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Correlates of the Nicotine Metabolite Ratio in Alaska Native People Who Smoke Cigarettes

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Research on nicotine metabolism has primarily focused on white adults. This study examined associations between nicotine metabolism, tobacco use, and demographic characteristics among Alaska Native adults who smoke cigarettes. Participants ($N = 244$) were Alaska Native adults who smoked and who provided a plasma sample at baseline (70.1%) or follow-up (29.9%) of a randomized controlled trial of a cardiovascular risk behavior intervention. At baseline, participants self-reported age, sex, Alaska Native heritage, cigarettes per day, time to first cigarette upon wakening, menthol use, perceived difficulty staying quit, tobacco withdrawal symptoms, and past-month tobacco product use, binge drinking, and cannabis use. At 3-, 6-, 12-, and 18-month follow-ups, participants self-reported 7-day point prevalence abstinence from smoking. Height and weight were measured to calculate body mass index (BMI). Participants' nicotine metabolite ratio (NMR), calculated as the ratio of plasma cotinine and *trans*-3' hydroxycotinine, was log-transformed. The sample (52.0% male, age $M = 47.0$ years [$SD = 13.8$], 60.3% of Inupiaq heritage) averaged 12.5 cigarettes per day ($SD = 10.5$); 64.0% smoked within 30 min of wakening. NMR was not significantly associated with age, sex, Alaska Native heritage, BMI, cigarettes per day, time to first cigarette upon wakening, menthol use, perceived difficulty staying quit, past-month dual tobacco product use, withdrawal symptoms, past-month binge drinking, past-month cannabis use, or abstinence from smoking (all p-values $> .050$). Characteristics that relate to NMR in Alaska Native adults may differ from those typically identified among white adults. Specifically, results may suggest that Alaska Native adults with slower nicotine metabolism do not titrate their nicotine intake when smoking.

Public Significance

Research on the associations between nicotine metabolism, smoking characteristics, and cessation has primarily focused on white adults. The present study suggests that like Black adults who smoke cigarettes, Alaska Native adults with slower nicotine metabolism may not change their nicotine intake according to how quickly they metabolize nicotine.

Keywords: nicotine metabolite ratio, Alaska Native, tobacco, smoking, nicotine metabolism

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Vogel contributed to conceptualization, formal analysis, and writing (original draft). Benowitz contributed to conceptualization, funding acquisition, investigation, resources, and writing (reviewing and editing). Skan and Schnellbaecher contributed to investigation and writing (reviewing and editing). Prochaska contributed to conceptualization, funding acquisition, investigation, supervision, and writing (reviewing and editing). All authors have read and approved the final manuscript.

Benowitz and Prochaska have served as expert witnesses against the tobacco companies in lawsuits for which they have received fees for the work and have provided consultation to pharmaceutical and technology companies that make medications and other treatments for quitting smoking. Vogel, Skan, and Schnellbaecher have no disclosures to report.

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The rate of nicotine metabolism varies across individuals (Benowitz et al., 1982). Genetic variations affect the activity of liver enzymes CYP2A6 and CYP2B6 that metabolize nicotine into cotinine and *trans*-3' hydroxycotinine (3HC). The ratio of 3HC to cotinine, called the nicotine metabolite ratio (NMR), is a biomarker of the metabolic clearance of nicotine by CYP2A6 (Dempsey et al., 2004). NMR captures both genetic and environmental influences on nicotine metabolism (Ray et al., 2009). Compared to slower metabolizers, individuals with higher NMR metabolize nicotine quickly and tend to smoke more cigarettes per day (West et al., 2011), have higher levels of inflammation and exposure to toxicants (Carroll et al., 2020), have a poorer response to nicotine patch (Lerman et al., 2006, 2015; Schnoll et al., 2009) and placebo NRT or placebo bupropion (Ho et al., 2009; Patterson et al., 2008), and experience greater cravings and withdrawal symptoms (Kubota et al., 2006; Lerman et al., 2006; Liakoni et al., 2019). Faster metabolizers respond better to varenicline than to nicotine patch, while slow metabolizers do not experience this benefit and may have more side effects from varenicline (Lerman et al., 2015). Therefore, understanding variation in NMR has important smoking cessation treatment implications (Allenby et al., 2016).

NMR varies by personal characteristics, with evidence of racial differences. Overall, white individuals typically have faster nicotine metabolism than Black individuals (Chenoweth et al., 2014; Kandel et al., 2007; Patterson et al., 2008; Pérez-Stable et al., 1998; Schnoll et al., 2009). Among both white and Black individuals, NMR is higher among females, older individuals, and those with lower body mass index (BMI; Benowitz et al., 2006; Chenoweth et al., 2014; Ho et al., 2009; Kandel et al., 2007; Liakoni et al., 2019; Mooney et al., 2008; Mwenifumbo et al., 2007; Patterson et al., 2008; Schnoll et al., 2009; St. Helen et al., 2019; Swan et al., 2009). Additionally, use of estrogenic medication appears to increase NMR in both white and Black women (Benowitz et al., 2006; Chenoweth et al., 2014). One study found a positive association between NMR and alcohol use (Chenoweth et al., 2014); however, others have not (Liakoni et al., 2019; Mwenifumbo et al., 2007; Swan et al., 2009). One study examined the association between NMR and cannabis use, finding no significant relationship (Mwenifumbo et al., 2007).

Notably, a systematic review found weaker than expected relationships between NMR and cigarettes per day or commonly used self-report dependence measures (e.g., Fagerström Test of Nicotine Dependence, Hooked on Nicotine Checklist, Wisconsin Index of Smoking Motives) (West et al., 2011). The relationship between NMR and nicotine dependence may be less apparent in groups that tend to smoke fewer cigarettes per day, potentially due to differences in smoking motives. For example, NMR has a weaker association with cigarettes per day among Black than white people who smoke (Ross et al., 2016), and it has been suggested that positive reinforcement (i.e., "peak-seeking"; Russell & Feyerabend, 1978) may drive smoking among Black individuals, while relief from withdrawal symptoms and stabilization of mood (i.e., "trough-maintaining"; Russell & Feyerabend, 1978) may drive smoking in white individuals (Ross et al., 2016). Indeed, white individuals with higher NMR typically titrate their cigarettes per day to match their rate of nicotine metabolism and maintain a constant nicotine level; however, Black individuals, for whom cigarettes per day tend to be lower (Centers for Disease Control and Prevention [CDC], 2019a), typically do not titrate their cigarettes per day (Ross et al., 2016; St. Helen et al., 2019). Furthermore, menthol use can decrease nicotine metabolism (Benowitz et al., 2004), and disproportionately high menthol use among Black individuals who smoke may partially—but not entirely—explain the association between NMR and race (Ho et al., 2009; Ross et al., 2016).

Less is known about nicotine metabolism among Alaska Native people. Despite smoking fewer cigarettes per day on average than White people who smoke (CDC, 2019b), Alaska Native people have high smoking prevalence and high tobacco-related disease burden (CDC, 2019b). Alaska Native people frequently experience discrimination, lack of access to health insurance, wealth inequality, and other structural inequities that increase their risk for smoking and cardiovascular disease (Breathett et al., 2020). Additionally, previous research has identified differences in variant allele frequencies in Alaska Native Yup'ik people that influence nicotine metabolism (Binnington et al., 2012; Zhu et al., 2013). Similar to white people who smoke cigarettes, Yup'ik individuals with slower nicotine metabolism had lower daily nicotine intake, as assessed by urine total nicotine equivalents (Zhu, Binnington, et al., 2013). Nonetheless, similar to Black people who smoke, Yup'ik individuals did not reduce their cigarettes per day to compensate for slower nicotine metabolism (Zhu, Binnington, et al., 2013). It remains unclear whether previously identified correlates of NMR in white and Black individuals apply to Alaska Native people who smoke cigarettes. Moreover, previous research on nicotine metabolism in Alaska Native people has primarily recruited participants of Yup'ik descent.

This study examined correlates of NMR in a diverse sample of Alaska Native people living in the Norton Sound Region of Alaska. Approximately 82% of Norton Sound residents are Alaska Native, primarily Inupiaq and Yup'ik (Boedeker & Foster, 2011). More than half (52.3%) of Alaska Native adults in Norton Sound report current cigarette smoking (Dilley et al., 2013).

Method

Participants, Design, and Procedure

Participants were enrolled in the Healing and Empowering Alaskan Lives Toward Healthy-Hearts (HEALTHH) Project, a randomized clinical trial of two culturally-tailored interventions for tobacco use and other cardiovascular disease risk behaviors among Alaska Native people (Prochaska et al., 2018). Eligible participants were self-identified Alaska Native adults, age 19+ years, who spoke English, resided in the Norton Sound region, smoked 5+ cigarettes per day at study entry, and had high blood pressure or high cholesterol. Participants were recruited in 2015–2019 through community outreach including radio announcements, flyers, and communications from local health providers (Prochaska et al., 2018). Participants were randomized to receive a culturally and individually tailored intervention for tobacco cessation or blood pressure/cholesterol management based on the transtheoretical model (Prochaska & DiClemente, 1983). Assessments were conducted at baseline and 3, 6, 12, and 18 months at the local community clinics (Prochaska et al., 2018). The present study analyzed data from the baseline assessment, which consisted of a self-report survey and body measures, and self-reported cigarette smoking status at follow-up assessments. Participants were compensated $30 for completing the baseline assessment, $40 for

completing assessments at 3, 6, and 12 months, and $50 for completing the 18-month assessment (Prochaska et al., 2018). Participants were asked to provide a blood sample at baseline to test for NMR. If missed, the blood sample was requested at a follow-up assessment, if still smoking cigarettes. For the current analyses, all self-report measures (except abstinence from smoking) and 70.1% of plasma samples were obtained at baseline. Ethical approval was granted by the Stanford University School of Medicine Institutional Review Board.

Measures

NMR

NMR was calculated using the ratio of plasma 3HC to cotinine. Plasma samples were analyzed using liquid chromatography with tandem mass spectrometry (Jacob et al., 2011).

Demographic Characteristics

Participants reported their age, sex (male/female), Alaska Native heritage (Inupiaq, Yup'ik, other, or multiple heritages) and identification with their heritage (1 = *not at all*, 4 = *very much*), Norton Sound community of residence (coded as Nome vs. other), education (elementary, some high school, high school graduate/GED, some college, college graduate, graduate degree), subjective social status (a validated measure of socioeconomic status; 1 = *lowest standing in one's community*, 10 = *highest standing*; Adler et al., 2000), employment (employed; unemployed; retired, on disability, or other), and general health (1 = *poor*, 5 = *excellent*). BMI was calculated from height and weight measured at the time of plasma sample collection or the closest available assessment point.

Tobacco and Other Substance Use

Smoking characteristics measured were cigarettes per day, time to first cigarette (within/not within 30 min. of waking), menthol cigarette use (nonmenthol only, menthol only, both menthol and nonmenthol), perceived difficulty with sustaining a quit attempt (1 = *lowest difficulty*, 10 = *greatest difficulty*; Hall et al., 1990), and nicotine withdrawal symptoms (8-item Minnesota Tobacco Withdrawal Scale, rated 0 = *none* to 4 = *severe*; Hughes & Hatsukami, 1986). Participants reported the date of last use of: snuff or chewing tobacco, Iqmik or Blackbull, cigar or pipe tobacco, and e-cigarettes. Past-month use of any noncigarette tobacco product was categorized as positive versus none. Past-month binge drinking (yes/no) was determined by self-reported number of days having 4+ drinks (*for women*) or 5+ drinks (*for men*) in a row within a couple of hours. Participants also reported past-month cannabis use (yes/no). Seven-day point prevalence abstinence from smoking was indicated by self-reported zero past-week cigarettes at any follow-up assessment (yes/no).

Analyses

NMR and cigarettes per day were log-transformed for analyses (log-transformed NMR = Ln[cotinine/3HC + 1]). Associations between participant characteristics and log-transformed NMR were tested using Pearson's correlations, independent samples t-tests, and one-way ANOVAs. Because the association between sex and NMR is presumably driven by estrogen and may weaken among postmenopausal females (Benowitz et al., 2006; Chenoweth et al., 2014), linear regression tested the relationship between NMR and sex, adjusting for age. As a sensitivity analysis, participant characteristics were tested in association with NMR dichotomized by quartile into slow versus normal/fast metabolism (i.e., lowest quartile of NMR versus three higher quartiles) using independent-samples *t*-tests, chi-square tests, and logistic regression. As a proxy for daily nicotine dose (Ross et al., 2016), the molar sum of 3HC and cotinine was tested in association with participant characteristics using Pearson's correlations, independent samples *t*-tests, and one-way ANOVAs. Prior research found that the molar sum of 3HC and cotinine was strongly correlated with daily intake of nicotine (r = .92; Benowitz et al., 2010).

Results

Participant characteristics are presented in Table 1. The sample (N = 244) was 52.0% male, with a mean age of 47 years

Table 1
Sample Descriptive Characteristics

Demographic characteristics	*M (SD) or N (%)*
Age	47.0 (13.8)
Male sex	127 (52.0%)
Body mass index (BMI)	28.2 (7.2)
AN heritage	
Inupiaq	146 (60.3%)
Yup'ik	66 (27.3%)
Other (Aleut, Athabascan, Eskimo, Tlingit)	11 (4.5%)
Multiple	19 (7.9%)
Identification with AN heritage	
Not at all	2 (0.8%)
Very little	34 (14.0%)
Somewhat	64 (26.3%)
Very much	143 (58.8%)
Residence in Nome	61 (25.0%)
Education	
Less than high school	50 (20.6%)
High school graduate/GED	142 (58.4%)
Some college or higher	51 (21.0%)
Subjective standing in community[a]	5.3 (2.1)
Employment	
Employed	107 (44.0%)
Unemployed	91 (37.4%)
Retired, on disability, or other	45 (18.5%)
General health	
Excellent or very good	35 (14.7%)
Good	94 (39.5%)
Fair or poor	109 (45.8%)
Tobacco and other substance use	*M (SD) or N (%)*
Cigarettes per day	12.5 (10.5)
Smokes within 30 min of waking	153 (64.0%)
Nonmenthol use only	160 (65.8%)
Perceived difficulty staying quit[b]	6.1 (3.0)
Past-month other tobacco product use	25 (10.2%)
Tobacco withdrawal symptoms[c]	7.9 (6.4)
Past-month binge drinking	76 (31.1%)
Past-month cannabis use	130 (54.2%)
Reported abstinence (% yes)[d]	27 (11.1%)

[a] Range: 1 = lowest to 10 = highest perceived standing in community.
[b] Range: 1 = lowest to 10 = highest perceived difficulty.
[c] Range: 0 = no symptoms to 32 = eight severe symptoms.
[d] Self-reported abstinence from cigarette use in the past 7 days at 1 + follow-up assessments.

(SD = 13.8), and mean BMI of 28.3 (SD = 7.2), which is in the overweight range. Most participants were of Inupiaq (60.3%) or Yup'ik (27.3%) heritage. Most (85.2%) identified with their heritage "somewhat" to "very much." Mean NMR was 0.58 (SD = 0.35) with a range of 0.02–2.65 and a median of 0.51 (IQR: 0.35–0.71). On average, participants smoked 12.5 cigarettes per day (SD = 10.5), with a range of 1–70 and a median of 10. Smoking within 30 min of wakening, an indicator of dependence, was reported by 64% of participants. On a scale of 1 (*least*) to 10 (*most*), participants rated the difficulty of staying quit at M = 6.1 (SD = 3.0). Most (65.8%) reported smoking nonmenthol cigarettes only; 10.2% used other tobacco products in the past month; 31.1% reported past-month binge drinking; 54.2% past-month cannabis use; and 11.1% reported abstinence from smoking cigarettes at one or more follow-up assessments.

NMR was not associated with age (r = .09, p = .182), sex [$t(242) = -.22$, p = .824], BMI ($r = -.12$, p = .059), Alaska Native heritage [$F(3, 238) = 1.44$, p = .233], cigarettes per day ($r = -.03$, p = .617), time to first cigarette upon wakening [$t(237)$ = .84, p = .404], menthol use [$t(241)$ = .95, p = .342], perceived difficulty staying quit ($r = -.03$, p = .614), past-month dual tobacco product use [$t(242)$ = .65, p = .519], tobacco withdrawal symptoms ($r = -.02$, p = .793), past-month binge drinking [$t(242)$ = .87, p = .386), past-month cannabis use [$t(238)$ = 1.87, p = .063], or abstinence from smoking at a follow-up [$t(242)$ = .74, p = .462). When adjusting for age, sex was still not significantly associated with NMR ($B < .001$, p = .987). Comparing slow metabolizers to normal/fast metabolizers produced the same pattern of results (p-values > .05), except that slow metabolizers were less likely to have used cannabis in the past month than normal/fast metabolizers (40.0% vs. 59.1%; $\chi^2(1) = 7.27$, p = .007). Defining slow metabolism as NMR < .31 (Lerman et al., 2015) produced the same pattern of results (n = 46 with slow metabolism). To determine whether the null association between CPD and NMR was specific to light smokers, we examined the correlation between CPD and NMR within the highest and lowest tertiles of CPD, and found no association (p-values > .05).

The molar sum of cotinine and 3HC was positively (though weakly) associated with cigarettes per day (r = .17, p = .010), reflecting greater daily nicotine intake among participants who smoked more cigarettes at baseline. The molar sum of cotinine and 3HC was not significantly associated with NMR ($r = -.02$, p = .785). Molar sum of cotinine and 3HC per cigarette averaged 0.19 (SD = 0.22, range = 0–2.30). Results suggest that smoking behavior was not driven by rate of nicotine metabolism. Additionally, participants who quit smoking during the follow-up period had lower average daily nicotine intake [$t(242) = 2.18$, p = .031); however, daily nicotine intake was not associated with any other demographic or smoking characteristics.

Discussion

The current study examined correlates of the rate of nicotine metabolism in a sample of 244 Alaska Native people who smoke cigarettes living in the Norton Sound Region of Alaska. NMR was not significantly associated with smoking behavior or any measured sociodemographic characteristic or other substance use variable. Despite lighter smoking, Alaska Native people have disproportionately high tobacco-related disease burden (CDC, 2019b). The current study found that the number of cigarettes smoked per day was not significantly associated with NMR, suggesting that Alaska Native people who smoke cigarettes did not titrate their cigarette use to match their nicotine metabolism. The finding is similar to that found in Black individuals (Ross et al., 2016; St. Helen et al., 2019), who also experience disproportionately high prevalence of tobacco-related disease despite tending to smoke fewer cigarettes per day than white individuals (CDC, 2019a). Also similar to a study of Black people with light smoking, the current study found that sex and time to first cigarette were not associated with NMR in Alaska Native people who smoke cigarettes (St. Helen et al., 2019). Findings suggest that Alaska Native men and women in the current sample metabolized nicotine at similar rates, and individuals with faster nicotine metabolism were not necessarily more dependent on smoking. Of 13 primary tests of association that were run to examine correlates of NMR, none were significant, despite a reasonable sample size.

There are several possible reasons for the pattern of null results observed in the current study. First, similar to Black individuals who smoke on average fewer cigarettes per day than white individuals (Ross et al., 2016), Alaska Native individuals may engage in "peak-seeking" smoking, such that they smoke primarily for positive reinforcement (Russell & Feyerabend, 1978). "Peak seekers" presumably obtain their smoking reward from the peak nicotine level immediately following a cigarette. Peak nicotine level is unaffected by NMR. Cigarettes per day are known to be correlated with urine total nicotine equivalents, but if Alaska Native people are more likely to engage in "peak-seeking" smoking, total nicotine equivalents may correlate with cigarettes per day, whereas nicotine metabolism may not. In contrast, "trough maintainers" presumably obtain their smoking reward from a consistent nicotine level throughout the day, possibly related in part to desensitization of nicotinic receptors. Thus, trough maintainers would be more likely to titrate their daily intake of nicotine to their NMR (Ross et al., 2016). Future research could assess smoking motives in Alaska Native people to better understand peak seeking versus trough maintaining smoking behavior. Second, Alaska Native individuals have a faster average nicotine metabolism than white or Black individuals (Binnington et al., 2012). Studies of the relationship between NMR and cigarettes per day find that the greatest impact is seen in the slowest quartile of metabolizers, with relatively little change across higher levels of metabolism (Lerman et al., 2015; Schnoll et al., 2009). Importantly, in this study, a sensitivity analysis of NMR in quartiles still found no significant difference between slow metabolizers and normal/fast metabolizers in the association between NMR and cigarettes per day. Third, social determinants of health may be stronger predictors of cigarette smoking behavior than biological phenotypes such as NMR. Racism and other adverse experiences appear to contribute to cigarette smoking behavior among AN people (Breathett et al., 2020).

Findings in the current study showed no significant associations between NMR and participants' demographic and smoking characteristics. Notably, other studies have found weak associations between individuals' characteristics and their NMR. For example, in a study of Black and white people who smoke cigarettes, race, sex, estrogen use, BMI, cigarettes per day, and alcoholic beverages per week each accounted for less than 2% of total NMR variation (Chenoweth et al., 2014). In a study of Black people who engaged in light smoking, sex, cigarettes per day, and time to first cigarette were

not associated with NMR (St. Helen et al., 2019). Although slow metabolizers were less likely to have used cannabis, compared to normal/fast metabolizers, no other associations were significant in sensitivity analyses. Overall, results suggest no meaningful differences in smoking or demographic characteristics between slow and normal/fast metabolizers in this study.

Moreover, over the 18-month follow-up period, current study participants' likelihood of quitting smoking cigarettes was not associated with their NMR despite lower average daily nicotine intake in those who quit smoking. This finding is consistent with a prior study of primarily white people who smoke cigarettes, in which NMR was not associated with abstinence (Lerman et al., 2006). However, slower metabolizers in studies of primarily white and Black individuals have found that slower metabolizers benefit more from nicotine patch than do faster metabolizers (Lerman et al., 2006, 2015; Schnoll et al., 2009). Research has not yet examined differences in pharmaceutical smoking cessation treatment response by NMR in Alaska Native people who smoke. Because Alaska Native people in this study did not appear to titrate their nicotine intake to their metabolism, we may expect a positive response to combination (i.e., slow-acting and fast-acting) NRT or varenicline. Combination NRT helps maintain a steady nicotine level and manage acute cravings, while varenicline blocks the acute rewarding effects of nicotine.

Study limitations include reliance on self-reported smoking behaviors, which may not fully capture smoking characteristics. For example, while cigarettes per day did not differ by NMR, there may have been differences in smoking topography, such that faster metabolizers took in more nicotine per cigarette (Zhu, Binnington, et al., 2013). Alaska Native heritage was self-identified, and participants may have differed in the strength of their Alaska Native ancestry, resulting in a genetically heterogeneous sample. It is unclear whether smoking topography differed by NMR because urine total nicotine equivalents, the gold standard for daily intake of nicotine, were not measured. The molar sum of 3HC and cotinine (i.e., a proxy for daily nicotine intake) was found to significantly correlate only with cigarettes per day and was not associated with other measured participant characteristics in this sample. Nonetheless, future research should measure total nicotine equivalents in Alaska Native individuals who smoke for a more comprehensive view of titration of smoking by NMR. Future research could also match white and AN individuals on cigarettes per day to determine whether relationships between NMR and smoking are race-specific. Substance use was coded according to whether participants had engaged in any cannabis use or binge drinking in the past month. A more fine-grained measure, capturing recency and quantity of use, may have provided more nuanced results.

Conclusions

Research on the associations between nicotine metabolism, smoking characteristics, and cessation has primarily focused on white adults. Relative to white people who smoke, Black and Alaska Native people tend to smoke fewer cigarettes per day, and the present study suggests that like Black individuals, Alaska Native people with slower nicotine metabolism may not titrate their nicotine intake accordingly. Consistent with clinical practice guidelines, behavioral counseling with cessation medications is recommended for treatment of Alaska Native adults who smoke cigarettes, including a combination of short-acting and long-acting nicotine replacement therapy, bupropion, and varenicline.

References

Adler, N. E., Epel, E. S., Castellazzo, G., & Ickovics, J. R. (2000). Relationship of subjective and objective social status with psychological and physiological functioning: Preliminary data in healthy, White women. *Health Psychology*, *19*, 586–592.

Allenby, C. E., Boylan, K. A., Lerman, C., & Falcone, M. (2016). Precision medicine for tobacco dependence: Development and validation of the nicotine metabolite ratio. *Journal of Neuroimmune Pharmacology*, *11*, 471–483. https://doi.org/10.1007/s11481-016-9656-y

Benowitz, N. L., Dains, K. M., Dempsey, D., Yu, L., & Jacob, P., III. (2010). Estimation of nicotine dose after low-level exposure using plasma and urine nicotine metabolites. *Cancer Epidemiology, Biomarkers & Prevention*, *19*(5), 1160–1166.

Benowitz, N. L., Herrera, B., & Jacob, P. R. (2004). Mentholated cigarette smoking inhibits nicotine metabolism. *The Journal of Pharmacology and Experimental Therapeutics*, *310*(3), 1208–1215. https://doi.org/10.1124/jpet.104.066902

Benowitz, N. L., Jacob, P. R., Jones, R. T., & Rosenberg, J. (1982). Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *The Journal of Pharmacology and Experimental Therapeutics*, *221*(2), 368–372.

Benowitz, N. L., Lessov-Schlaggar, C. N., Swan, G. E., & Jacob, P. R. (2006). Female sex and oral contraceptive use accelerate nicotine metabolism. *Clinical Pharmacology and Therapeutics*, *79*(5), 480–488. https://doi.org/10.1016/j.clpt.2006.01.008

Binnington, M. J., Zhu, A. Z. X., Renner, C. C., Lanier, A. P., Hatsukami, D. K., Benowitz, N. L., & Tyndale, R. F. (2012). CYP2A6 and CYP2B6 genetic variation and its association with nicotine metabolism in South Western Alaska Native people. *Pharmacogenetics and Genomics*, *22*, 429–440. https://doi.org/10.1097/FPC.0b013e3283527c1c

Boedeker, B., & Foster, S. (2011). *2010 census counts for Alaska Natives/American Indians alone or in combination with one or more other races*. https://www.ihs.gov/sites/alaska/themes/responsive2017/display_objects/documents/pop_reports/Census2010publicationInternet.pdf

Breathett, K., Sims, M., Gross, M., Jackson, E. A., Jones, E. J., Navas-Acien, A., Taylor, H., Thomas, K. L., Howard, B. V., & the American Heart Association Council on Lifestyle and Cardiometabolic Health. (2020). Cardiovascular health in American Indians and Alaska Natives: A scientific statement from the American Heart Association. *Circulation*, *141*, e948–e959. https://doi.org/10.1161/CIR.0000000000000773

Carroll, D. M., Murphy, S. E., Benowitz, N. L., Strasser, A. A., Kotlyar, M., Hecht, S. S., Carmella, S. G., McClernon, F. J., Pacek, L. R., Dermody, S. S., Vandrey, R. G., Donny, E. C., & Hatsukami, D. K. (2020). Relationships between the nicotine metabolite ratio and a panel of exposure and effect biomarkers: Findings from two studies of U.S. commercial cigarette smokers. *Cancer Epidemiology, Biomarkers & Prevention*. Advance online publication. https://doi.org/10.1158/1055-9965.EPI-19-0644

Centers for Disease Control and Prevention. (2019a, November 18). *African Americans and tobacco use*. Tobacco-Related Disparities. https://www.cdc.gov/tobacco/disparities/african-americans/index.htm

Centers for Disease Control and Prevention. (2019b, November 25). *American Indians/Alaska Natives and tobacco use*. Tobacco-Related Disparities. https://www.cdc.gov/tobacco/disparities/american-indians/index.htm

Chenoweth, M. J., Novalen, M., Hawk, L. W. J., Schnoll, R. A., George, T. P., Cinciripini, P. M., Lerman, C., & Tyndale, R. F. (2014). Known and novel sources of variability in the nicotine metabolite ratio in a large sample of treatment-seeking smokers. *Cancer Epidemiology, Biomarkers & Prevention*, *23*(9), 1773–1782. https://doi.org/10.1158/1055-9965.EPI-14-0427

Dempsey, D., Tutka, P., Jacob, P. R., Allen, F., Schoedel, K., Tyndale, R. F., & Benowitz, N. L. (2004). Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. *Clinical Pharmacology and Therapeutics*, *76*(1), 64–72. https://doi.org/10.1016/j.clpt.2004.02.011

Dilley, J. A., Peterson, E., Hiratsuka, V. Y., & Rohde, K. (2013). Discovering unique tobacco use patterns among Alaska Native people. *International Journal of Circumpolar Health*, *72*(1), 21208. https://doi.org/10.3402/ijch.v72i0.21208

Hall, S. M., Havassy, B. E., & Wasserman, D. A. (1990). Commitment to abstinence and acute stress in relapse to alcohol, opiates, and nicotine. *Journal of Consulting and Clinical Psychology*, *58*(2), 175–181.

Ho, M. K., Mwenifumbo, J. C., Al Koudsi, N., Okuyemi, K. S., Ahluwalia, J. S., Benowitz, N. L., & Tyndale, R. F. (2009). Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. *Clinical Pharmacology and Therapeutics*, *85*(6), 635–643. https://doi.org/10.1038/clpt.2009.19

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry*, *43*(3), 289–294. https://doi.org/10.1001/archpsyc.1986.01800030107013

Jacob, P. R., Yu, L., Duan, M., Ramos, L., Yturralde, O., & Benowitz, N. L. (2011). 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. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences*, *879*(3–4), 267–276. https://doi.org/10.1016/j.jchromb.2010.12.012

Kandel, D. B., Hu, M.-C., Schaffran, C., Udry, J. R., & Benowitz, N. L. (2007). Urine nicotine metabolites and smoking behavior in a multiracial/multiethnic national sample of young adults. *American Journal of Epidemiology*, *165*(8), 901–910. https://doi.org/10.1093/aje/kwm010

Kubota, T., Nakajima-Taniguchi, C., Fukuda, T., Funamoto, M., Maeda, M., Tange, E., Ueki, R., Kawashima, K., Hara, H., Fujio, Y., & Azuma, J. (2006). CYP2A6 polymorphisms are associated with nicotine dependence and influence withdrawal symptoms in smoking cessation. *The Pharmacogenomics Journal*, *6*, 115–119.

Lerman, C., Schnoll, R. A., Hawk, L. W. J., Cinciripini, P., George, T. P., Wileyto, E. P., Swan, G. E., Benowitz, N. L., Heitjan, D. F., Tyndale, R. F., & the PGRN-PNAT Research Group. (2015). 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. *The Lancet. Respiratory Medicine*, *3*, 131–138. https://doi.org/10.1016/S2213-2600(14)70294-2

Lerman, C., Tyndale, R., Patterson, F., Wileyto, E. P., Shields, P. G., Pinto, A., & Benowitz, N. (2006). Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. *Clinical Pharmacology and Therapeutics*, *79*(6), 600–608. https://doi.org/10.1016/j.clpt.2006.02.006

Liakoni, E., Edwards, K. C., St. Helen, G., Nardone, N., Dempsey, D. A., Tyndale, R. F., & Benowitz, N. L. (2019). Effects of nicotine metabolic rate on withdrawal symptoms and response to cigarette smoking after abstinence. *Clinical Pharmacology and Therapeutics*, *105*(3), 641–651. https://doi.org/10.1002/cpt.1238

Mooney, M. E., Li, Z., Murphy, S. E., Pentel, P. R., Le, C., & Hatsukami, D. K. (2008). Stability of the nicotine metabolite ratio in ad libitum and reducing smokers. *Cancer Epidemiology, Biomarkers & Prevention*, *17*(6), 1396–1400. https://doi.org/10.1158/1055-9965.EPI-08-0242

Mwenifumbo, J. C., Sellers, E. M., & Tyndale, R. F. (2007). Nicotine metabolism and CYP2A6 activity in a population of black African descent: Impact of gender and light smoking. *Drug and Alcohol Dependence*, *89*, 23–33. https://doi.org/10.1016/j.drugalcdep.2006.11.012

Patterson, F., Schnoll, R. A., Wileyto, E. P., Pinto, A., Epstein, L. H., Shields, P. G., Hawk, L. W., Tyndale, R. F., Benowitz, N., & Lerman, C. (2008). Toward personalized therapy for smoking cessation: A randomized placebo-controlled trial of bupropion. *Clinical Pharmacology and Therapeutics*, *84*(3), 320–325. https://doi.org/10.1038/clpt.2008.57

Pérez-Stable, E. J., Herrera, B., Jacob, P. R., & Benowitz, N. L. (1998). Nicotine metabolism and intake in Black and White smokers. *Journal of the American Medical Association*, *280*(2), 152–156.

Prochaska, J. J., Epperson, A., Skan, J., Oppezzo, M., Barnett, P., Delucchi, K., Schnellbaecher, M., & Benowitz, N. L. (2018). The Healing and Empowering Alaskan Lives Toward Healthy-Hearts (HEALTHH) Project: Study protocol for a randomized controlled trial of an intervention for tobacco use and other cardiovascular risk behaviors for Alaska Native People. *Contemporary Clinical Trials*, *71*, 40–46. https://doi.org/10.1016/j.cct.2018.06.003

Prochaska, J. O., & DiClemente, C. C. (1983). Stages and processes of self-change of smoking: Toward an integrative model of change. *Journal of Consulting and Clinical Psychology*, *51*(3), 390–395.

Ray, R., Tyndale, R. F., & Lerman, C. (2009). Nicotine dependence pharmacogenetics: Role of genetic variation in nicotine-metabolizing enzymes. *Journal of Neurogenetics*, *23*(3), 252–261. https://doi.org/10.1080/01677060802572887

Ross, K. C., Gubner, N. R., Tyndale, R. F., Hawk, L. W. J., Lerman, C., George, T. P., Cinciripini, P., Schnoll, R. A., & Benowitz, N. L. (2016). Racial differences in the relationship between rate of nicotine metabolism and nicotine intake from cigarette smoking. *Pharmacology, Biochemistry, and Behavior*, *148*, 1–7. https://doi.org/10.1016/j.pbb.2016.05.002

Russell, M. A. H., & Feyerabend, C. (1978). Cigarette smoking: A dependence on high-nicotine boli. *Drug Metabolism Reviews*, *8*(1), 29–57. https://doi.org/10.3109/03602537808993776

Schnoll, R. A., Patterson, F., Wileyto, E. P., Tyndale, R. F., Benowitz, N., & Lerman, C. (2009). Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: A validation study. *Pharmacology, Biochemistry, and Behavior*, *92*, 6–11. https://doi.org/10.1016/j.pbb.2008.10.016

St. Helen, G., Benowitz, N. L., Ahluwalia, J. S., Tyndale, R. F., Addo, N., Gregorich, S. E., Pérez-Stable, E., & Sanderson Cox, L. (2019). Black light smokers: How nicotine intake and carcinogen exposure differ across various biobehavioral factors. *Journal of the National Medical Association*, *111*(5), 509–520. https://doi.org/10.1016/j.jnma.2019.04.004

Swan, G. E., Lessov-Schlaggar, C. N., Bergen, A. W., He, Y., Tyndale, R. F., & Benowitz, N. L. (2009). Genetic and environmental influences on the ratio of 3'hydroxycotinine to cotinine in plasma and urine. *Pharmacogenetics and Genomics*, *19*, 388–398. https://doi.org/10.1097/FPC.0b013e32832a404f

West, O., Hajek, P., & McRobbie, H. (2011). Systematic review of the relationship between the 3-hydroxycotinine/cotinine ratio and cigarette dependence. *Psychopharmacology*, *218*, 313–322. https://doi.org/10.1007/s00213-011-2341-1

Zhu, A. Z. X., Binnington, M. J., Renner, C. C., Lanier, A. P., Hatsukami, D. K., Stepanov, I., … Tyndale, R. F. (2013). Alaska Native smokers and smokeless tobacco users with slower CYP2A6 activity have lower tobacco consumption, lower tobacco-specific nitrosamine exposure and lower tobacco-specific nitrosamine bioactivation. *Carcinogensis*, *34*(1), 93–101. https://doi.org/10.1093/carcin/bgs306

Zhu, A. Z. X., Renner, C. C., Hatsukami, D. K., Benowitz, N. L., & Tyndale, R. F. (2013). CHRNA5-A3-B4 genetic variants alter nicotine intake and interact with tobacco use to influence body weight in Alaska Native tobacco users. *Addiction*, *108*, 1818–1828. https://doi.org/10.1111/add.12250

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