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Comparing the Smoking Topography of Usual Brand Cigarettes in Pregnant and Non-Pregnant Smokers

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COMPARING THE SMOKING TOPOGRAPHY OF USUAL BRAND CIGARETTES IN PREGNANT AND NON-PREGNANT SMOKERS

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Abstract

Introduction: Most pregnant smokers report abruptly reducing their cigarettes per day (CPD) by ~50% shortly after learning of pregnancy and of making further smaller reductions over the remainder of their pregnancy. Laboratory and naturalistic studies with non-pregnant smokers have found that these types of reductions often lead to changes in smoking topography (i.e., changes in smoking intensity to maintain a desired blood-nicotine level). [19, 20] If pregnant women engage in compensatory smoking, they may expose themselves and their offspring to the same level of toxicants despite reporting reductions in CPD.

Methods: Pregnant and non-pregnant female smokers (n = 17 and 91, respectively) participated. At the experimental session, after biochemical confirmation of acute abstinence, all participants smoked one of their usual brand cigarettes ad lib through a Borgwaldt CReSS Desktop Smoking Topography device. Carbon monoxide (CO) and measures of nicotine withdrawal, craving, and reinforcement derived from smoking were also collected.

Results: The two groups did not differ on any demographic or smoking characteristics at screening, except nicotine metabolism rate, which as expected, was faster in pregnant smokers. Analyses suggest that none of the smoking topography parameters differed between pregnant and non-pregnant smokers, although pregnant smokers had a significantly smaller CO boost. Both groups reported similar levels of relief of withdrawal and craving after smoking, but other self-report data suggest that pregnant smoker find smoking less reinforcing than non-pregnant smokers.

Conclusions: Pregnant smokers do not smoke cigarettes differently as compared to non-pregnant female smokers, but appear to find smoking less reinforcing.

Citation Page

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Comprehensive Literature Review

Smoking during pregnancy is the leading preventable cause of poor pregnancy outcomes in the U.S. (U.S. Department of Health and Human Services [USDHHS], 2014). Women who smoke during pregnancy put themselves and their children at increased risk for a wide range of poor outcomes (Dietz et al., 2010; Hackshaw, Rodeck, & Boniface, 2011). Smoking while pregnant increases the risk of placental abruption, placenta previa, and miscarriage (Aliyu et al., 2011; Pineles, Park & Samet, 2014). Adverse fetal and neonatal effects include intrauterine growth restriction, low birth weight, preterm birth and birth defects (Cohen, Jeffery, Lagercrantz, & Katz-Salamon, 2010; Dietz et al., 2010; Hackshaw et al., 2011) which contribute to longer, and therefore more costly, postnatal hospital stays (Adams, Melvin, Raskind-Hood, Joski, & Galactionova, 2011). The adverse consequences continue into childhood and beyond in the form of increased risk for sudden infant death syndrome (SIDS), cognitive impairments, obesity, metabolic syndrome, Type 2 diabetes, and cardiovascular disease (Cohen et al., 2010; Bruin, Gerstein, & Holloway, 2010; Heinonen, et al., 2011; Moylan et al., 2015).

Changes in Smoking during Pregnancy

Most pregnant women know that smoking during pregnancy increases adverse outcomes for both the fetus/neonate and the mother (Arnold et al., 2001) and also report being the target of strong social stigma (Abrahamsson, Springett, Karlsson, & Ottosson, 2005; Wigginton & Lee, 2013). Nonetheless, most women cannot quit smoking on their own after learning of pregnancy (Heil et al., 2014; Solomon & Quinn, 2004). Instead, most report spontaneously reducing their cigarette use in an effort to reduce fetal toxicant exposure (Graham, Flemming, Fox, Heirs, & Sowden, 2014). Across a wide variety of studies, the majority of pregnant smokers reliably report decreasing their cigarettes per day (CPD) by approximately 50% between learning of pregnancy and entering prenatal care (Coleman et al., 2012; Dornelas et al., 2006; Heil et al., 2008; Higgins et al., 2004; Higgins et al., 2014; Pollak et al., 2007; Rigotti et al., 2006; Ussher et al., 2015) and recent work by our group examined the time course of this change for the first time (Heil et al., 2014). In our research clinic, women enrolling in clinical trials testing whether financial incentives increase abstinence in pregnant smokers complete a timeline follow-back interview where they retrospectively self-reported their CPD each day between when they learned they were pregnant and when they entered prenatal care an average of five weeks later. This analysis specifically characterized the timing of CPD reductions in the days after learning of pregnancy in 107 of these women. Results indicated that 22% reported quitting smoking between learning of pregnancy and entering prenatal care, 62% significantly reduced the number of

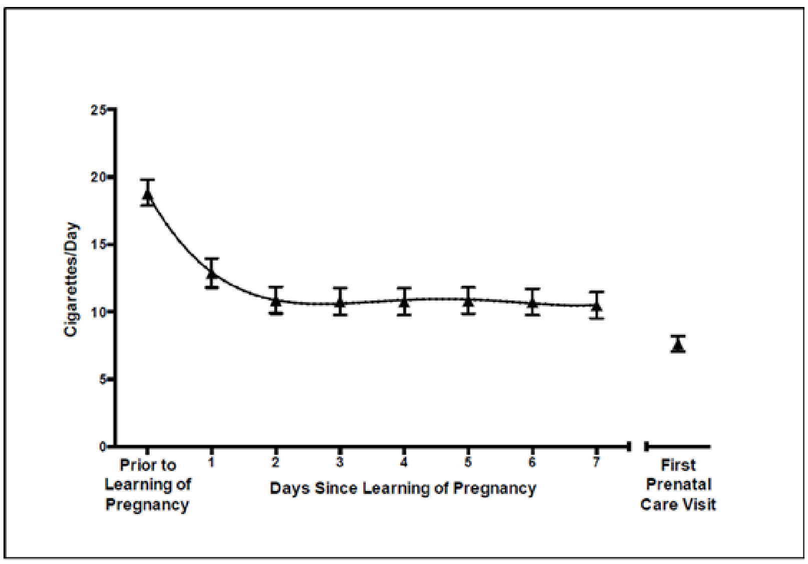

Figure 1. Mean ± standard error of the mean for cigarettes/day before and after learning of pregnancy among women who self-report reducing cigarettes/day upon learning of pregnancy. Adapted from "Examining the timing of changes in cigarette smoking upon learning of pregnancy," by S. H> Heil, E.S. Herrmann, G. J. Badger, L. J. Solomon, I. M. Bernstein, S. T. Higgins, *Preventive Medicine,* 68, 58-61.

cigarettes they smoked each day, and 16% reported making no changes in their smoking at all during this time period. Focusing on those who reduced, as expected, most reported a characteristic 50% reduction in CPD. Interestingly, most of this reduction occurred in the first two days after learning of pregnancy (Figure 1), a remarkable reduction over a short period given the persistent and tenacious nature of cigarette smoking. A potential limitation of these data is our use of self-reported CPD. As noted previously, stigma could be expected to contribute to some extent of under-reporting of smoking rates, although this clearly did not prevent the majority of participants from reporting continued smoking and a sizeable percentage from reporting that they had not changed their smoking at all since learning of pregnancy. Nevertheless, without biochemical data, it is difficult to know whether self-reported reductions in CPD truly decrease toxicant exposure.

Correspondence between Self-Report and Biochemical Measures of Cigarette Use.

To examine this further, we conducted another analysis where the correspondence between self-report and biochemical measures of smoking could be assessed (Heil, Solomon, Skelly, Bernstein, & Higgins, 2015). Data were collected from a different set of pregnant women participating in the same series of randomized clinical trials testing financial incentives for smoking cessation described above. CPD and biochemical measures of smoking were examined among a subset of 156 women who reported smoking and had complete data at each of three research assessments completed during the pregnancy, the first at Intake at ~10 weeks gestation, the second four weeks later (Early Pregnancy), and the third at approximately ~28 weeks gestation (Late Pregnancy).

The biochemical measures of smoking were breath carbon monoxide (CO) and urine cotinine. CO is one of the primary toxic components of cigarette smoke. The elimination half-life of CO is only a few hours (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987), thus levels are indicative of very recent smoking. Cotinine is the primary metabolite of nicotine. The elimination half-life is approximately five times longer than that of CO (Dempsey, Jacob & Benowitz, 2002), making it a better measure of smoking over the last few days. On average, women in this analysis reported further significant reductions in CPD, from 11 CPD at Intake to 7-8 CPD at the Early and Late Pregnancy assessments (Figure 2). Despite this significant 31% decrease in CPD between the Intake and Early Pregnancy assessments, however, urine cotinine only decreased by 10% and breath CO did not change appreciably. At the Late Pregnancy assessment, urine cotinine was not statistically different from Early Pregnancy assessment.

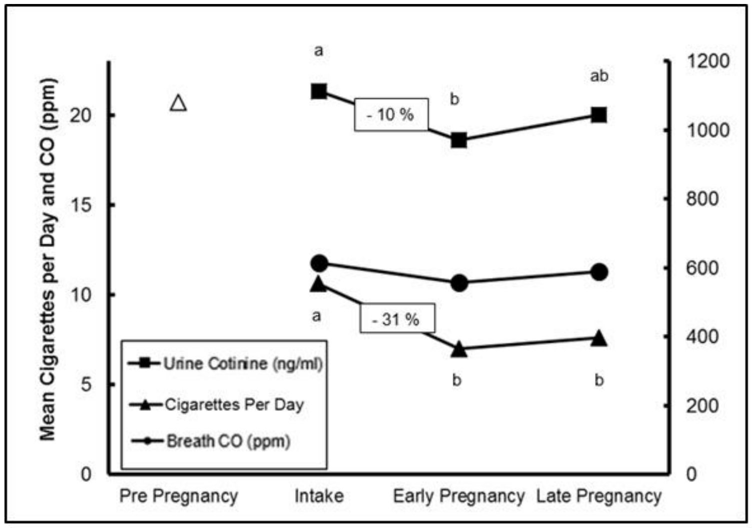

Figure 2. Mean ± SEM urine cotinine in nanograms per milliliter, breath CO in parts per million and cigarettes per day at ~ 10 weeks estimated gestational age (Intake), ~ 14 weeks estimated gestational age (Early Pregnancy) and ~26 weeks estimated gestational age (Late Pregnancy). Data points with letters in common are not statistically different from one another. Repeated measures ANOVAs indicated a significant effect of time on urine cotinine and CPD but not CO. Data points with letters in common were not statistically different from one another in post hoc analyses. Adapted from "Correspondence between Self-Report and Biochemical Measures of Cigarette Use in Pregnant Women" by S. H. Heil, L. J. Solomon, J. M. Skelly, I. M. Bernstein, & S. T. Higgins, presented at the College on Problems of Drug Dependence Annual meeting, June 2015.

Prior studies of the correspondence between self-report and biochemical measures of smoking in pregnant women have often reported similar discrepancies and have frequently hypothesized that (1) inaccurate self-report, (2) changes in metabolism, and/or (3) changes in smoking topography account for these inconsistencies (Boyd, Windsor, Perkins & Lowe, 1998; Dukic, Niessner, Benowitz, Hans, & Wakschlag, 2007; Ellard, Johnstone, Prescott, Ji-Xian, & Jian-Hua, 1996; Klebanoff, Levine, Clemens, DerSimonian, & Wilkins, 1998; Lindqvist, Lendahls, Tollbom, Aberg, & Hakansson, 2002; Pickett, Rathouz, Kasza, Wakschlag, & Wright, 2005). In the sections that follow, current knowledge about each of these potential explanations is briefly reviewed.

Inaccurate Self-Report among Pregnant Smokers. As with the use of any drug, it is not recommended to rely on self-report of smoking as participants may be unable or unwilling to accurately report use (Connor Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009; Magura & Kang, 1996; National Institute of Drug Abuse, 2012). As a result, self-report is often verified by biochemical markers of smoking like breath CO and urine cotinine. Many studies have examined the relationship between self-report and biochemical markers of smoking among pregnant women and used these data to estimate the rate of inaccurate reporting in terms of smoking status (i.e., differentiating smokers from nonsmokers) as well as smoking rate (e.g., differentiating lighter, moderate, and heavier smokers from each other). One review of 15 studies found that the rate of inaccurate self-report of smoking status ranged between 0-35%, with a median of 21% (Russell, Crawford, & Woodby, 2004). There are fewer studies examining smoking rate, but similar to smoking status, correlations between CPD and biochemical markers tend to vary widely, with a range of .32 - .74 and a median of .44 (Boyd et al., 1998; Ellard et al., 1996; Klebanoff et al. 1998; Pickett et al., 2005). Given strong social stigma against smoking during pregnancy, it is not surprising that pregnant women might underreport smoking status and rate. But because estimations of underreporting are based on studies of the relationship between self-report and levels of biochemical markers, and levels of biochemical markers could be altered by metabolism and topography differences during pregnancy, it has remained unclear how much of the discrepancy between self-report and biochemical markers is due to true inaccurate self-report and how much could be due to confounding changes in metabolism and/or smoking topography. In fact, most of the studies in this literature have used biochemical cut points that were based on cut points established for non-pregnant smokers as there were few data on metabolism and topography during pregnancy to guide adjustments. In the next two sections, the extant data on metabolism and topography during pregnancy are reviewed.

Changes in Metabolism among Pregnant Smokers. Dempsey and colleagues conducted the seminal study of nicotine and cotinine metabolism during the perinatal period. In this within-subject study, pregnant women were admitted inpatient and infused with labeled nicotine and cotinine to determine the pharmacokinetics of each drug. The procedure was then repeated during the postpartum period. Given the common report of substantial smoking reductions among pregnant women, the authors hypothesized that nicotine and cotinine metabolism would be slower during pregnancy. Surprisingly, the data indicated higher rates of metabolism during pregnancy as compared to postpartum (Dempsey et al., 2002). For example, nicotine clearance was 60% faster during pregnancy vs. postpartum. While this study documented this change for the first time, the design of the study left the timing of the change unclear.

A recent longitudinal cohort study by Bowker and colleagues (2015) begins to help clarify the timing (Bowker, Lewis, Coleman & Cooper, 2015). Rather than infusing nicotine and directly measuring subsequent metabolism, these investigators used a simple, but validated, method to estimate nicotine metabolism in biological matrices known as the nicotine metabolite ratio (NMR; Dempsey et al., 2004; Levi, Dempsey, Benowitz, & Sheiner, 2007). NMR is calculated by dividing the level of trans-3'-hydroxycotinine, the primary metabolite of cotinine, by the level of cotinine. In the Bowker et al. (2015) study, pregnant women (N=101) were asked to provide saliva samples at three time points throughout their pregnancy and twice postpartum. Each sample was assayed for trans-3'-hydroxycotinine and cotinine and an NMR was calculated. Compared to their NMR at 12 weeks postpartum, NMR approached statistical significance at 8-14 weeks and was significantly higher at 18-22 and 32-36 weeks estimated gestational age, but was lower and not significantly different at 4 weeks postpartum. These results confirm Dempsey et al.'s findings of higher rates of metabolism during pregnancy and further suggest that nicotine metabolism accelerates very early in the pregnancy, remains elevated throughout the pregnancy, and returns to lower levels early in the postpartum period.

More recently, our group examined the time course of NMR changes during pregnancy and postpartum. Forty-six women enrolled in a trial to test the effectiveness of financial incentives to increase abstinence among pregnant smokers and who continued to smoke during pregnancy and into postpartum provided urine samples at two assessments during pregnancy at ~10 weeks and ~28 weeks estimated gestational age and one assessment at 6 months postpartum. Consistent with the two earlier reports, NMR was significantly higher at both pregnancy assessments compared to the postpartum assessment. Additionally, NMR was significantly higher at the later pregnancy assessment compared to the earlier pregnancy assessment, adding credence to the borderline trend observed by Bowker and colleagues. Since metabolism appears to increase throughout the antepartum period, it is unlikely that metabolism differences explain the discrepancies between self-report and biochemical measures of smoking described above.

Changes in Smoking Topography among Pregnant Smokers. To our knowledge, there are no data examining smoking topography in pregnant smokers. However, data from non-pregnant smokers suggests that reductions in CPD like those reported by pregnant smokers might lead to changes in smoking topography. In a rigorous laboratory study on this topic, participants who normally smoked 37 CPD during unrestricted use were given only 15, 10 and 5 cigarettes a day while residing on an inpatient clinical research ward (Benowitz, Jacob, Kozlowski & Yu, 1986). Researchers collected urine and blood samples at regular intervals to measure changes in the levels of tar (a toxic byproduct of combusted tobacco), nicotine, and carboxyhemoglobin (indicative of decreased oxygen delivery throughout the body). Of particular interest here are the changes in these measures of cigarette exposure when participants went from smoking 37 CPD to 15 CPD, a 60% reduction, as this reduction most closely approximates the 50% reduction typically reported by pregnant smokers upon learning of pregnancy (Heil et al., 2014 and Figure 1 in this document). When participants in the Benowitz et al. study decreased their CPD by 60%, tar, nicotine, and carboxyhemoglobin levels only decreased by 15%, 32%, and 26%, respectively (Figure 3). While statistically significant, these decreases were not proportional to the reduction in CPD. It was also notable that none of the participants reported any difficulty smoking just 15 CPD, with some participants quoted as saying it was "no hardship" and that it was "very easy". Similar, but more extreme results were observed when smokers were limited to 10 and 5 CPD (73% and 86% reductions, respectively). The authors concluded that participants changed their smoking topography when the number of CPD was limited, likely by puffing on each cigarette more frequently and/or more intensely, to maintain their desired nicotine blood levels.

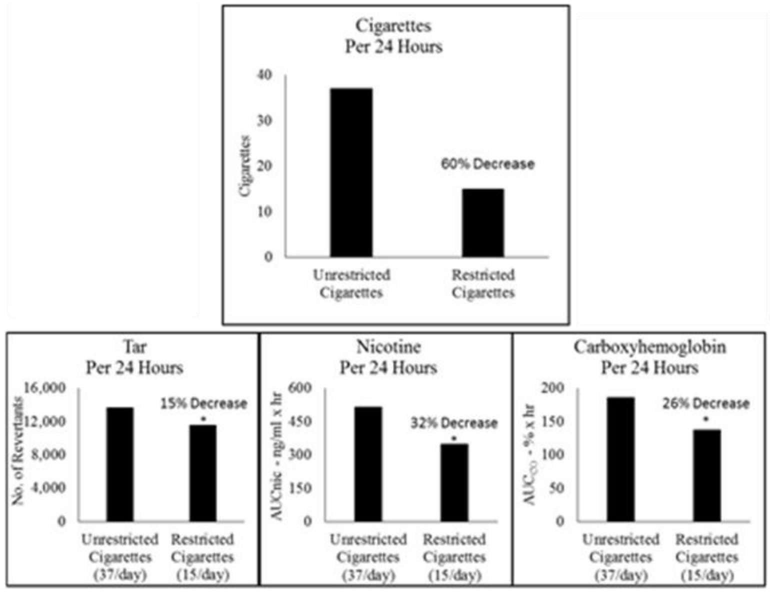

Figure 3. Percent change in cigarettes, tar, nicotine and carboxyhemoglobin per 24 hours during unrestricted and restricted cigarette use. Significant differences are indicated by an asterisk. Adapted from "Influence of smoking fewer cigarettes on exposure to tar, nicotine and carbon monoxide." By N. L. Benowitz, P. Jacob, L. T. Kozlowski, & L. Yu, 1986, *The New England Journal of Medicine, 315*, 1310-1316.

A similar conclusion was reached in a more naturalistic longitudinal analysis of cross-sectional data collected in the National Health and Nutrition Examination Survey. The authors compared daily CPD and levels of serum cotinine in nationally representative samples of cigarettes smokers assessed between 1988-1994 to those assessed between 1999-2012 (Jarvis, Giovino, O'Connor, Kozlowski & Bernert, 2014). The results indicated that mean CPD decreased significantly over time from 17.3 to 13.9 CPD, a 20% reduction, very similar to the changes reported by pregnant smokers in early pregnancy (Heil et al., 2015 and Figure 2 in this document). However, serum cotinine levels were not significantly different, decreasing from 223.7 to just 219.2 ng/ml, a 2% reduction. The authors conclude that these results are suggestive of increased inhalation to offset reduced cigarette consumption. Together, the results of these two studies suggest that smokers maintain nicotine exposure after reducing their CPD by engaging in compensatory smoking, which in turn continues to expose them to similar levels of toxicants.

Current Study

Whether changes in smoking topography help account for the apparent discrepancies between self-reported CPD and biochemical markers of smoking among pregnant smokers has not been examined to date to our knowledge. If it is determined that pregnant women do smoke cigarettes more intensely than non-pregnant women, these changes may offset presumed benefits of reductions in self-reported CPD.

Chapter 1

Comparing Smoking Topography of Usual Brand Cigarettes

in Pregnant and Non-Pregnant Smokers

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ABSTRACT

Introduction: Most pregnant smokers report abruptly reducing their cigarettes per day (CPD) by ~50% shortly after learning of pregnancy and of making further smaller reductions over the remainder of their pregnancy. Laboratory and naturalistic studies with non-pregnant smokers have found that these types of reductions often lead to changes in smoking topography (i.e., changes in smoking intensity to maintain a desired blood-nicotine level). [19, 20] If pregnant women engage in compensatory smoking, they may expose themselves and their offspring to the same level of toxicants despite reporting reductions in CPD.

Methods: Pregnant and non-pregnant female smokers (n = 17 and 91, respectively) participated. At the experimental session, after biochemical confirmation of acute abstinence, all participants smoked one of their usual brand cigarettes ad lib through a Borgwaldt CReSS Desktop Smoking Topography device. Carbon monoxide (CO) and measures of nicotine withdrawal, craving, and reinforcement derived from smoking were also collected.

Results: The two groups did not differ on any demographic or smoking characteristics at screening, except nicotine metabolism rate, which as expected, was faster in pregnant smokers. Analyses suggest that none of the smoking topography parameters differed between pregnant and non-pregnant smokers, although pregnant smokers had a significantly smaller CO boost. Both groups reported similar levels of relief of withdrawal and craving after smoking, but other self-report data suggest that pregnant smoker find smoking less reinforcing than non-pregnant smokers.

Conclusions: Pregnant smokers do not smoke cigarettes differently as compared to non-pregnant female smokers, but appear to find smoking less reinforcing.

INTRODUCTION

Maternal cigarette smoking is the leading preventable cause of poor pregnancy outcomes.[1] Despite this, approximately 15% of pregnant women are regular cigarette smokers. Fifty percent reductions in cigarettes per day (CPD) in early pregnancy have been reliably reported across many studies.[2-6] In one study by our group, pregnant women self-reported that the bulk of this change in smoking behavior takes place within the first few days after learning of their pregnancy.[7] Surprisingly, this reduction in CPD occurs despite an increase in the metabolism of nicotine during pregnancy;[8, 9] in non-pregnant populations, higher rates of nicotine metabolism are associated with smoking more CPD.[10]

While pregnant smokers report making reductions in CPD to reduce harm to their offspring,[11] previous research indicates that self-reported reductions do not necessarily correspond with toxicant reduction. Data from our research group indicate that self-reported reductions in CPD among pregnant smokers enrolled in a clinical trial to increase abstinence with financial incentives are not always paralleled by the same level of reduction in biochemical markers of smoking.[12] Specifically, despite having reported a one third reduction in CPD between 10 weeks and 14 weeks gestation, urine cotinine levels among those pregnant smokers reduced by only 10% and carbon monoxide (CO) levels remained unchanged. Research by others tells a similar story: correlations between CPD and biochemical markers tend to vary widely among pregnant smokers, with a range across reports of .32 - .74 and a median of .44.[13-16]

One commonly cited potential explanation for variations in the relationship between nicotine exposure and CPD is that pregnant smokers change their smoking topography (e.g., increase the number of puffs per cigarette, the duration of each puff, the volume of each puff, etc.) in an effort to maintain the same blood nicotine level despite smoking fewer CPD (i.e., compensatory smoking).[13-18] To our knowledge, no studies have examined smoking topography among pregnant smokers, but evidence from laboratory studies and naturalistic studies with non-pregnant smokers report similar discrepancies between the level of reduction in CPD and the level of reductions in smoking biomarkers that have been attributed to changes in smoking topography.[19, 20] If pregnant women engage in compensatory smoking, they may expose themselves and their offspring to the same level of toxicants despite reporting reductions in CPD. The present study compared the smoking topography of usual brand cigarettes in non-pregnant women of low socioeconomic status (SES) to pregnant smokers who have reported reductions in their CPD since learning of their pregnancy.

METHOD

Participants and Inclusion/Exclusion Criteria

Pregnant and non-pregnant smokers were recruited via ads on Facebook, Craigslist, and in local newspapers; flyers on community bulletin boards; and from a local OB/GYN clinic. All potential participants completed a brief phone screen and those who appeared eligible were invited to attend an in-person screening session to determine final eligibility. After providing informed consent, participants submitted breath samples

(Micro+ Smokerlyzer; coVita/Bedfont, Haddonfield, NJ) and urine samples (NicAlert cotinine test strip; Nymox, Hasbrouck Heights, NJ) to verify smoking status. Urine was also tested to determine pregnancy status and to quantify cotinine levels via enzyme immunoassay (MGC240; Microgenics, Fremont, CA). Additionally, participants provided saliva samples which were analyzed for cotinine and trans-3'-hydroxycotinine (3-HC), the major metabolite of cotinine. 3-HC was divided by cotinine to calculate a nicotine metabolite ratio (NMR), which is strongly correlated with nicotine clearance.[21]

Next, potential participants completed demographic (e.g., age, race/ethnicity, education, marital status, etc.) and medical history questionnaires developed in our laboratory, and then filled out a series of standardized questionnaires about their tobacco use, including the Fagerström Test for Nicotine Dependence [22-24] (see Appendix A).

Eligible non-pregnant participants had to self-report smoking at least 5 CPD for the past year and have an intake breath CO sample > 8 ppm. There was no minimum CPD or breath CO level for the pregnant participants. Rather, smoking status was confirmed among pregnant participants with a urine cotinine value > 100 ng/ml (> 2 on NicAlert strip). Low SES was also an inclusion criterion because socioeconomically disadvantaged women are at increased risk for (1) smoking, (2) nicotine dependence, (3) smoking more CPD, (4) smoking higher nicotine yield cigarettes and (5) continuing to smoke after becoming pregnant. [25, 26] Education level served as a proxy for SES and all participants had to have less than an Associate's degree. Individuals were excluded if they reported exclusively rolling their own cigarettes, if they reported using other tobacco or nicotine products more than 9 days in the last 30 days, if they reported intentions to quit in the next 7 days if pregnant and 30 days if non-pregnant, or if they reported any smoking cessation product use in the last 30 days. All participants were without current serious mental disorder. Participants also could not show evidence of recent illicit drug use, but opioid-dependent women who were stable in opioid agonist maintenance treatment were eligible. "Stable" was defined as having (1) >70% of urine drug screens in the past month negative for all drugs of abuse and (2) been on the same methadone or buprenorphine dose for the past 7 days if pregnant and 30 days if not pregnant. Pregnant women experience an acceleration in the metabolism of opioid agonist medication during pregnancy, so dose increases to prevent opioid withdrawal are not uncommon.[27, 28]. Stability in treatment was confirmed with treatment providers. All potential participants were compensated $50 for completing the screening session.

Procedures

If deemed eligible, participants were invited back for an experimental session. Participants were instructed to abstain prior to the session and had to meet at least a 50% reduction in their screening breath CO level in order to begin the experimental session; this criterion is widely used as a marker of acute abstinence in smoking research.[29, 30] After abstinence was confirmed, all participants took two puffs from their usual brand cigarette to equate time since last cigarette. Thirty minutes after taking two puffs, participants smoked one usual brand cigarette through a CReSS Desktop smoking topography device (Borgwaldt, Richmond, VA) with no instruction (i.e., *ad libitum* puffing) (see Appendix B). The device measured and recorded a number of smoking topography parameters, namely: (1) number of puffs per cigarette, (2) puff duration, (3) inter-puff interval, (4) puff volume and (5) maximum puff velocity (see Appendix C). The CReSS smoking topography device has been shown to have good reliability and validity.[31, 32] This part of the session took place in a room with a ventilation system specifically designed to allow for cigarette smoking indoors.

Immediately after smoking the cigarette, participants completed the modified Cigarette Evaluation Questionnaire (mCEQ). The mCEQ consists of 12 items which query how smoking the cigarette made the participant feel (e.g., “Did the cigarette taste good?”, “Did the cigarette help you concentrate?”) (see Appendix D). [33] Designated items are averaged to generate five subscale scores, namely (1) Satisfaction, (2) Psychological Reward, (3) Aversion, (4) Enjoyment of Respiratory Tract Sensations and (5) Craving Reduction. The measure has demonstrated good reliability and validity. [34]

CO was collected in 15-minute increments in the hour that followed smoking to assess CO boost, another measure of smoke exposure and intensity of smoking.[35, 36] To measure CO boost, pre-cigarette CO was subtracted from each CO value measured after smoking the cigarette. Withdrawal and craving were also measured in 15-minute increments using the Minnesota Nicotine Withdrawal Scale (MNWS) and Questionnaire of Smoking Urges-Brief Scale (QSU). The MNWS measured eight nicotine withdrawal symptoms (e.g., craving, irritability, anxiety) (see Appendix E).[37-39] Mean withdrawal is derived as the average of seven of the eight symptoms (range, 0-4), with the item “Desire or Craving to Smoke" analyzed separately.[40] Previous studies have shown this measure has good reliability and validity.[37-39] The QSU is comprised of 37 statements indicating current cravings to smoke (e.g., "A cigarette would taste good right now.", "I could control things better right now if I could smoke.") (see Appendix F). [41, 42] The instrument is scored such that two factors are derived, with Factor 1 often described as a measure of the positive reinforcing effects of smoking and Factor 2 a measure of the negative reinforcing effects of smoking. Previous studies have indicated that it is a reliable and valid measure of smoking urges.[42, 43]

Participants were compensated for their time and for successfully abstaining prior to the experimental session. Pregnant participants ended their participation after this session. For non-pregnant women, this session was their first in a larger 14-visit study designed to test the acute effects of cigarettes with varying nicotine levels. Data from later sessions completed by non-pregnant women have been reported elsewhere.[44]

Statistical Method

Independent t-tests and Fisher's exact tests were used to compare demographic and smoking characteristics between the two groups.

All topography measures were log-transformed to meet normal distribution requirements so that parametric tests could be used to compare the two groups. Smoking topography measures were compared using independent t-tests. To explore whether topography changes as a function of increasing gestational age, a Pearson productmoment correlation coefficient was computed to assess whether estimated gestational age (EGA) and any of the smoking topography parameters were related.

The five mCEQ subscales were compared between pregnant and non-pregnant smokers using independent t-tests. CO boost, mean total MNWS score, MNWS item 'desire to smoke', QSU Factor 1 and QSU Factor 2 were compared between the two groups and across time points using repeated measures analysis of variance, with time as the within-subjects factor and pregnancy status as the between-subject factor. CO boost was also characterized and compared using area under the curve. To do so, trapezoids were constructed with the x- and y-axis coordinates for each data point and the combined area of the three trapezoids summed.

Significance for all tests was set at $p < .05$.

RESULTS

Participant Characteristics

Seventeen pregnant and 91 non-pregnant female smokers completed the experimental session. The two groups were remarkably similar on demographic and smoking characteristics. On average, participants were 30 years old, Caucasian, had a high school education or less, and were unmarried (Table 1). Women in both groups had an average body mass index of 33, which falls in the overweight range. One-third of participants were opioid-maintained. Pregnant smokers were 24 weeks EGA on average. All but one of the smoking characteristics examined did not differ significantly between groups. At screening, both groups reported smoking approximately 14 CPD, with pregnant women reporting cutting down from smoking 22 CPD prior to pregnancy (a 43% reduction). Women in both groups also tended to smoke high nicotine yield, non-menthol cigarettes, had moderate levels of nicotine dependence, started smoking around 15 years of age and had average urine cotinine levels of 850 ng/ml. The only significant difference between groups was on NMR, which was, as expected, significantly higher among pregnant smokers as compared to non-pregnant smokers ($p = .01$). [8, 9]

Smoking Topography

There were no statistically significant differences in smoking topography between pregnant and non-pregnant women, with differences across parameters averaging less than 5% (Figure 1). Within the pregnant smoker sample, there were no significant correlations between EGA and topography measures.

CO boost was significantly higher in non-pregnant as compared to pregnant smokers ($p < .05$) and decreased in a parallel fashion in both groups over time ($p < .001$; Figure 2). Area under the curve analyses indicated CO boost was 24% higher among non-pregnant as compared to pregnant smokers ($p < .05$).

mCEQ

Of the five subscales, only the Satisfaction subscale was significantly different, with lower scores among pregnant women as compared to non-pregnant women ($p < .001$; Figure 3). Although not significant, pregnant women also trended towards higher scores on the Aversion subscale and lower scores on the Enjoyment of Respiratory Tract Sensations subscale as compared to non-pregnant women (*p*s = .06 and .07, respectively).

MNWS

There were no significant differences between groups on mean MNWS scores or on the MNWS item "Desire or Craving to Smoke". Both groups did report significant changes over time on these measures, with decreased scores 15 min after smoking the cigarette followed by increasing scores across subsequent time points ($p < .001$; Figure 4, top panel). This U-shaped function is consistent with acute relief of withdrawal after smoking a cigarette.

QSU

There were significant differences between groups on both QSU Factor 1 and QSU Factor 2 scores. While scores on both factors appeared equivalent in both groups prior to smoking a usual brand cigarette through the CReSS device, after smoking, pregnant women reported significantly lower positive and negative reinforcing effects of smoking as compared to non-pregnant smokers (*p*s < .001; Figure 4, bottom panel). Scores in both groups then increased in a parallel fashion across subsequent time points on both factors (*p*s < .001; Figure 4, bottom panel).

DISCUSSION

To our knowledge, this was the first study comparing the smoking topography of pregnant and non-pregnant smokers. Despite reporting decreases in their CPD and experiencing increases in nicotine metabolism rate, there were no differences in smoking topography between pregnant and non-pregnant female smokers. Although no differences were observed on any topography parameters, pregnant smokers had a smaller CO boost, suggesting they may experience less toxicant exposure per cigarette. This smaller CO boost may be explained by changes in the respiratory system during pregnancy that are a response to increased demand for oxygen for the fetus and the mother. [45] These adaptations are largely facilitated by hormonal and anatomical changes. For example, progesterone has been shown to heighten central nervous system chemoreceptor sensitivity to CO_2. As another example, as the uterus expands, the diaphragm elevates and the subcostal angle (the upside-down 'V' shaped section below the sternum) widens. Together, these changes lead to a decreased residual volume (the air left in the lungs after an exhale) and increased inspiratory capacity (the amount that can be inhaled after normal expiration), thereby increasing overall tidal volume (the total amount of air in one inhale and one exhale combined). Since there were no differences in smoking topography between groups in the present study, it suggests that pregnant smokers take in the same amount of cigarette smoke, including CO, from smoking one cigarette as non-pregnant smokers. However, because pregnant smokers have a larger tidal volume, more CO can be exhaled with every breath, leading to a smaller CO boost. Observation of a smaller CO boost is also consistent with evidence from our group and others suggesting that CO levels associated with abstinence are lower in pregnant smokers compared to non-pregnant smokers.[46, 47] In sum, it appears that pregnant smokers may experience less exposure to toxicants like CO after smoking, although not by way of changes in smoking topography.

Across self-report questionnaires, two overarching findings emerged. The first was that both groups experienced similar levels of relief from withdrawal and craving after smoking, with consistent results from the mean total MNWS and the mCEQ Psychological Reward subscale (despite the title, four of the five items on this subscale ask about withdrawal symptoms also queried on the MNWS) regarding withdrawal and consistent results from the MNWS "Desire or Craving to Smoke" item and the mCEQ Craving Reduction subscale regarding craving. The second overarching finding was that multiple self-report measures suggested that pregnant smokers do not find smoking as reinforcing (either positively or negatively) as non-pregnant smokers. QSU Factor 1 and 2 scale scores, measures of the positive and negative reinforcing effects of smoking, were lower among pregnant smokers, as were mCEQ Satisfaction subscale scores. The observation of trends towards lower scores on mCEQ Enjoyment of Respiratory Tract Sensations subscale and higher scores on mCEQ Aversion subscale among pregnant smokers added to this overall picture of smoking being less reinforcing for this group. It is possible that decreases in the overall enjoyment of cigarette smoking facilitates the substantial reductions most female smokers report during pregnancy and may also explain why they do not engage in compensatory smoking following such dramatic reductions.

It was surprising that baseline cotinine levels did not differ between pregnant and non-pregnant smokers. While both groups reported smoking about the same number of CPD, NMR was 30% faster among pregnant smokers, suggesting that their cotinine levels should have been lower if they were smoking approximately the same number of CPD and given no differences in smoking topography. This discrepancy suggests that there may still be some social pressure on pregnant smokers to underreport their level of smoking even if they are not seeking treatment and have declared they do not have intentions of quitting for at least another week.

The present data provide a unique opportunity to explore potential differences in exposure between the socioeconomically disadvantaged women who participated in the current study and general population smokers. One prior study that collected smoking topography measures in general population male and female smokers (education level not specified) under conditions similar to the present study (i.e., same smoking topography device, following acute abstinence) reported that they had a total puff volume (average puff volume X average number of puffs) of 553 ml.[31] In comparison, the socioeconomically disadvantaged pregnant and non-pregnant smokers in the current study had average total puff volumes of 782 ml and 808 ml, respectively, approximately 30% higher. As previously described, socioeconomically disadvantaged women are known to be at increased risk for (1) smoking, (2) nicotine dependence, (3) smoking more

CPD, (4) smoking higher nicotine yield cigarettes and (5) continuing to smoke after becoming pregnant, all of which contribute to worse health outcomes in this population.[31, 32] The present data suggest that how they smoke may also contribute to these poor outcomes.

These findings should be considered in light of some limitations. First, the pregnant sample in this study is relatively small. However, previous studies with similar sample sizes have found differences in smoking topography.[31, 48] Additionally, the control group was closely matched on a number of demographic and smoking characteristics which eliminated variability that may have made it more difficult to detect differences between the groups. Furthermore, the differences in topography measures between non-pregnant and pregnant smokers were relatively small (< 5% on average), which does not suggest that the study was underpowered. Another potential limitation involves collecting smoking topography data through the CReSS device in a laboratory setting. Research is inconsistent on whether smoking a cigarette in an artificial laboratory environment alters smoking behavior.[49, 50] Even if smoking through the CReSS device is not perfectly representative of smoking in the natural environment, the fact that both groups smoked through these devices allows relative comparisons of their smoking topography to be made.

This study has notable strengths and makes a contribution to the scientific literature. To our knowledge, it is the first study to capture a variety of variables during a single cigarette smoking bout among pregnant smokers. Specifically, this study documented (1) smoking topography of usual brand cigarettes, (2) changes in CO in the hour that followed smoking, and (3) subjective effects of this smoking bout. Most noteworthy among these is smoking topography. For the past 20 years, researchers have speculated about whether pregnant smokers engage in compensatory smoking. This was the first study to directly address this question. In addition, a large sample of non-pregnant female smokers who did not differ from the pregnant smokers on important demographic or smoking characteristics was included for comparison. More generally, the present study speaks to the importance of using a variety of approaches to research smoking during pregnancy. The overwhelming majority of the research conducted to date has been randomized controlled trials testing interventions to promote cessation during pregnancy. While this is understandable to some degree given the serious adverse consequences of smoking during pregnancy, a recent Cochrane Review found 72 such trials conducted over more than 30 years with more than 20,000 pregnant smokers and reported that these interventions have only produced an average 6% increase in abstinence compared to control conditions.[51] The present study underscores the importance of conducting laboratory and other types of studies to help better understand smoking during pregnancy, research that may lead to more efficacious treatments in the future.

There are a number of future directions that could be explored. First, in regards to studying smoking topography during pregnancy, future studies should replicate this study in different contexts. For example, smoking topography can be measured using a portable version of the CReSS device used in the present study that can be sent home with participants to record data across multiple smoking bouts in the participant's normal smoking environment. These studies would help validate the findings reported in this paper. Additional studies are also needed to more firmly establish the relationship between CPD and biochemical markers of smoking during pregnancy. A recent study by Denlinger and colleagues (2016) assessed non-pregnant smokers in a controlled, but not entirely artificial, environment (i.e., a hotel that permitted smoking) for 5 days.[52] This study allowed researchers to precisely quantify how many CPD participants smoked and the levels of cotinine and other biomarkers that resulted. A similar study with pregnant women could generate population estimates that could be used for research and clinical purposes.

In summary, results of the present study suggest that the smoking topography of pregnant smokers does not differ from that of non-pregnant female smokers and that pregnant smokers find smoking less reinforcing. These changes in reinforcement may help pregnant smokers make the substantial reductions in CPD typically reported during pregnancy and may also protect them from engaging in compensatory smoking.

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Table 1. Demographics and smoking characteristics.

	Pregnant (n=17)	Non-Pregnant (n=91)	*p* value
Demographics			
Age	30.4 ± 4.9	30.2 ± 7.0	.89
% White	94	96	.55
% High school graduate or less	59	52	.56
% Never married	71	57	.62
Body mass index	34.8 ± 22.2	31.1 ± 6.6	.18
% Opioid-dependent	41	32	.58
Estimated weeks gestational age	24.1 ± 9.5	N/A	
Smoking Characteristics			
Pre-pregnancy cigarettes per day	22.4 ± 8.5	N/A	
Cigarettes per day at screening	12.9 ± 5.8	15.3 ± 5.7	.12
Nicotine yield for usual brand cigarette	1.0 ± 0.4	1.1 ± 0.2	.59
% Menthol	25	24	.98
Fagerström Test for Nicotine Dependence	4.1 ± 0.5	4.6 ± 2.2	.35
Age first started smoking	14.7 ± 3.5	15.6 ± 3.0	.26
Biochemical Measures			
Urine cotinine (ng/ml)	785.4 ± 546.2	920.5 ± 488.7	.27
Nicotine metabolite ratio	0.62 ± 0.29	0.46 ± 0.35	.01

Note: Values in the table are reported as means ± standard deviations unless otherwise noted. Nicotine yield values come from the Federal Trade Commission's Tar, Nicotine and Carbon Monoxide Report from 1999-2005. Nicotine metabolite ratio was log-transformed prior to statistical comparison.

Figure Legends

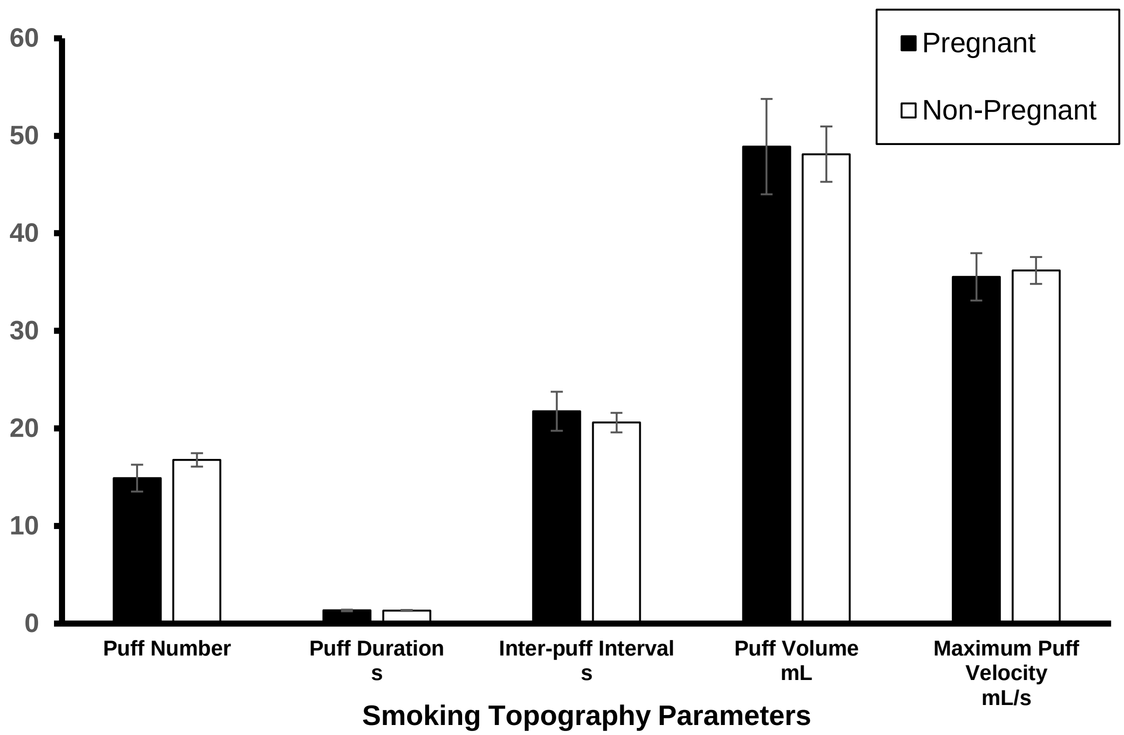
Figure 1. Mean ± SEM for smoking topography parameters for pregnant and non-pregnant smokers as measured by the CReSS Desktop Smoking Topography device. There were no significant differences between groups on any parameter.

Figure 2. Mean ± SD CO boost at 15, 30, 45 and 60 minutes after pregnant and non-pregnant smokers smoked one usual brand cigarette. There were significant effects of group and time (*p*s < .05), but no interaction.

Figure 3. Mean ± SEM Modified Cigarette Evaluation Questionnaire subscale scores immediately after smoking usual brand cigarettes in pregnant and non-pregnant smokers. An asterisk (*) indicates a significant effect of group ($p < .001$).

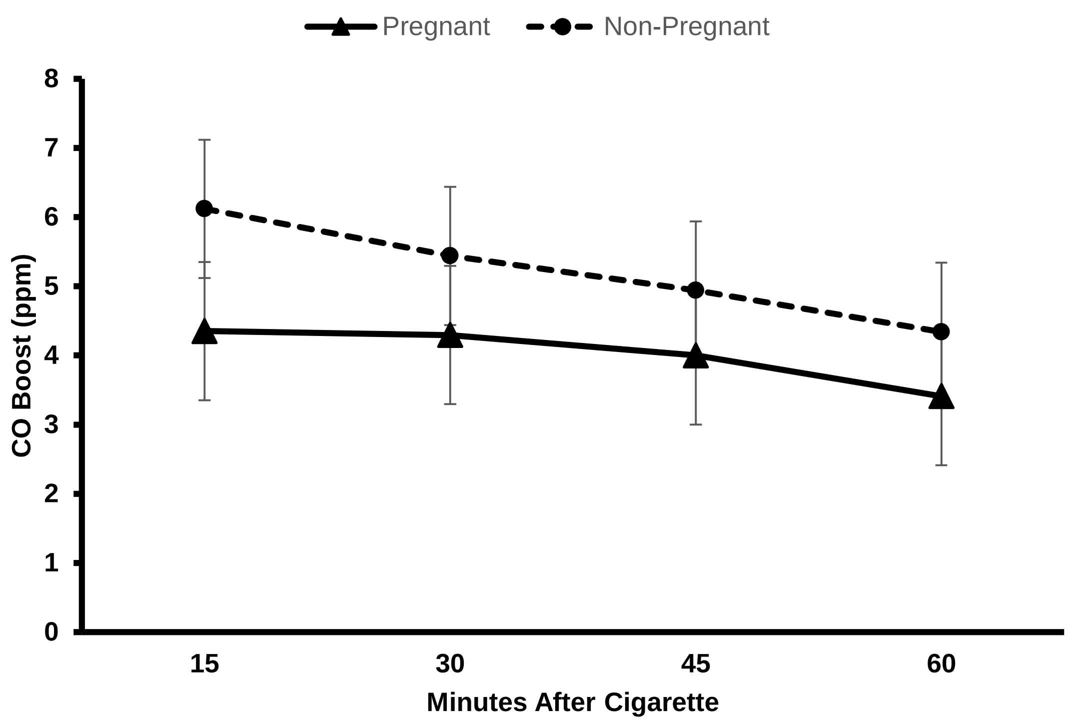
Figure 4. Mean ± SEM scores for the Minnesota Nicotine Withdrawal Scale (MNWS) total score (top left panel), MNWS item 'desire or craving to smoke' (top right panel), and Questionnaire of Smoking Urges (QSU) Factor 1 and QSU Factor 2 (bottom left and right panels, respectively) before and 15, 30, 45 and 60 minutes after pregnant and non-pregnant smokers smoked one usual brand cigarette. There was a significant effect of time on all measures. There was also a significant effect of group for QSU Factors 1 and 2 (*p*s < .01), but not on MNWS measures, nor were there any interactions.

Figure 1.



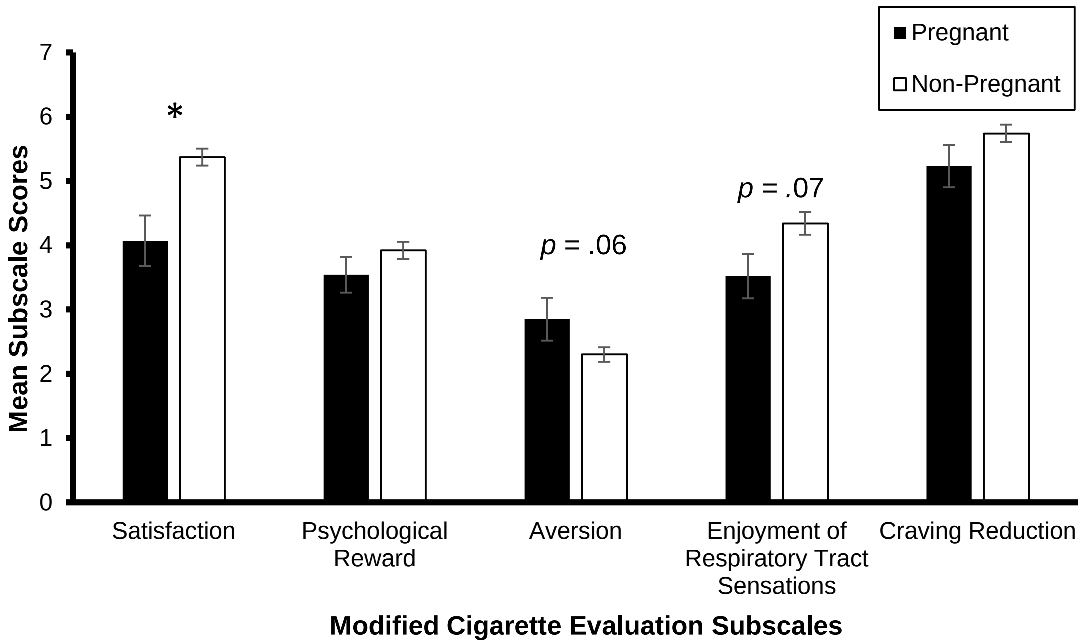
Pregnant
Non-Pregnant
60
50
40
30
20
10
0
Puff Number
Puff Duration s
Inter-puff Interval s
Puff Volume mL
Maximum Puff Velocity mL/s
Smoking Topography Parameters

Figure 2.



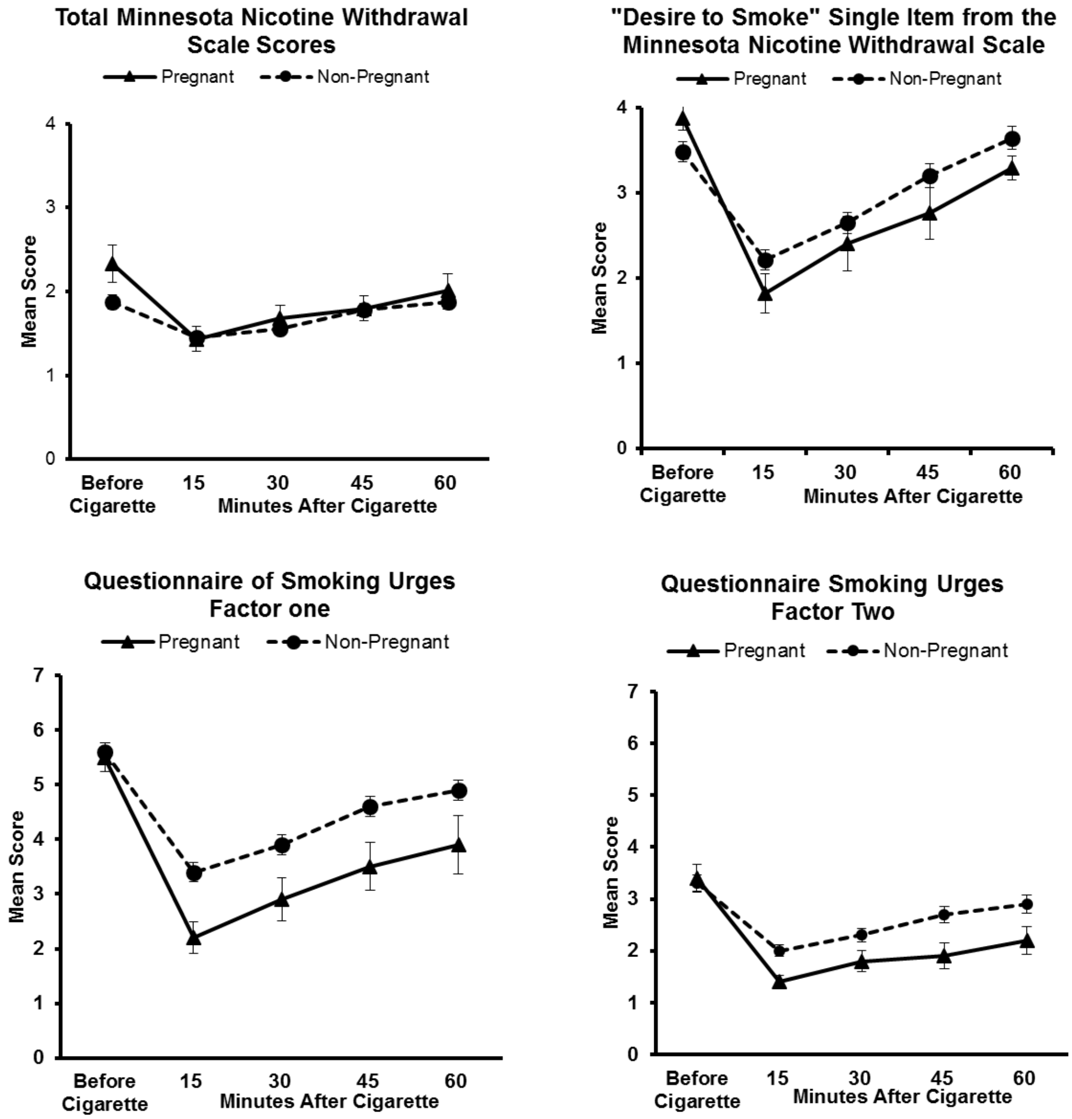
Pregnant
Non-Pregnant
8
7
6
5
4
3
2
1
0
CO Boost (ppm)
15
30
45
60
Minutes After Cigarette

Figure 3.



Pregnant
Non-Pregnant
Mean Subscale Scores
7
6
5
4
3
2
1
0
*
p = .06
p = .07
Satisfaction
Psychological Reward
Aversion
Enjoyment of Respiratory Tract Sensations
Craving Reduction
Modified Cigarette Evaluation Subscales

Figure 4.



Total Minnesota Nicotine Withdrawal Scale Scores
Pregnant
Non-Pregnant
Mean Score
0
1
2
3
4
Before Cigarette
15
30
45
60
Minutes After Cigarette
"Desire to Smoke" Single Item from the Minnesota Nicotine Withdrawal Scale
Pregnant
Non-Pregnant
Mean Score
0
1
2
3
4
Before Cigarette
15
30
45
60
Minutes After Cigarette
Questionnaire of Smoking Urges Factor one
Pregnant
Non-Pregnant
Mean Score
0
1
2
3
4
5
6
7
Before Cigarette
15
30
45
60
Minutes After Cigarette
Questionnaire Smoking Urges Factor Two
Pregnant
Non-Pregnant
Mean Score
0
1
2
3
4
5
6
7
Before Cigarette
15
30
45
60
Minutes After Cigarette

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Appendix A

Fagerström Test for Nicotine Dependence

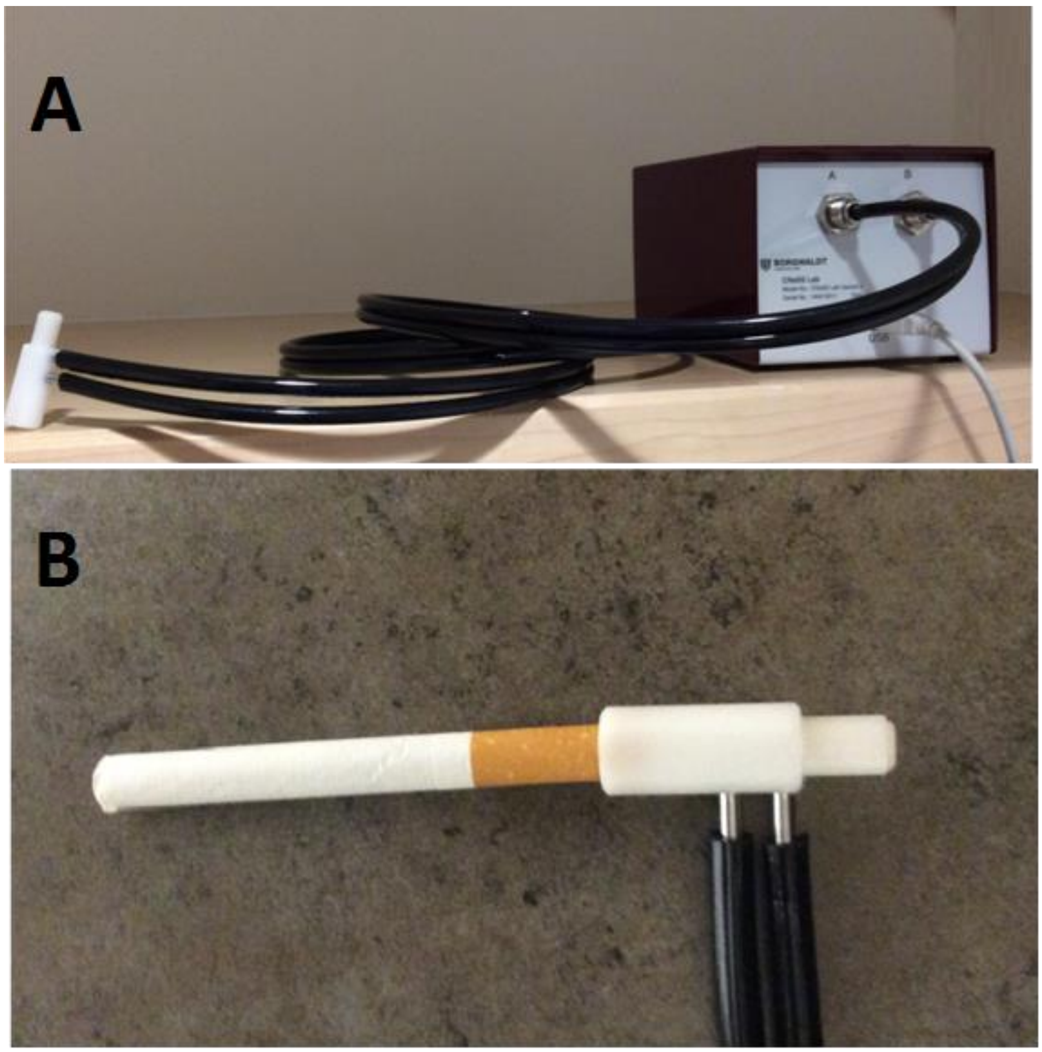
Description: A 6-item measure of intensity of nicotine dependence. Yes/no items are scored 0 or 1 and multiple choice items are scored from 0 to 3. Total scores are calculated by summing the score of all items and can range from 0-10. Higher scores indicate greater nicotine dependence.

1. How soon after you wake up do you smoke your first cigarette?	☐ 0-5 minutes ☐ 6-30 minutes ☐ 31-60 minutes ☐ More than 60 minutes
2. Do you find it difficult to refrain from smoking in places where it is forbidden (such as in church, at the library, theater or doctor's office)?	☐ Yes ☐ No
3. Which cigarette would you hate most to give up?	☐ The first one in the morning ☐ Any other
4. How many cigarettes a 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 when you are so ill that you are in bed most of the day?	☐ Yes ☐ No

Appendix B

CReSS Desktop Smoking Topography Device

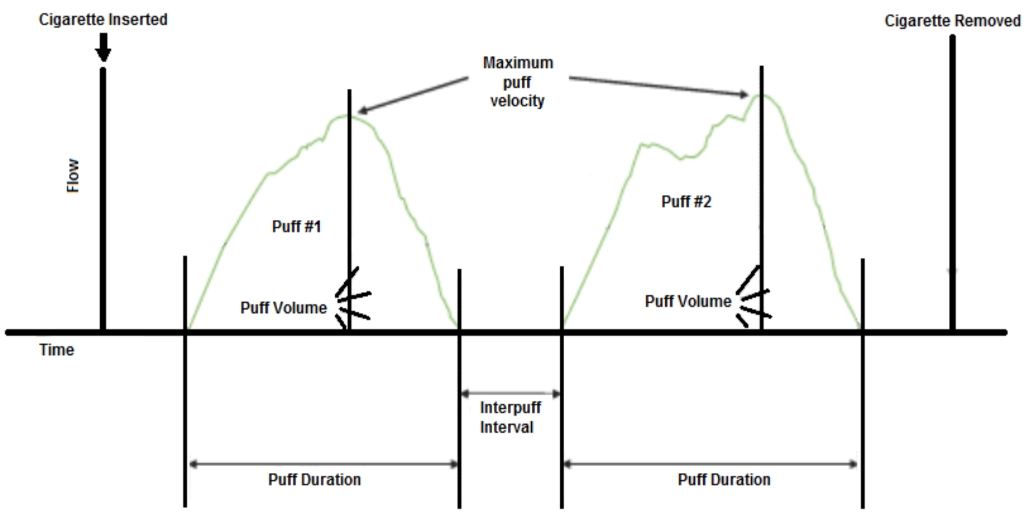
Description: The CReSS device is an 8” X 6” X 5” console with two tubes connected to the front (Panel A). The tubes extend about three feet and connect to a mouthpiece which holds a cigarette (Panel B). Individuals smoke the cigarette through the mouthpiece. The device measures and records a number of smoking topography parameters, namely: (1) number of puffs per cigarette, (2) puff duration, (3) inter-puff interval, (4) puff volume, and (5) maximum puff velocity. All data are transferred from the console to a desktop PC via a USB cord.



Appendix C

Smoking Topography Parameters

Description: A representation of two puffs and corresponding puff topography parameters as measured by the CReSS Desktop Smoking Topography Device.



Appendix D

Modified Cigarette Evaluation Questionnaire (mCEQ)

Description: A 12-item questionnaire assessing how smoking a cigarette made the participant feel. Participants answer each question with a Likert scale ranging from one to seven. An answer of zero indicates "not at all", and seven indicates "extremely". Certain items are averaged to create subscale scores. The mCEQ is made up of five subscales (i.e., Satisfaction, Psychological Reward, Aversion, Enjoyment of Respiratory Tract Sensations, and Craving).

Subscale	Question	Not at all						Extremely
Satisfaction	Was smoking satisfying?	1	2	3	4	5	6	7
Satisfaction	Did the cigarette taste good?	1	2	3	4	5	6	7
Enjoyment of Respiratory Tract Sensations	Did you enjoy the sensations in your throat and chest?	1	2	3	4	5	6	7
Psychological Reward	Did smoking calm you down?	1	2	3	4	5	6	7
Psychological Reward	Did smoking make you feel more awake?	1	2	3	4	5	6	7
Psychological Reward	Did smoking make you feel less irritable?	1	2	3	4	5	6	7
Psychological Reward	Did smoking help you concentrate?	1	2	3	4	5	6	7
Psychological Reward	Did smoking reduce your hunger for food?	1	2	3	4	5	6	7
Aversion	Did smoking make you dizzy?	1	2	3	4	5	6	7
Aversion	Did smoking make you nauseous?	1	2	3	4	5	6	7
Craving Reduction	Did smoking immediately reduce your craving for cigarettes?	1	2	3	4	5	6	7
Satisfaction	Did you enjoy smoking?	1	2	3	4	5	6	7

Appendix E

Minnesota Nicotine Withdrawal Scale (MNWS)

Description: The MNWS measures nicotine withdrawal symptoms. Participants reported on the presence of a given symptom with an answer of 'None', 'Slight', 'Mild', 'Moderate', and 'Severe'. Responses were then assigned a score of 0 to 4, with 0 representing None and 4 reflecting Severe. Mean withdrawal is derived as the average of seven of the eight symptoms (range, 0-4), with the item "Desire or Craving to Smoke" analyzed separately (Hughes & Hatsukami, 1998). Higher scores indicate greater withdrawal or craving.

	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	☐	☐	☐	☐	☐

Appendix F

Questionnaire of Smoking Urges (QSU)

Description: The QSU is comprised of 10 statements regarding current cravings to smoke. Participants assigned each statement a number from one to seven. An answer of zero indicates "strongly disagree", and seven indicates "strongly agree". The QSU is scored such that two factors are derived, with Factor 1 often described as a measure of positive reinforcing effects of smoking and Factor 2 a measure of the negative reinforcing effects of smoking.. Factor scores are calculated by averaging scores from the individual item scores that make up each factor (Factor 1 = six items, Factor 2 = four items). Factor scores range from 1 to 7. Higher scores indicate greater craving/urges to smoke.

Factor	Question	Strongly DISAGREE						Strongly AGREE
1	I have a desire for a cigarette right now	1	2	3	4	5	6	7
1	Nothing would be better than smoking a cigarette right now.	1	2	3	4	5	6	7
1	If it were possible, I probably would smoke right now.	1	2	3	4	5	6	7
2	I could control things better right now if I could smoke.	1	2	3	4	5	6	7
2	All I want right now is a cigarette.	1	2	3	4	5	6	7
1	I have an urge for a cigarette.	1	2	3	4	5	6	7
1	A cigarette would taste good right now	1	2	3	4	5	6	7
2	I would do almost anything for a cigarette right now.	1	2	3	4	5	6	7
2	Smoking would make me less depressed.	1	2	3	4	5	6	7
1	I am going to smoke as soon as possible.	1	2	3	4	5	6	7