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Nicotine biomarkers and rate of nicotine metabolism among cigarette smokers taking buprenorphine for opioid dependency

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Abstract

Background—Individual differences in the rate of nicotine metabolism contribute to differences in tobacco use, dependence, and efficacy of smoking cessation treatments and can be assessed using the nicotine metabolite ratio (NMR), a validated biomarker for CYP2A6 activity. Despite the high cigarette smoking rates observed in opioid users, no data have been reported on NMR among this population as they have been largely excluded from previous studies that have examined the relationship between tobacco use characteristics and rate of nicotine metabolism.

Methods—A linear regression model was used to examine the relationship between tobacco use characteristics and NMR among smokers taking buprenorphine for opioid dependency (N=141). The relationship between buprenorphine dose and NMR was also examined. All participants were enrolled in an intervention designed to promote cigarette-smoking cessation, though participants did not need to stop smoking to enroll.

Results and conclusions—Rate of nicotine metabolism assessed using the NMR was positively associated with cigarettes smoked in the past 24 hours, but was not related to time to first cigarette or past year quit attempts. Dose of buprenorphine was not associated with NMR,

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Clinical Trial Registration

[Clinicaltrials.gov](https://clinicaltrials.gov): registration NCT01350011, May 5, 2011.

Contributors

Drs. Gubner, Guydish, and Hall developed the idea for this manuscript and the data analytic plan using data from a trial conducted by Dr. Hall and Dr. Humfleet. Dr. Benowitz's research group conducted the laboratory analyses of nicotine metabolites. Dr. Gubner conducted the statistical analyses and wrote the primary draft of this manuscript with consultation, feedback, and editing assistance by Drs. Hall, Guydish, and Benowitz. All authors read and approved the final manuscript.

Conflict of Interest

Dr. Benowitz has been a consultant to pharmaceutical companies that market smoking cessation medications, and has been an expert witness in litigation against tobacco companies. Sharon Hall has consulted with Carrot Sense, Inc., BioReim, Inc., the NIH, and the State of Florida. All other authors have no conflicts of interest to declare.

suggesting no association with rate of nicotine metabolism. Our results suggest that NMR is related to tobacco use among persons enrolled in opioid treatment, as reported in general population smokers and may be a useful biomarker to include in future research assessing efficacy of tobacco cessation interventions in this population.

Keywords

tobacco; buprenorphine; opioid; opiate; substance abuse; treatment; drug abuse

1. Introduction

There is a high prevalence of tobacco use among opioid users, estimates ranging from 84% to 94% (Clemmey et al., 1997; Nahvi et al., 2006; Richter et al., 2001). Individuals with opioid dependence smoke more cigarettes per day, have greater nicotine dependence, and have poorer smoking cessation outcomes (Clemmey et al., 1997; Okoli et al., 2010). Higher doses of methadone have been found to be associated with heavier smoking (Chait and Griffiths, 1984; Schmitz et al., 1994; Stark and Campbell et al., 1993). Tobacco-related diseases remain a leading cause of premature death in individuals with substance abuse (Bandiera et al., 2015; Hurt et al., 1996) and there is an urgent need to improve smoking cessation interventions in this population.

Differences in the rate of nicotine metabolism may contribute to differences in tobacco use and dependence. Individuals with faster rates of nicotine metabolism smoke more cigarettes per day (Benowitz et al., 2003; Tyndale and Sellers, 2001), have greater nicotine withdrawal symptoms (Rubinstein et al., 2008; Sofuoglu et al., 2012), and decreased efficacy of nicotine replacement therapy (NRT) for smoking cessation (Lerman et al., 2006; 2015).

Nicotine is primarily metabolized into cotinine by the enzyme CYP2A6, which is further metabolized to trans-3'-hydroxycotinine (3HC) nearly exclusively by the same enzyme (Benowitz et al., 2009). Rate of nicotine metabolism can be assessed using the ratio of 3HC/cotinine, termed the nicotine metabolite ratio (NMR), a validated biomarker for CYP2A6 activity that can be measured in blood, saliva or urine. (Dempsey et al., 2004). A higher NMR indicates greater CYP2A6 enzyme activity and faster rate of nicotine metabolism. In vitro and rodent studies indicate that buprenorphine can weakly inhibit CYP2A6 enzyme activity (Ohtani, 1993; 2007; Umehara et al., 2002; Zhang et al., 2003), which could result in a lower rate of nicotine metabolism.

Despite the high rates of smoking in individuals with substance abuse problems, most studies that have assessed NMR have been conducted in populations that exclude such individuals. To our knowledge, there are no published data on NMR in opioid dependent smokers and this is the first study to examine the relationship between buprenorphine dose and rate of nicotine metabolism in humans. It is important to understand the relationship between rate of nicotine metabolism and cigarette consumption and dependence in an opioid treatment population, as this knowledge may help to inform future smoking cessation interventions in this population.

Thus, the goals of the current study were: (1) to characterize saliva NMR levels in buprenorphine maintained cigarette smokers, (2) to examine the relationship between NMR and tobacco use behaviors and dependence measures in cigarette smokers in opioid treatment and (3) to determine if buprenorphine dose was associated with differences in NMR. It was hypothesized that in an opioid treatment population, a faster rate of nicotine metabolism would be associated with greater cigarettes smoked per day, as is found in the general population.

2. Methods

2.1 Participants

The parent study assessed the efficacy of a smoking cessation intervention in buprenorphine maintained cigarette smokers and was conducted in the Integrated Buprenorphine Intervention Service (IBIS), a buprenorphine treatment program operated under the San Francisco Department of Public Health (SFDPH). Details of parent study recruitment and procedure are published in ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01350011), NCT01350011; Hall et al., 2017). Eligible participants had to smoke 5 cigarettes per day during the past week (at the time of screening) but did not need to want to quit smoking to be eligible for the study. Participants had to have been in IBIS for at least three months, reflecting stabilization on buprenorphine and be 18 years of age or older, have a diagnosis of opioid dependence, and live in San Francisco, and eligible for treatment through SFDPH. Patients dependent on benzodiazepines or alcohol, had an uncontrolled medical or psychiatric condition, had a pain syndrome requiring opioid analgesics, or were pregnant or planning to become pregnant, were treated elsewhere in the SFDPH system. Individuals with a history of schizophrenia, bipolar disorder, cardiovascular disease (myocardial infarction within 3 months, uncontrolled high blood pressure) were excluded. All study procedures were approved by the Institutional Review Board of the University of California, San Francisco.

The current analyses included 141 buprenorphine maintained cigarette smokers with complete biomarker data; excluded were 16 participants that did not provide a saliva sample, and 5 participants that had 3HC levels below the level of quantification. A saliva cotinine cutoff of 10.0 was used for the current analysis to ensure participants were active smokers (6 participants with salivary cotinine levels <10 were excluded).

2.2 Procedure and Measures

Demographic variables included age, sex, race, body mass index (BMI) and education. Number of days in the past month drinking alcohol or using (cocaine, amphetamine, marijuana, heroin); having a doctor recommendation for treatment for hepatitis C; being prescribed medication to treat a psychological/emotional problem in the past 30 days; and current dose of buprenorphine (mg/day) were also assessed. Usual cigarettes smoked per day, cigarettes smoked during the past 24 hours, and number of past year cigarette quit attempts (lasting at least 24 hours) were assessed by self-report. Individuals also reported time to first cigarette (TTFC) smoked after waking, which was used as a measure of nicotine dependence (Baker et al., 2007). Saliva samples were collected at the end of the baseline

assessment session to ensure that participants had not smoked or eaten for at least 30 minutes before sample collection.

2.3 Analytical Chemistry

Saliva samples were analyzed for concentrations of cotinine and trans-3'-hydroxycotinine (3-HC) using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) as previously described (Dempsey et al., 2004; Jacob et al., 2011). Biochemical analyses were conducted in the Clinical Pharmacology Laboratory at Zuckerberg San Francisco General Hospital.

2.4 Data Analysis

NMR was calculated as the ratio of 3HC/cotinine. Log-transformed NMR was used in the regression model because NMR was not normally distributed and Log-transformed NMR has been found to be a better predictor of nicotine clearance (Levi et al., 2007). A linear regression model was used to determine if NMR was associated with tobacco use variables adjusting for other factors (Table 2). Three subjects had NMR values there were greater than 2.5 standard deviations above or below the sample mean. The regression model was run with and without these 3 outliers. The model, reported in the manuscript, excluding these outliers was found to better predict cigarettes in the past 24 hrs. As expected, usual cigarettes smoked per day and cigarettes smoked in the past 24 hours were correlated ($r=0.81$, $p<0.001$). Number of cigarettes smoked in the past 24 hours (versus usual cigarettes smoked per day) was found to be a better predictor of NMR. For this reason, the regression model only included cigarettes smoked in the past 24 hours.

Means are presented $\pm$ standard deviation (SD). Associations were considered significant at an alpha level of 0.05 or less. All statistical analyses were performed using SPSS 24 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1 Sample Characteristics

The baseline demographic and smoking variables for the sample ($N=141$) are shown in Table 1.

Mean age of the sample was 40.6 ± 10.3 , and the majority were male (74.5%) and White (69.5%). The mean dose of buprenorphine was 16.1 ± 7.4 (range 2–32 mg/day). Mean usual cigarettes smoked per day was 14.9 ± 7.3 , and mean cigarettes smoked in the past 24 hours was 14.1 ± 7.6 . Overall 64.3% smoked their first cigarette of the day within 30 minutes of waking and the mean number of past year quit attempts (lasting at least 24 hours) was 1.8 ± 4.9 .

3.2 Biomarkers And Rate Of Nicotine Metabolism

For the sample, mean saliva cotinine was 273.6 ± 209.8 ng/mL, saliva 3HC levels was 134.1 ± 139.9 ng/mL, and NMR was 0.53 ± 0.37 (see Table 1).

3.2 Relationship Between NMR And Tobacco Use Characteristics In Individuals In Opioid Treatment

In the regression model (Table 2), log-transformed NMR was only a significant predictor of cigarettes smoked in the past 24 hours. Controlling for demographic characteristics, higher NMR (faster rate of nicotine metabolism) was associated with smoking more cigarettes ($b=0.009$, $p=0.007$). The mean number of cigarettes smoked in the past 24hrs by NMR quartiles was NMR Q1 (mean=11.03, SD=6.20), NMR Q2 (mean= 15.66, SD=6.66), NMR Q3 (mean=15.03, SD=7.68), and NMR Q4 (mean=14.86, SD=9.07).

NMR was not found to be significantly related to time to first cigarette smoked in the morning, the number of quit attempts made in the past year, or other demographic characteristics. NMR was not associated with dose of buprenorphine that participants were taking.

4. Discussion

To our knowledge this is the first study to assess rate of nicotine metabolism using the NMR in an opioid treatment population, a population that has been largely excluded from previous studies that have examined the relationship between tobacco use characteristics and rate of nicotine metabolism. Among this sample NMR was found to be positively associated with number of cigarettes smoked in the past 24hrs, consistent with findings in the general population (Benowitz et al., 2003; Tyndale and Sellers, 2001). If the current finding is confirmed in a larger sample, it may warrant the tailoring of smoking cessation interventions among individuals with opioid dependence to target interventions that work well with faster nicotine metabolizers. For example, Lerman et al. (2015) recently reported a large clinical trial showing that faster metabolizers of nicotine quit at a substantially higher rate when treated with varenicline compared to NRT.

Weak inhibition of CYP2A6 by buprenorphine has been reported in some but not all animal and in-vitro studies (Ohtani, 1993; 2007; Umehara et al., 2002; Zhang et al., 2003). Our data suggest that buprenorphine dose was not associated with differences in NMR, indicating that clinically relevant doses of buprenorphine (2–32 mg/day) did not result in differences in rate of nicotine metabolism.

Overall, there was a large degree of variability in tobacco use and biomarkers, including NMR in this sample. Cotinine levels in our study of smokers in opioid treatment were similar to mean values found in smokers in the United States (Jarvis et al., 2014). This suggests that among our sample, opioid dependence was not associated with taking in more nicotine than typical smokers. However, nicotine intake could vary by opioid use or treatment populations.

We did not find a relationship between NMR and nicotine dependence as measured by time to first cigarette smoked in the morning. A relationship between nicotine dependence and NMR has been found in some, but not all studies (Rubinstein et al., 2008; Schnoll et al., 2014; Sofuoglu et al., 2012). Our data suggest that NMR may not be associated with nicotine dependence, as measured by time to first cigarette, in persons enrolled in an opioid

treatment. However, it is quite possible that this relationship would be observed with a larger sample or using other measures of nicotine dependence, such as withdrawal symptoms after abstinence. It is also possible that time to first cigarette as a measure of nicotine dependence may be limited in this population, since a majority of the sample lived in situations that often have environmental restrictions on smoking (e.g., half-way houses, shelters, or group houses). Nicotine directly activates the endogenous opioid system in the brain (Kishioka et al., 2014) and timing of cigarette smoking may also be different among persons in opioid treatment (Richter et al., 2007).

There are several limitations to this study. The majority of the sample was white males and results may not translate to other demographic groups. Detailed data on specific medications (psychiatric, anti-fungal, anti-tuberculosis, etc.) or use of other smoking cessation aids was not collected, and their use could contribute to differences in NMR. Individuals with opioid dependence as a population have a high rate of co-occurring physical diseases, mental health disorders, and use of alcohol and other drugs (Krausz, et al., 1998), a primary reason why this population is excluded from the majority of research on tobacco use and NMR.

In conclusion, we found that NMR was positively associated with cigarettes smoked in the past 24 hours in a population of buprenorphine maintained smokers. Dose of buprenorphine was not associated with differences in NMR. NMR may be a useful biomarker to include in future research assessing efficacy of tobacco cessation interventions in this population.

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References

- Baker TB, Piper ME, McCarthy DE, Bolt DM, Smith SS, Kim SY, Colby S, Conti D, Giovino GA, Hatsukami D, Hyland A, Krishnan-Sarin S, Niaura R, Perkins KA, Toll BA. Time to first cigarette in the morning as an index of ability to quit smoking: Implications for nicotine dependence. *Nicotine Tob Res.* 2007; 9(Suppl 4):S555–570. DOI: 10.1080/14622200701673480 [PubMed: 18067032]
- Bandiera FC, Anteneh B, Le T, Delucchi K, Guydish J. Tobacco-related mortality among persons with mental health and substance abuse problems. *PLoS One.* 2015; 10:e0120581.doi: 10.1371/journal.pone.0120581 [PubMed: 25807109]
- Benowitz NL, Pomerleau OF, Pomerleau CS, Jacob P 3rd. Nicotine metabolite ratio as a predictor of cigarette consumption. *Nicotine Tob Res.* 2003; 5:621–624. doi:6DCURVYMPL1C6UQ5. [PubMed: 14577978]
- Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol.* 2009; 192:29–60. DOI: 10.1007/978-3-540-69248-5_2
- Chait LD, Griffiths RR. Effects of methadone on human cigarette smoking and subjective ratings. *J Pharmacol Exp Ther.* 1984; 229:636–640. [PubMed: 6726650]
- Clemmey P, Brooner R, Chutuape MA, Kidorf M, Stitzer M. Smoking habits and attitudes in a methadone maintenance treatment population. *Drug Alcohol Depend.* 1997; 44:123–132. [PubMed: 9088784]

- Dempsey D, Tutka P, Jacob P 3rd, Allen F, Schoedel K, Tyndale RF, Benowitz NL. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. *Clin Pharmacol Ther.* 2004; 76:64–72. DOI: 10.1016/j.clpt.2004.02.011 [PubMed: 15229465]
- Hall SM, Humfleet G, Gasper J, Delucchi KL, Hersh D, Guydish J. Cigarette Smoking Cessation Intervention for Buprenorphine Treatment Patients. *Nicotine Tob Res.* 2017; In press. doi: 10.1093/ntr/ntx113
- Hurt RD, Offord KP, Croghan IT, Gomez-Dahl L, Kottke TE, Morse RM, Melton LJ 3rd. Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. *JAMA.* 1996; 275:1097–1103. DOI: 10.1001/jama.1996.03530380039029 [PubMed: 8601929]
- Jacob P 3rd, Yu L, Duan M, Ramos L, Yturalde O, Benowitz NL. Determination of the nicotine metabolites cotinine and trans-3'-hydroxycotinine in biologic fluids of smokers and non-smokers using liquid chromatography-tandem mass spectrometry: biomarkers for tobacco smoke exposure and for phenotyping cytochrome P450 2A6 activity. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011; 879:267–276. DOI: 10.1016/j.jchromb.2010.12.012
- Jarvis MJ, Giovino GA, O'Connor RJ, Kozlowski LT, Bernert JT. Variation in nicotine intake among U.S. cigarette smokers during the past 25 years: Evidence from NHANES surveys. *Nicotine Tob Res.* 2014; 16:1620–1628. DOI: 10.1093/ntr/ntu120 [PubMed: 25063772]
- Kishioka S, Kiguchi N, Kobayashi Y, Saika F. Nicotine effects and the endogenous opioid system. *J Pharmacol Sci.* 2014; 125:117–124. DOI: 10.1254/jphs.14R03CP [PubMed: 24882143]
- Krausz M, Degkwitz P, Kühne A, Verthein U. Comorbidity of opiate dependence and mental disorders. *Addict Behav.* 1998; 23:767–783. [PubMed: 9801715]
- Lerman C, Tyndale R, Patterson F, Wileyto EP, Shields PG, Pinto A, Benowitz N. Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. *Clin Pharmacol Ther.* 2006; 79:600–608. DOI: 10.1016/j.clpt.2006.02.006 [PubMed: 16765148]
- Lerman C, Schnoll RA, Hawk LW Jr, Cinciripini P, George TP, Wileyto EP, Swan GE, Benowitz NL, Heitjan DF, Tyndale RF, PGRN-PNAT Research Group. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: A randomised, double-blind placebo-controlled trial. *Lancet Respir Med.* 2015; 3:131–138. DOI: 10.1016/S2213-2600(14)70294-2 [PubMed: 25588294]
- Levi M, Dempsey DA, Benowitz NL, Sheiner LB. Prediction methods for nicotine clearance using cotinine and 3-hydroxy-cotinine spot saliva samples II. Model application. *J Pharmacokinet Pharmacodyn.* 2007; 34:23–34. DOI: 10.1007/s10928-006-9026-0 [PubMed: 17206525]
- Nahvi S, Richter K, Li X, Modali L, Arnsten J. Cigarette smoking and interest in quitting in methadone maintenance patients. *Addict Behav.* 2006; 31:2127–2134. DOI: 10.1016/j.addbeh.2006.01.006 [PubMed: 16473476]
- Ohtani M, Kotaki H, Santa T, Sawada Y, Iga T. Effect of repeated administration of buprenorphine, an opioid analgesic, on its oxidative metabolism in rats. *Yakubutu Doutai.* 1993; 8:1219–1227.
- Ohtani M. Basic pharmacology of buprenorphine. *Eur J Pain Suppl.* 2007; 1:69–73.
- Okoli CT, Khara M, Procyshyn RM, Johnson JL, Barr AM, Greaves L. Smoking cessation interventions among individuals in methadone maintenance: A brief review. *J Subst Abuse Treat.* 2010; 38:191–199. DOI: 10.1016/j.jsat.2009.10.001 [PubMed: 20015608]
- Richter KP, Gibson CA, Ahluwalia JS, Schmelzle KH. Tobacco use and quit attempts among methadone maintenance clients. *Am J Public Health.* 2001; 91:296–299. [PubMed: 11211643]
- Richter KP, Hamilton AK, Hall S, Catley D, Cox LS, Grobe J. Patterns of smoking and methadone dose in drug treatment patients. *Exp Clin Psychopharmacol.* 2007; 15:144–153. DOI: 10.1037/1064-1297.15.2.144 [PubMed: 17469938]
- Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB. Rate of nicotine metabolism and withdrawal symptoms in adolescent light smokers. *Pediatrics.* 2008; 122:e643–647. DOI: 10.1542/peds.2007-3679 [PubMed: 18762498]
- Schmitz JM, Grabowski J, Rhoades H. The effects of high and low doses of methadone on cigarette smoking. *Drug Alcohol Depend.* 1994; 34:237–242. [PubMed: 8033762]
- Schnoll RA, George TP, Hawk L, Cinciripini P, Wileyto P, Tyndale RF. The relationship between the nicotine metabolite ratio and three self-report measures of nicotine dependence across sex and

race. *Psychopharmacology (Berl)*. 2014; 231:2515–2523. DOI: 10.1007/s00213-013-3421-1 [PubMed: 24402139]

Sofuoglu M, Herman AI, Nadim H, Jatlow P. Rapid nicotine clearance is associated with greater reward and heart rate increases from intravenous nicotine. *Neuropsychopharmacology*. 2012; 37:1509–1516. DOI: 10.1038/npp.2011.336 [PubMed: 22334123]

Stark MJ, Campbell BK. Cigarette smoking and methadone dose levels. *Am J Drug Alcohol Abuse*. 1993; 19:209–217. [PubMed: 8484357]

Tyndale RF, Sellers EM. Variable CYP2A6-mediated nicotine metabolism alters smoking behavior and risk. *Drug Metab Dispos*. 2001; 29:548–552. [PubMed: 11259349]

Umehara K, Shimokawa Y, Miyamoto G. Inhibition of human drug metabolizing cytochrome P450 by buprenorphine. *Biol Pharm Bull*. 2002; 25:682–685. [PubMed: 12033517]

Zhang W, Ramamoorthy Y, Tyndale RF, Sellers EM. Interaction of buprenorphine and its metabolite norbuprenorphine with cytochromes p450 in vitro. *Drug Metab Dispos*. 2003; 31:768–772. [PubMed: 12756210]

Highlights

- Differences in the rate of nicotine metabolism contribute to differences in tobacco use
- The nicotine metabolite ratio (NMR) is a validated biomarker for CYP2A6 activity
- NMR and tobacco use were examined in smokers using buprenorphine for opioid dependency
- NMR was positively associated with cigarettes smoked in the past 24 hours
- NMR was not associated with dose of buprenorphine

Table 1

Baseline demographics, tobacco use history, and nicotine metabolites among smokers maintained on buprenorphine.

Variable	Full sample (N=141)
Age, M $\pm$ SD (Range)	40.6 $\pm$ 10.3 (22–64)
Sex, % male	74.5 %
Race/ethnicity, %	
White	69.5 %
African American	10.6 %
Other	19.9 %
Education, %	
< High school (HS)	8.5 %
HS or GED equivalent	62.4 %
College degree	29.1 %
BMI, M $\pm$ SD	25.9 $\pm$ 4.5
Hepatitis C diagnosis, %	36.9%
Prescribed medication for psychological/emotional problem in past month, %	41.1%
Buprenorphine dose (mg/day), M $\pm$ SD (Range)	16.1 $\pm$ 7.4 2–32
Alcohol, days drank in past month, M $\pm$ SD	4.8 $\pm$ 8.7
Cocaine, days used in the past month, M $\pm$ SD	1.7 $\pm$ 5.3
Amphetamine, days used in the past month, M $\pm$ SD	0.8 $\pm$ 3.6
Marijuana, days used in the past month, M $\pm$ SD	7.1 $\pm$ 11.1
Heroin, days used in the past month, M $\pm$ SD	0.2 $\pm$ 0.8
Usual cigarettes per day, M $\pm$ SD (Range)	14.9 $\pm$ 7.3 (5–50)
Cigarettes smoked in past 24 hrs, M $\pm$ SD (Range)	14.1 $\pm$ 7.6 (2–50)
Time to first cigarette, %	
Within 5 min of waking	38.3 %
6–30 min of waking	26.2 %
31–60 min of waking	16.3 %
After 60 min of waking	19.1 %
Past year cigarette quit attempts, M $\pm$ SD (Range)	1.8 $\pm$ 4.9 (0–50)

Variable	Full sample (N=141)
Saliva cotinine (ng/mL), M±SD (Range)	273.6 ± 209.8 (10.8–1027.3)
Saliva 3HC (ng/mL), M±SD (Range)	134.1 ± 139.9 (6.99–1006.8)
Nicotine metabolite ratio (NMR), M±SD (Range)	0.53 ± 0.37 (0.02–2.72)

3HC = trans-3'-hydroxycotinine; Nicotine metabolite ratio= 3HC/cotinine; M= mean; SD= standard deviation; BMI=Body mass index.

Table 2

Linear regression model predicting demographic and tobacco use characteristics associated with log-transformed NMR

Variable	b	95% CI	p
Age	0.003	(−0.001, 0.01)	0.08
Sex	0.10	(−0.02, 0.21)	0.09
Race	0.02	(−0.02, 0.06)	0.28
Education	−0.002	(−0.09, 0.09)	0.97
BMI	−0.004	(−0.02, 0.008)	0.54
Hepatitis C diagnosis	−0.04	(−0.15, 0.06)	0.41
Prescribed medication for psychological/emotional problem in past month	0.06	(−0.04, 0.17)	0.24
Buprenorphine dose (mg/day)	0.002	(−0.005, 0.008)	0.62
Alcohol, days drank in past month	−0.002	(−0.008, 0.005)	0.60
Cocaine, days used in the past month	0.005	(−0.02, 0.005)	0.33
Amphetamine, days used in the past month	0.001	(−0.02, 0.02)	0.97
Marijuana, days used in the past month	0.002	(0.003, 0.007)	0.35
Heroin, days used in the past month	0.02	(−0.05, 0.08)	0.55
Cigarettes, past 24 hrs	0.009	(0.003, 0.02)	0.007
Time to first cigarette	−0.04	(−0.09, 0.01)	0.13
Past year cigarette quit attempts	0.003	(−0.007, 0.01)	0.61

NMR= nicotine metabolite ratio, 3HC/cotinine. Bold p-values indicate a significant association with NMR.