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Nicotine Metabolite Ratio (NMR) Prospectively Predicts Smoking Relapse: Longitudinal Findings From ITC Surveys in Five Countries

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Abstract

Introduction: The ratio of trans 3'-hydroxycotinine (3HC) to cotinine (nicotine metabolite ratio [NMR]) is a biomarker of the rate of nicotine metabolism, with higher NMR indicating faster metabolism. Higher NMR has been found to be associated with higher daily cigarette consumption and less success stopping smoking in cessation trials. This study examines differences in NMR among population-based samples of smokers in the five countries and explores the relationship between NMR and smoking abstinence.

Methods: Participants ($N = 874$) provided saliva samples during International Tobacco Control (ITC) surveys in the United States, United Kingdom, Mauritius, Mexico, and Thailand conducted in 2010/2011 with follow-up surveys in 2012/2013. When all samples were received, they were sent to a common laboratory for analysis using liquid chromatography and tandem mass spectroscopy.

Results: There was significant variation in NMR across countries ($F = 15.49$, $p < .001$). Those who reported smoking at follow-up had a mean NMR of 0.32, compared to a mean NMR of 0.42 in participants who reported that they had stopped ($F = 8.93$; $p = .003$). Higher mean NMR values were also associated with longer quit duration ($p = .007$). There was no substantial difference in NMR between current smokers who made a failed quit attempt and those who made no attempt—both had significantly lower NMR compared to those who quit and remained abstinent. Smokers with a higher NMR were more likely to report that they stopped smoking compared to those with a lower NMR (odds ratio = 2.67; 95% confidence interval: 1.25 to 5.68).

Conclusions: These results suggest faster nicotine metabolizers may be less likely to relapse following a quit attempt. This finding differs from results of clinical trials testing stop smoking medications, where slower metabolizers have been found to be more likely to maintain abstinence from smoking.

Implications: Results of this study suggest faster nicotine metabolizers may be less likely to relapse following a quit attempt. This finding differs from results of clinical trials testing stop smoking medications, where slower metabolizers have been found to be more likely to maintain abstinence from smoking.

Introduction

Nicotine, the primary addictive component of tobacco, is metabolized to cotinine by the liver enzyme CYP2A6, which also metabolizes cotinine to trans-3'-hydroxycotinine (3HC). The nicotine metabolite ratio (NMR) of 3HC to cotinine, which can be measured in blood, saliva, or urine, is a biomarker of the rate of nicotine metabolism.¹ NMR is correlated with certain smoking behaviors and demographic characteristics.²

Benowitz et al. hypothesized that those who metabolize nicotine quickly would need to take in more nicotine from their cigarettes to sustain desired blood levels and therefore would smoke more cigarettes than those who metabolize nicotine slowly. Indeed, NMR was significantly correlated with the number of cigarettes smoked per day (CPD) but not with the Fagerstrom Test for Nicotine Dependence (FTND). These findings supported the initial hypothesis that nicotine metabolism rate (NMR) is positively related to CPD,³ a finding supported by subsequent studies. A study of 545 UK smokers who were enrolled in a trial of smoking cessation by nicotine replacement therapy (NRT) found higher NMR in females and older participants but no association with FTND.⁴ Results from another study showed no significant association between NMR and smokeless tobacco (ST) units per week, years of use, or dependence among ST users enrolled in a cessation trial.⁵

The interrelationships among individual characteristics, NMR, and tobacco dependence are complex. A study of 833 smokers in a cessation trial found that NMR was positively associated with nicotine dependence based on the FTND and Heaviness of Smoking Index (HSI) among males but not females.⁶ Among African American participants (but not Caucasians), NMR was associated with time to first cigarette after waking. Additional analyses showed an association between NMR and CPD overall, among men, and among Caucasians. Overall, these results suggest that the variation in smoking behavior across measures of sex and race may be due at least in part to an association between NMR and CPD.⁶ Another study examining the relationship between urine nicotine metabolites and smoking behavior in a sample of 900 participants aged 18-26 years found females had higher NMR than males and Whites and Hispanics had higher NMRs than Blacks or Asians. The study found no significant association between NMR and CPD or FTND.⁷ A study that included 585 smokers among Hawaii's 3 main racial/ethnic groups found NMRs higher in Whites compared to Japanese and intermediate in native Hawaiians. When adjusted for CPD, NMRs were lower in Japanese compared to Hawaiians and Whites.⁸

Studies have also suggested that NMR is a predictor of smoking topography and biomarkers of specific carcinogens. In a sample of 109 current smokers, NMR was positively associated with total cigarette puff volume and total 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco smoke carcinogen. In this study, faster nicotine metabolizers showed a greater total puff volume and NNAL.⁹

NMR and Quitting Smoking

A number of investigators have posited that speed of nicotine metabolism may influence ability of smokers to abstain from smoking, with slower metabolizers typically shown to have better quit success. In a group of treatment-seeking smokers, Lerman and colleagues found that among smokers treated with nicotine patch, those with higher plasma NMRs were significantly less likely to remain abstinent.¹⁰ In a recent clinical trial, quit rates were

similar with nicotine patch or varenicline among slow metabolizers (NMR < 0.31). Among normal metabolizers, however, quit rates were considerably lower with nicotine patch compared to varenicline.¹¹ Similar results showing faster nicotine metabolizers were significantly less likely to quit smoking were found among a community-based sample of treatment-seeking smokers.¹² Ho and colleagues observed Blacks smoking 10 or fewer CPD were slower metabolizers (assessed by NMR) and were more likely to achieve 7-day point prevalence abstinence at end of treatment and 26-week follow-up.¹³ Chenoweth et al. showed that adolescent slow metabolizers (assessed by CYP2A6 genotype) were more likely to achieve 12-month abstinence in a cohort study.² However, this association between metabolism and quitting is not a universal finding. Indeed, in Lerman's initial publication, NMR was related to cessation only in the nicotine patch arm and not the nicotine nasal spray arm.¹⁰ Ebbert et al. showed that while NMR was positively associated with lozenge use among ST users during a clinical trial, it was not associated with quitting outcome.⁵ Styn et al. showed that those with CYP2A6 genotypes associated with slower metabolism showed no difference in odds of quitting over 1 year in a screening clinic sample.¹⁴ Chen et al. showed that pharmacotherapy (specifically NRT) significantly reduced relapse over 90 days among fast, rather than slow, metabolizers.¹⁵ Importantly, Chen found that in the placebo group quit rates were higher and relapse rates lower in slow metabolizers, which is similar to other study findings.^{10,16}

As opposed to findings in clinical trials of smoking cessation therapy, there are few population-based studies measuring NMR levels and evaluating the relationship between NMR and likelihood of quitting smoking. This is important to study given that cessation is more complex, and treatments effects observed to be weaker, in the population than is observed in the randomized trials. There are also no studies examining the relationship between NMR levels and quitting in smokers across different countries. The present study aims to fill these gaps in the research literature by comparing differences in the rate of nicotine metabolism among population-based samples in the United States, United Kingdom, Mauritius, Mexico, and Thailand and prospectively exploring the relationship between NMR and spontaneous quitting.

Methods

Participants (daily and nondaily smokers) from the United States, United Kingdom, Mauritius, Mexico, and Thailand were asked to provide saliva samples during International Tobacco Control (ITC) surveys conducted in 2010/2011. Follow-up surveys were conducted in each country in 2012/2013. The ITC surveys are designed to follow respondents longitudinally to ascertain the individual behavioral and psychological impacts of national tobacco control policies.¹⁷ Survey information obtained from participants in the study included demographic data and self-reported smoking behaviors.

The surveys and sample collections were either administered in a face-to-face setting in the home of the participant (Mauritius, Mexico, and Thailand) or via phone and postal mail (United States and United Kingdom). Research protocols received ethics approval from Roswell Park Cancer Institute, the University of Waterloo, and respective ethics boards in the study countries. Participants were informed that the saliva samples would be used to test for chemicals related to nicotine and tobacco use. More detail on the sample collection protocol is available as supplemental material.

Saliva samples were collected using Salivette (Sarstedt, Inc., Newton, NC) tubes. Participants were instructed to place the cotton roll in their mouth for 2 minutes, making a chewing motion to stimulate saliva. Two tubes were collected from each participant in order to maximize the available saliva sample for analysis. In face-to-face collections, the specimens were placed in coolers (approx. 0°C) before transfer to freezers (−20°C) for long-term storage. In mail collection, the participant placed the samples in a preaddressed return envelope. Samples returned by mail were placed in −20°C freezers on receipt. When all samples were received, they were sent on dry ice by common carrier to the Roswell Park Cancer Institute (RPCI) laboratory. Samples were then aggregated and shipped to the University of California, San Francisco Clinical Pharmacology laboratory for analysis. Trans 3'-hydroxycotinine (HC) and cotinine were determined using liquid chromatography tandem mass spectroscopy employing previously published methods.¹⁸

This analysis uses 2 survey waves of data from participants in each country. During the first survey wave, 1062 participants provided saliva samples that were analyzable and also provided complete survey data. The total sample size for this analysis is the 874 participants who completed the subsequent survey wave. Table 1 shows the number of survey participants in the initial data collection, the number of samples assayed, and the number of participants who provided usable samples at the time of the initial data collection and participated in the subsequent ITC survey in each country. Rates of analyzable samples did not differ by collection method.

Successful quitting was defined as a participant self-report of being a nonsmoker at the time of the follow-up survey. The NMR was calculated as the ratio of HC to cotinine (unconjugated) in saliva. The geometric means of NMR are reported because the ratio is not normally distributed, and the log NMR is most highly correlated with the metabolic clearance of nicotine.¹⁹ NMR was compared with demographic factors as reported during the first survey and nicotine dependence (as measured by CPD). In addition, an analysis of variance (ANOVA) was used to compare the mean NMR of participants who reported that they were still smoking during the follow-up survey wave with the mean NMR of those who reported that they had stopped smoking. Because of the variance in the lowest quartile of NMR across countries, we elected to treat NMR as a continuous variable. A univariate analysis of variance examining the relationship between mean NMR, and smoking cessation within each country was also conducted. Finally, a multivariate logistic regression was conducted to examine predictors of smoking abstinence, with NMR included as a covariate.

All statistical analyses were performed using SPSS 21.0.

Results

Sample Characteristics

In the sample under consideration ($N = 874$), there were more males (69.3%) than females and more non-Whites (61.6%) than Whites. In terms of age distribution, 6.9% were 18–24 years, 23.7% were 25–39 years, 41.8% were 40–54 years, and 27.6% were 55 years and older. In terms of smoking behavior, 62% of the sample reported smoking their first cigarette within 30 minutes of waking. The mean number of cigarettes smoked per day was 12. The majority (85.2%) of smokers included in this analysis reported smoking daily at the time of the survey. Overall, 8.0% of the sample reported quitting at the time of the second survey wave. In terms of participant age, of the $n = 226$ participants who were aged 55+, 11.9% reported

successfully quitting at the time of the follow-up survey. This is the highest proportion within any of the age categories (3.5% aged 18–24; 6.2% aged 25–35; 7.4% aged 45–54) but not statistically significant ($\chi^2 = 7.51$; $p = .057$) compared to the other age categories. Significant differences were observed between countries for CPD, sex, and age.

Bivariate Associations

The mean 3HC, cotinine, and 3HC-cotinine ratios (i.e., NMR) are presented in Table 2. Smokers from the United States had the highest NMR values, followed by smokers from the United Kingdom, Mexico, Mauritius, and Thailand. Females, participants older than 40 years of age, and those who smoked more than 20 CPD had higher NMR values when compared to males, those younger than 40, and those who smoked 20 or fewer CPD, respectively. The means and ranges of values reported here are consistent with other published reports.^{2,5,10,11} The within-subject Spearman correlation between CPD values across waves for continuing smokers was 0.78 ($p < .001$). At wave 1 we observed a significant association between CPD and NMR ($r_s = 0.15$, $p < .001$). Time to first cigarette was not significantly associated with NMR ($r_s = -0.01$, $p = 0.77$).

An ANOVA was conducted in order to examine the differences in mean NMR in smokers who reported that they were still smoking during the follow-up survey and those who self-reported not smoking. Those who reported continuing to smoke at follow-up had a mean NMR of 0.32, compared to a mean NMR of 0.42 among participants who reported not smoking, $F(1, 874) = 8.93$ ($p = .003$). These results are presented in Table 3. To assess whether population stratification plays a role, we replicated the analyses among White participants from the United States and United Kingdom only and found NMRs were similar (0.43 vs. 0.40, $p = .496$). A univariate ANOVA was conducted to compare the differences in mean NMR between self-reported smokers and quitters adjusting for country. Similar to the results mentioned earlier, a lower mean NMR was observed in those who continued to smoke than in those who stopped smoking in each country, $F(1, 868) = 3.03$ ($p = .082$). The cross-country difference in NMR is also observed here, $F(4, 868) = 15.49$ ($p < .001$). We conducted a sensitivity analysis, based on smoking status, to replicate the analyses used to generate the results presented in Table 3. There were no differences between the values and patterns in these restricted models when compared to the original analyses that included daily and nondaily smokers.

To assess whether NMR was related to the duration of time since a smoker had quit, or smoking pattern, another ANOVA was conducted examining differences in NMR among daily smokers, nondaily smokers, those who reported that they had stopped smoking 0–6 months prior to the survey, and those who had reported quitting for more than 6 months prior to their survey date. Those who reported that they had quit more than 6 months prior to the survey had the highest mean NMR value, $F(3, 867) = 4.1$ ($p = .007$). These results are presented in Table 4.

We also examined whether those who made a failed quit attempt differed from those who succeeded in remaining abstinent from smoking and those who did not try to stop smoking. We found that there was no substantial difference between the geometric mean NMR of those who made a failed quit attempt (0.31; 95% confidence interval [CI]: 0.29 to 0.34) and those who made no attempt (0.33; 95%CI: 0.31 to 0.35)—both had significantly lower NMR compared to those who remained abstinent from smoking (0.42; 95%CI: 0.35 to 0.49; $F(2, 869) = 5.37$; $p = .005$).

Table 1. Sample Size Breakdown

Country	Dates of data collection for present study (ITC survey wave in that country)	Survey mode	Number of survey respondents at the first ITC survey wave	Kits collected (% of respondents)	Samples assayed (% of kits collected)	Completed both survey waves and NMR assay (% of respondents at the first ITC survey wave)
United States	2010–2011 + 2013 (Waves 8 + 9)	Phone/Mail	1651	372 (22.5%)	270 (72.6%)	194 (11.8%)
United Kingdom	2010–2011 + 2013 (Waves 8 + 9)	Phone/Mail	1325	207 (15.6%)	180 (87.0%)	126 (9.5%)
Mauritius	2010 + 2011 (Waves 2 + 3)	Face to Face	601	300 (49.9%)	246 (82.0%)	239 (39.8%)
Thailand	2011 + 2012 (Waves 5 + 6)	Face to Face	2175	300 (13.8%)	248 (82.7%)	207 (9.5%)
Mexico	2011 + 2012 (Wave 5 + 6)	Face to Face	433 ^a	170 (39.3%)	130 (76.5%)	108 (24.9%)

ITC = International Tobacco Control; NMR = nicotine metabolite ratio. Only respondents residing in Mexico City were invited to participate in the saliva collection component of the study due to logistical issues around sample storage in other cities where ITC Mexico collects data.

Finally, we analyzed only those who made and failed at a quit attempt ($n = 335$) to determine whether length of time abstinent was related to NMR. Overall, the time quit variable was very skewed, with many values more than 7 days. We therefore categorized the data for analysis, first, into 4 groups (< 1 day, 1–6 days, 7–30 days, and > 30 days) and then dichotomized at 7 days. In the first instance, those who quit for 0 days (0.28) or 1–6 days (0.27) had significantly lower NMR than those who quit for at least a week (0.34) or more than a month (0.43), $F(1, 335) = 5.3$ ($p < .001$). When these are collapsed the general pattern holds such that those quit 7 days or more (0.37, 95% CI: 0.33 to 0.41) have higher NMR than those quit for less time (0.27, 95% CI: 0.24 to 0.30), $F(1, 335) = 14.7$ ($p < .001$).

Multivariate Model of Quitting Outcome

In a multivariate logistic regression model treating NMR as a continuous variable and predicting smoking cessation as the outcome, subjects with a higher NMR were more likely to quit than those with a lower NMR (adjusted odds ratio [aOR] = 2.48; 95%CI:1.23 to 4.99). These results are presented in Table 5. When the dichotomized variable (normal vs. slow) is used, the effect is nonsignificant but in the same direction with normal/fast metabolizers being more likely to have quit (aOR = 1.35, $p = .355$).

We tested interactions between CPD and NMR, time to first cigarette and NMR, and country and NMR in separate multivariate logistic regression models. In all e3, NMR remained statistically significant (higher NMR associated with greater likelihood of remaining abstinent from smoking). However, no statistically significant interactions between NMR and the variables described were observed in any of the models. This suggests that NMR has an overall effect on quitting but no differential effects between NMR and CPD, time to first cigarette, and country. We conducted a sensitivity analysis, based on smoking status, to replicate the analyses used to generate the results presented in Table 5. There were no differences between the values and patterns in these restricted models when compared to the original analyses that included daily and nondaily smokers. We also conducted an intent-to-treat-type analysis, integrating data from all smokers who provided a saliva sample during the first data collection but did not complete a follow-up interview. Treating the lost to follow-up group as smokers increased the total sample size to 1062 (989 smokers and 73 quitters). Analyzing the data in this manner did not change the pattern of results in terms of direction of the association general outcomes although the NMR effect was attenuated.

We are limited in our ability to analyze questions related to medication use because of the lack of reported medication use in 3 of 5 countries under consideration. Among United States and United Kingdom participants who quit between the first and second waves of data collection, 60% (28 of 47) reported use of a cessation pharmacotherapy. No significant differences were observed between the mean NMR of those who used pharmacotherapy (0.490) and those who did not (0.479), $F(1, 318) = 0.071$ ($p = .790$). More specifically, 38% (18 of 47) reported using NRT in an attempt to stop smoking, and no significant differences were observed between the mean NMR of those who used NRT (0.558) and those who did not (0.530), $F(1, 46) = 0.045$, ($p = .833$).

Discussion

Across the five countries examined, NMR was positively associated with reported abstinence from smoking during the subsequent

Table 2. Geometric Mean Levels of Trans-3'-Hydroxycotinine, Cotinine, and Their Ratio at the Baseline Wave

	N	Mean 3HC (ng/mL)	Mean cotinine (ng/mL)	Mean 3HC/cotinine ratio (NMR)	Lowest quartile of NMR
Country					
United States	270	105.3	248.3	0.42	.29
United Kingdom	180	101.3	269.9	0.38	.26
Mauritius	246	72.0	245.3	0.29	.20
Thailand	248	58.8	228.6	0.26	.17
Mexico	130	29.1	79.1	0.37	.26
Sex					
Male	735	70.1	225.9	0.31	.21
Female	325	75.9	190.6	0.40	.26
Age					
<40	324	48.4	177.7	0.27	.19
40 +	736	85.6	235.1	0.37	.24
CPD					
≤10 CPD	530	49.9	165.7	0.30	.20
11–20 CPD	417	94.6	265.1	0.36	.24
>20 CPD	110	142.6	343.8	0.42	.30

CPD = cigarettes smoked per day; HC = hydroxycotinine; NMR = nicotine metabolite ratio.

Table 3. Results of a Univariate Analysis of Variance Examining NMR and Quitting Overall and Within Each Country (Total *N* = 874)

Respondent type	Country	<i>n</i>	Geometric mean	95% Confidence interval	
				Lower bound	Upper bound
Smokers	Overall	804	0.32	0.31	0.34
	United States	169	0.41	0.37	0.45
	United Kingdom	104	0.37	0.33	0.41
	Mauritius	231	0.29	0.27	0.32
	Thailand	200	0.26	0.24	0.28
	Mexico	100	0.37	0.33	0.42
Quitters	Overall	70	0.42	0.35	0.49
	United States	25	0.47	0.40	0.56
	United Kingdom	22	0.43	0.36	0.51
	Mauritius	8	0.34	0.28	0.40
	Thailand	7	0.30	0.25	0.36
	Mexico	8	0.43	0.35	0.53

NMR = nicotine metabolite ratio.

Table 4. Results of an ANOVA Examining the Relationship Between NMR and smoking Status at the Subsequent Survey Wave (Total *N* = 871)

Respondent category	<i>n</i>	Geometric mean	95% Confidence interval	
			Lower bound	Upper bound
Daily Smokers	745	0.32	0.31	0.34
Nondaily Smokers	59	0.31	0.26	0.36
0–6 Month Quitters	27	0.36	0.28	0.47
> 6 Month Quitters	40	0.44	0.36	0.55

ANOVA = analysis of variance; NMR = nicotine metabolite ratio.

survey wave. That is, smokers with a higher NMR were more likely to be abstinent at follow-up, and more likely to have been abstinent for longer, suggesting that faster metabolizers were more successful at quitting. This pattern was consistent across countries and in an intent-to-treat analysis, where those lost to follow-up are treated as continuing smokers. Further, analyses among White participants only yielded a similar pattern of results. Higher NMR was also associated with greater duration of a quit attempt among those who had relapsed. Thus, multiple sets of analyses converged to suggest that

higher NMR serves as a protective factor for relapse after smoking cessation.

Our results differ from many, though not all, prior studies. To date, the majority of the studies that have examined the relationship between NMR and smoker characteristics have been conducted among particular groups of smokers, such as those enrolled in clinical trials of cessation.^{5,6,10,11,16} However, our study is the first that we are aware of to examine NMR and spontaneous quitting (i.e., not part of a structured treatment intervention like a trial) at the

population level across different countries. Although the quit rate among US and UK participants was higher than the quit rate among participants residing in Mexico, Mauritius, and Thailand, the relationship between higher NMR and higher likelihood of quitting is consistent across countries. It is possible that the country variation represents wider variation in amount smoked per day and that in low-level smokers, NMR is a less reliable measure of actual nicotine metabolism. In regular smokers, where cotinine and 3HC are in relative steady state, NMR is stable throughout the day. However, in occasional smokers the NMR can be quite variable depending on number of CPD and when the last cigarette was smoked. In order to address this point, a sensitivity analysis replicating the analyses used to generate the results presented in Tables 3 and 5 was conducted among only daily smokers at the first wave of data collection. In both cases, there were no differences between the values and patterns in these restricted models when compared to the original analyses that included daily and nondaily smokers.

It is possible that those smokers who choose to enroll in clinical trials of cessation are fundamentally different (dependence level, motivation, and compliance) from “free-living” smokers who make spontaneous attempts to quit. The current sample is likely broader in both demographic composition and range of smoking behaviors than those in clinical trials, which typically have a restricted CPD range and exclude individuals with medical/psychiatric conditions. Trials and population studies illustrate the trade-off between internal and external validity—randomized controlled trials test treatment efficacy, while this study is most comparable to a “standard-of-care” arm (but with a much broader sample). More fundamentally, there is also a difference between the type of controlled cessation attempts typical of clinical trials and naturalistic attempts (often unassisted) that occur in the population.²⁰ In trials, the quit date is often fixed and known, while population studies must rely on self-report of recalled quit attempts, which are subject to forgetting.²¹ Depending on one’s perspective and the measures and populations one evaluates, assisted, structured quitting is either better or worse than unassisted, naturalistic quitting.^{22–27} In trials, one is assigned to a particular treatment, while in the naturalistic setting, one self-selects to a treatment. That

raises the possibility that while in the trial context, NMR should be independent of treatment, it is likely that NMR may be correlated (or even subtly drive) with treatment selection in the real world.

Within a given (assigned) treatment modality, slower metabolizers may be advantaged on a dose-for-dose basis. But in a free-living population, which self-selects to treatment, faster metabolizers may do better in selecting effective strategies to achieve smoking abstinence, possibly because they are more acutely affected by withdrawal symptoms. Fast metabolizers experience greater withdrawal and reward from smoking following abstinence,²⁸ and because they eliminate nicotine more quickly, are consistently shown to smoke more CPD³ which we also find. Their smoking, then, may be more contingent on tonic craving (vs. cued), and once tonic craving is resolved, craving no longer serves as a relapse risk factor. While the severity of withdrawal symptoms is initially greater in faster metabolizers, changes in the brain normalize more quickly because remaining nicotine is eliminated from the body more quickly, which could explain a lower likelihood of relapse.²⁹

There are data in adolescents that slow metabolizers are more likely to become dependent^{30–32} which may relate to longer residence of nicotine in the brain and greater neuroadaptation. This may be an important factor in lower CPD smokers, which comprise a substantial proportion of this sample, including virtually all sampled smokers in Mexico, whose smoking pattern is representative of the broader population.³³ At the same time, other studies showed that adolescent slow metabolizers were also more likely to quit.² As Ebbert et al. noted for smokeless users, “fast metabolizers may need to self-administer more nicotine replacement ... to achieve the same clinical response achieved by slower metabolizers ...” (page 366).⁵ Given that high metabolizers are typically more nicotine dependent (based on quantity/time to first cigarette assessments), and experience more withdrawal based cravings, their smoking may be contingent primarily upon blood nicotine levels. Thus, high metabolizers who persist through the 2–4 weeks of withdrawal-based cravings may be at lower risk of relapse in the long term. Indeed, faster metabolizers have been shown to experience greater nicotine withdrawal and higher rates of withdrawal over the first week of abstinence

Table 5. Multivariate Logistic Regression Model Predicting Successful Quitting (*N* = 871)

Predictor variable	% Quitters	Odds ratio	95% Confidence interval		<i>p</i>
			Lower bound	Upper bound	
Cigarettes per day (CPD)					
≤10 CPD	7.1	Ref.			.535
11–20 CPD	8.6	0.66	0.36	1.22	
> 21 CPD	10.3	0.57	0.23	1.40	
Sex					
Female	10.2	Ref.			.121
Male	7.1	1.71	0.96	3.06	
Age					
18–39	5.6	Ref.			.81
40 +	9.1	1.04	0.55	1.96	
Country					
United States	12.9	Ref.			<.001
United Kingdom	17.5	1.54	0.80	2.95	
Mauritius	3.3	0.17	0.07	0.43	
Thailand	3.4	0.18	0.07	0.46	
Mexico	7.4	0.43	0.17	1.09	
NMR		2.48	1.23	4.99	

NMR = nicotine metabolite ratio.

predicted more favorable cessation outcomes in a small pilot study.³⁴ That said, the relationship between NMR and the severity of withdrawal from nicotine has not been shown to be strong, but the data studying this relationship are quite limited.³⁵

A weakness of our study is the relatively small sample sizes (and thus low power) available to evaluate the relationship between NMR and smoking cessation when one begins to stratify data by country and smoker characteristics. Yet, we find a significant effect despite small sample size. The sample here is a subset of the larger ITC surveys, which are designed to be nationally representative of smokers in their respective countries. While we have compared those who provided samples to those who did not and found few systematic differences, we cannot completely rule out selection bias as an explanation for our findings. Second, the ITC surveys are designed to examine behaviors and perceptions related to tobacco control policies and follow the natural history of smoking. While ITC has been used to examine factors associated with smoking cessation,^{36,37} it should be recognized that smokers in this sample quit of their own volition, often during the intersurvey period, and thus the entire quitting process is not precisely captured. That said, this is still one of the largest population-based studies to examine the relationship between NMR and smoking cessation, and the results are generally consistent between countries and across a range of smoker characteristics examined. The results need to be replicated and in other population-based cohorts such as the Population Assessment of Tobacco and Health study.

Supplementary Material

Supplementary data are available at *Nicotine & Tobacco Research* online.

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Declaration of Interests

NLB has been a consultant to pharmaceutical companies that market smoking cessation medications and has been an expert witness in litigation against tobacco companies. KMC has received grant funding from the Pfizer, Inc, to study the impact of a hospital-based tobacco cessation intervention and has received funding as an expert witness in litigation filed against the tobacco industry. JFT has received funding as an expert witness in litigation involving the tobacco industry.

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