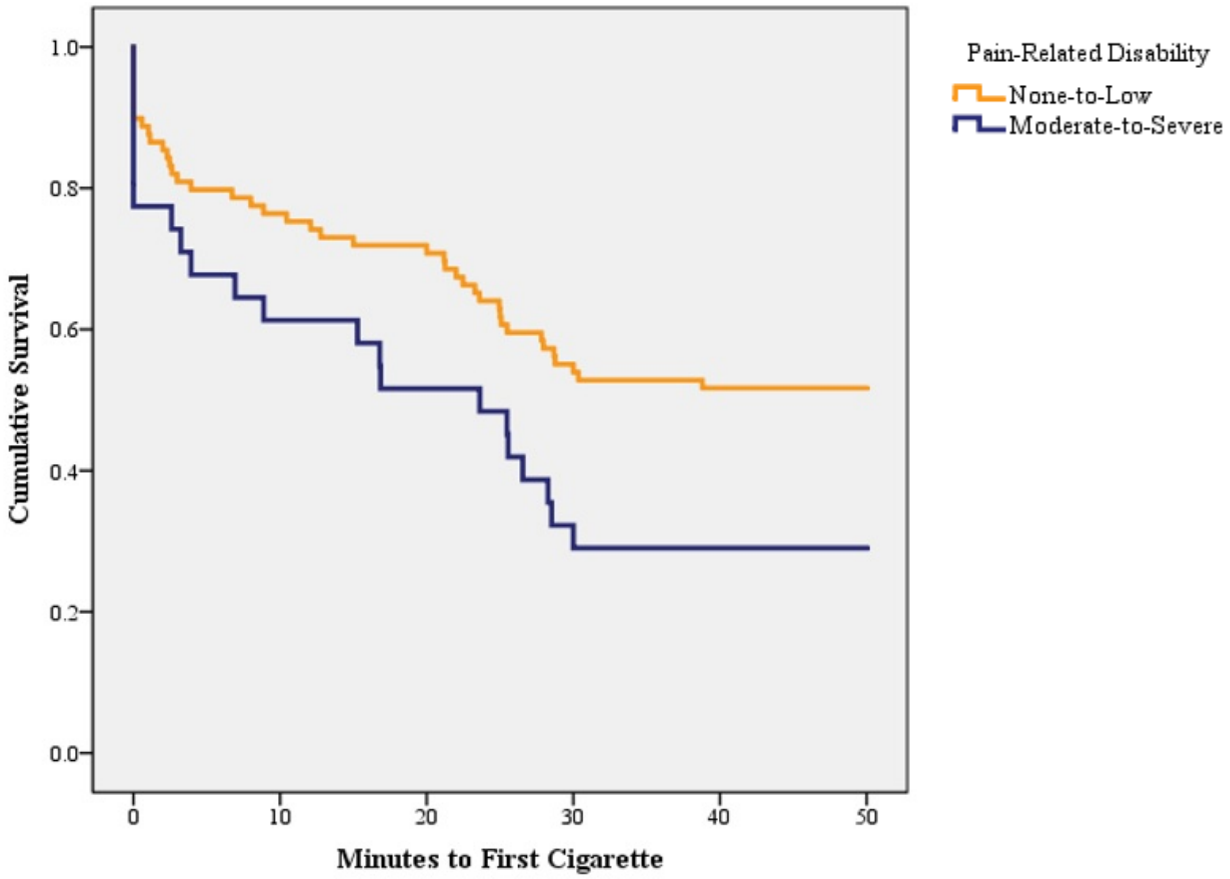

Figure 5. Kaplan-Meier Survival Curves of Minutes to First Cigarette (i.e., Lapse) during the Laboratory Paradigm as a Function of Pain-Related Disability.

Appendix A

Graded Chronic Pain Scale (GCPS)

1. How many days in the **last 6 months** have you had pain? _____ Days

2. How would you rate your pain **RIGHT NOW**? Use a scale from 0 to 10 where 0 is "no pain" and 10 is "pain as bad as could be."

No Pain										Pain as bad as could be
0	1	2	3	4	5	6	7	8	9	10

3. In the last 3 months, how would you rate your WORST pain? Use the same scale, where 0 is "no pain" and 10 is "pain as bad as could be."

No Pain										Pain as bad as could be
0	1	2	3	4	5	6	7	8	9	10

4. In the last 3 months, **ON AVERAGE**, how would you rate your pain? Use the same scale, where 0 is "no pain" and 10 is "pain as bad as could be." [*That is, your usual pain* at times you were in pain.]

No Pain										Pain as bad as could be
0	1	2	3	4	5	6	7	8	9	10

5. In the last 3 months, how many days did your pain keep your from doing your **USUAL ACTIVITIES** like work, school or housework?

Days: None	1	2	3-4	5-6	7-10	11-15	16-24	25-60	61-75	76-90
Score: 0	1	2	3	4	5	6	7	8	9	10

6. In the last 3 months, how much has pain interfered with your DAILY ACTIVITIES? Use a 0 to 10 scale, where 0 is "no interference" and 10 is "unable to carry on any activities."

No Interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

7. In the last 3 months, how much has pain interfered with your RECREATIONAL, SOCIAL AND FAMILY ACTIVITIES? Use the same scale, where 0 is “no interference” and 10 is “unable to carry on any activities.”

No Interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

8. In the last 3 months, how much has pain interfered with your ABILITY TO WORK, including housework? Use the same scale, where 0 is “no interference” and 10 is “unable to carry on any activities.”

No Interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

Appendix B

Minnesota Nicotine Withdrawal Scale (MNWS)

Please rate yourself for the period for the **LAST 12 HOURS**

	None 0	Slight 1	Mild 2	Moderate 3	Severe 4
1. Angry, irritable, frustrated	❍	❍	❍	❍	❍
2. Anxious, nervous	❍	❍	❍	❍	❍
3. Depressed mood, sad	❍	❍	❍	❍	❍
4. Desire or craving to smoke	❍	❍	❍	❍	❍
5. Difficulty concentrating	❍	❍	❍	❍	❍
6. Increased appetite, hungry, weight gain	❍	❍	❍	❍	❍
7. Insomnia, sleep problems, awakening at night	❍	❍	❍	❍	❍
8. Restless	❍	❍	❍	❍	❍
9. Impatient	❍	❍	❍	❍	❍
10. Constipation	❍	❍	❍	❍	❍
11. Dizziness	❍	❍	❍	❍	❍
12. Coughing	❍	❍	❍	❍	❍
13. Dreaming or nightmares	❍	❍	❍	❍	❍
14. Nausea	❍	❍	❍	❍	❍
15. Sore throat	❍	❍	❍	❍	❍

Appendix C

Fagerström Test for Nicotine Dependence (FTND)

1. How soon after you wake up do you smoke your first cigarette?

- Within 5 minutes
- 6 - 30 minutes
- 31 - 60 minutes
- After 60 minutes

2. Do you find it difficult to refrain from smoking in places where it is forbidden? For example, in church, at the library, at the movies etc.?

- Yes
- No

3. Which cigarette would you hate most to give up?

- The first one in the morning
- All others

4. How many cigarettes per day do you smoke?

- 10 or less
- 11 - 20
- 21 - 30
- 31 or more

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?

- Yes
- No

6. Do you smoke if you are so ill that you are in bed most of the day?

- Yes
- No

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