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GENDER DIFFERENCES IN SMOKERS AND EFFECTS ON NICOTINE UPTAKE

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Allshine Chen

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The thesis of Allshine Chen was reviewed and approved by the following:

Joshua E. Muscat

Professor of Health Evaluation Science

Thesis Adviser

Junjia Zhu

Assistant Professor of Biostatistics

Kristen Kjerulff

Professor of Public Health Sciences

Master of Public Health Sciences Program Director

*Signatures are on file in the Graduate School

ABSTRACT

Smoking profiles and nicotine uptake of conventional cigarettes vary greatly between individual smokers, but may be characterized by subject-specific factors. Previous studies suggest that men and women differ in smoking habits, cessation rates, and levels of nicotine absorption. However gender differences in puffing behaviors have not been widely explored. Our study is the first to describe gender differences of smoking topography measured in a naturalistic setting.The Pennsylvania Adult Smoking Study (PASS) of 332 adult cigarette smokers examined inhalation behaviors as predictors of nicotine uptake, utilizing portable handheld topography devices to capture the smokers' profiles in a naturalistic environment. Participants completed a one-time pre-study interview along with a questionnaire that investigated a wide range of subject-specific characteristics. Cotinine (COT) and 3-hydroxy-cotinine (3HC) were collected from smokers' saliva samples.Males had significantly higher puff volumes (52.95 ml versus 44.77 ml), cotinine levels (313.5 ng/ml versus 255.9 ng/ml), but lower nicotine metabolite ratio (0.396 versus 0.475) than females. Analyses of covariance (ANCOVA) was used to model the gender effect on nicotine uptake while accounting for covariates, and the Blinder-Oaxaca method was used to decompose the gender differences due to covariates[1-3]. The differences in covariates can explain up to 83% of the gender differences in nicotine uptake. Gender becomes superfluous in predicting nicotine uptake when height, weight, puff volume, and nicotine metabolism are taken into account. Having a thorough understanding of the dynamics of nicotine consumption will provide researchers further insight to aid in the development of treatment regimens, and give regulators necessary criteria to limit nicotine delivery in smoking tobacco.

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ABBREVIATIONS

cotinine (COT)

cigarettes per day (CPD)

mean puff volume (MPV)

mean puff duration (MPD)

mean interpuff interval (IPI),

mean puff duration (MPD)

nicotine metabolite ratio (NMR)

total daily puffs (TDP)

total daily puff volume (TDPV)

total salivary nicotine metabolites (TSNM)

trans-3’-hydroxycotinine (3HC)

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PREFACE

Moderate headway has been made into understanding the differences in smoking behavior, cessation and nicotine uptake between genders. Studies have shown that men tend to smoke more cigarettes per day than women, more intensely per cigarette, and consume more nicotine [4-6]. Others have found that women smoke for different reasons than men and have a harder time quitting smoking [7-10]. On the other hand, data suggests that gender differences in smoking habits are not driven by differences in gender biology but, instead, by social trends [5, 10, 11]. However, puffing behavioral differences between males and females, measured in their customary smoking setting, has not been explored or characterized.

Strong evidence points to nicotine uptake being correlated or even predicted by smoking topography [12]. In fact, a few studies have suggested that smoking topography and puffing profiles is a better predictor of nicotine uptake than cigarettes smoked per day. With recent advances in portable smoking topography devices, we are able to capture and measure the puffing topography of smokers as they go about their daily routines.

It remains unclear as to whether the gender differences in nicotine uptake are due to differences in puffing topography, nicotine metabolism, or other factors that affect men and women differently, and stands to reason that tobacco researchers have to consider whether or not to include gender as a confounding factor when studying cigarette smoking and nicotine uptake [13]. This study will describe gender differences in demographics, nicotine uptake, and smoking topography measured in a naturalistic setting and explore the underlying causes of gender differences in nicotine uptake.

STUDY DESCRIPTION

Pennsylvania Adult Smoking Study (PASS) is a cross-sectional, smoking topography and nicotine dependence study conducted in 14 contiguous counties of central Pennsylvania. The daily smoker recruitment phase lasted from June 2012 to April 2014, with primary recruiting methods relying on internet and social media, local radio advertisements, posted flyers, and word of mouth. Interested participants were screened for eligibility through a phone interview process. Eligible participants gave written consent and were scheduled for two study visits. Upon completion of two study visits, participants were provided with compensation. The study was received approval from the Penn State Hershey College of Medicine Institutional Review Board (Hershey, PA, USA).

DATA COLLECTION

Trained interviewers administered a multiple-domain, structured questionnaire that contained queries on cigarette-use history, socio-demographic measures (age, gender, race, marital status, education, income, occupation, domicile), smoking addiction items (quitting history, Fagerstrom and HONC), medical history, stress measures and other relevant smoking-related measures. The study incorporated items from the PhenX Toolkit version March 23, 2012, Ver 5.1. Participants were taught to use the Smoking Puff Analyzer-Mobile (SPA-M) (SODIM SAS, France) (shown in Figure 1) and were given the smoking machine on the first study visit to use over a 2-day period in conjunction with all of their cigarettes smoked in that period. The interviewer scheduled a second, follow-up visit to collect the SPA-M machine and obtained saliva samples for laboratory analyses of tobacco nicotine metabolites using Salimetrics® Oral Swabs. Study data was uploaded and managed using REDCap, a secure web-based application that supports data capture and management for research studies.

Figure 1: Smoking Puff Analyzer-Mobile (SPA-M)

MEASURES

The SPA/M is a human smoking profile analyzer of cigarettes that allows real-time storage of pressure change profiles, the air flow, as well as the atmospheric pressure of smoking. The light-weight, portable apparatus operates on batteries and stores the measured data on a memory card. It is equipped with a touch screen that enables users to create a log capturing the smoking profile of each individual use. The participant smokes the cigarette through a mouthpiece that is attached to the SPA-M, while flow and pressure changes are recorded using pressure sensors. Once the memory card is connected to a computer, the recorded data is interpreted by the SodAfc software thus permitting an analysis of the smoking profile. The software determines the puff flow (ml/s), the number of puffs, puff duration (s), the interval between puffs (s), and puff volume (ml). From the initial smoking parameters, we were able to calculate other related measures of each smoker, such as mean puff volume (MPV), mean puff duration (MPD), inter-puff interval (IPI), mean puff flow (MPF), total daily puff volume (TDPV), and total daily puff (TPD) throughout the course of a day.

Participants' saliva samples were analyzed using mass-spectrometry for tobacco nicotine metabolites. Primary nicotine metabolites measured were COT and 3HC, while total salivary nicotine metabolites (TSNM) and NMR were derived from the former measurements.

STATISTICAL ANALYSIS

Male and female differences in baseline characteristics were calculated for nicotine metabolites and smoking topography data. Questionnaire responses were summarized and compared between genders. We performed t-tests or Wilcoxon rank-sum test on continuous outcomes, grouping by gender. We described categorical and binary frequencies, stratifying by gender, and tested associations using Chi-squared or Fisher's exact tests.

All variables that had shown value as predictors of COT and TSNM in previous research or showed significant differences between females and males for our data (topography, demographics, and smoking addiction variables) were included in a stepwise regression, with bidirectional model selection based upon the Akaike Information Criterion. Since we had a large number of predictors, we checked for multi-collinearity and eliminated any predictors that had variance inflation factors > 3. With stepwise-selected predictors, we analyzed their predictive value on COT and TSNM, using an ANCOVA model.

The Blinder-Oaxaca decomposition technique was used to model gender differences in cotinine, TNM, and NMR. The technique is used frequently in econometrics and social sciences to identify and quantify the separate contributions of measurable differences between two groups. The decomposition is able to detect any confounding or interaction of a predictor by group levels and measure how it affects the differences in average response between groups. We

included the predictors from the chosen model of the stepwise regression in a two-fold decomposition, investigating the explained versus unexplained effects.

RESULTS

The total number of participants who had completed nicotine metabolite and questionnaire data was 351, while the total number of participants who had valid and complete smoking topography data was 332. The number (%) of female smokers was 200 (57%) and the number of male smokers was 151 (43%). Table 1 compares the demographic characteristics between females and males. As expected, there was a significant differences in mean height (females: 5.36 feet, males: 5.86 feet) and weight (females: 172.38 pounds, males: 195.52 pounds) between females and males. There were no significant differences in average age (females were slightly older) or annual household income (males had higher household income).

Table 1: Overall Descriptive Statistics and SES by Gender

Variable	Women Mean	Men Mean	P-value
Number of Subjects	191	141	
Age	38.46	37.13	0.29
Body Mass Index	27.80	29.26	0.06
Height (feet)	5.36	5.86	<0.01
Weight (pounds)	172.38	195.52	<0.01
People living in House	3.17	3.28	0.52
Total Annual Income	51965.2	57189.9	0.23
Race			>0.99
White(%)	87.13	86.75	
Black(%)	8.91	9.27	
Other(%)	3.96	3.97	
Marital Status			0.56
Married (%)	33.17	30.46	
Divorced (%)	14.85	12.58	
Living with Partner (%)	20.79	23.18	
Separated (%)	7.42	3.97	
Widowed (%)	0.99	0.66	

Table 2 reports the nicotine metabolite levels by gender. There was a strong association between COT levels and gender (313.5 ng/ml versus 255.8 ng/ml, P<0.001). TSNM and NMR also showed significant differences when compared using T-tests, with men showing higher levels for TSNM but lower NMR than women. 3HC did not differ by gender, with females and males having very similar levels of 3HC. Overall, gender is a significant predictor of COT, TSNM, and NMR levels.

Table 2: Levels of Nicotine Metabolites by Gender

Variable	Women Mean	Men Mean	P-value
Number of Subjects	191	141	
Cotinine	255.8	313.5	<0.01
3'-Hydroxycotinine	121.1	130.8	0.40
Total Salivary Nicotine Metabolites	385.1	448.6	0.01
Nicotine Metabolite Ratio	0.475	0.396	0.01

Smoking topography profiles between females and males, shown in Table 3. Smokers' summarized topography was calculated throughout an entire days' use of the smoking machine. Males had a higher mean puff volume than females (52.95 ml versus 44.77 ml). Males also had significantly higher mean puff duration, inter-puff interval, average puff flow, peak puff flow, total daily puff volume, and total puff volume per cigarette than females. Interestingly, females and males smoked the same number of cigarettes per day, took similar number of total puffs in a day, and didn't differ in number of puffs per cigarette. We investigated the Black subgroup in order to see if these results different from the main population and did not find any differences.

Table 3: Comparison of Smoking Topography by Gender

Variable	Women Mean	Men Mean	P-value
Average Puff Volume (ml)	44.77	52.95	<0.0001
Average Puff Duration (s)	1.48	1.65	0.0005
Average Interpuff Interval (s)	26.49	23.54	0.015
Average Puff Velocity (mm/s)	32.71	35.88	0.0031
Peak Puff Velocity (mm/s)	47.76	52.38	0.0136
Number of puffs/cigarette	11.60	11.73	0.831
Total Daily Puffs	110.5	122.3	0.190
Puff volume/cigarette (ml)	515.3	609.7	0.0053
Total Daily Puff Volume (ml)	4946.9	6341.3	0.0015
Cigarettes per day	17.41	15.92	0.092
Cigarette Butt length (mm)	0.795	0.587	0.616
Menthol cigarette smokers (%)	56.28%(112)	52.05%(76)	0.436
Roll Your Own cigarette smokers (%)	17.71%(34)	22.70%(32)	0.2594

Table 4 presents survey-based smoking behavior and addiction results by gender. Differences in HONC scores, time to first cigarette, and smoking habits at work are significant between women and men. Surprisingly, there were no differences in percentage of menthol smokers, roll-your-own smokers, the Fagerstrom Index, age at onset of smoking, the number of years of as a smoker, waking up at night to smoke, overall urges to smoke, and primary smoking location(outside versus inside). There was a borderline non-significant difference in urges to smoke at work, with women reporting stronger urges to smoke at work than men.

Table 4: Measures of Smoking Addiction Tables by Gender

Variable	Women Mean	Men Mean	P-value
Age at onset of smoking (years)	16.6	17.11	0.30
Years smoked	21.87	20.02	0.15
Fagerstrom Index	4.22	4.51	0.24
HONC Score	7.64	6.87	<0.01
Time to First Cigarette (min)	37.25	24.38	0.03
Family Smoked before 18 (%)	86.14	83.33	0.47
Wake to Smoke (%)	29.7	26.67	0.53
Smoke Usually Inside (%)	40.1	37.33	0.59
Smoke Usually Outside (%)	59.41	62.67	
Smokes at Work (%)	49.01	71.81	<0.01
Doesn't Smoke at Work (%)	15.35	2.68	
Not Applicable (%)	35.64	25.5	
Urge to Smoke at Work			0.06
No Urges (%)	2.97	5.96	
Slight Urges (%)	15.35	21.85	
Moderate Urges (%)	39.6	45.7	
Strong Urges (%)	27.23	18.54	
Very Strong Urges (%)	10.4	5.3	
Extremely Strong Urges (%)	4.46	2.65	
Overall Urge to Smoke Scale of 10	6.05	5.77	0.34

We performed AIC-based stepwise regression using covariates that have been shown in previous literature to model COT and TSNM. We removed two covariates from the model based on VIF>3 (TDPV was removed due to correlation with TDP and MPV; MD was removed due to correlation with MPV and MPF). The ANCOVA regression coefficients and p-values based upon the chosen stepwise regression models are shown in Table 5. After accounting for the covariates, gender becomes non-significant (gender was a significant predictor of COT, TSNM, and NMR, as shown previously in Table 2).

Table 5: Multiple-Predictor ANCOVA regression of COT and TSNM

	COT		TSNM	
Predictor	Coefficient	P-value	Coefficient	P-value
Mean Puff Volume (mL)	1.64	<0.01	0.000041	<0.01
Mean Puff Flow	-1.90	0.03	-0.000047	0.03
Gender	-10.95	0.62	-0.00034	0.54
Height	319.04	<0.01	0.0069	0.02
Weight	-1.30	<0.01	-0.000033	<0.01
Total Daily Puffs	0.34	<0.01	-0.000011	<0.01
Nicotine Metabolite Ratio	-112.54	<0.01	0.0016	0.013
Fagerstrom Index	14.94	<0.01	0.00039	<0.01
Time to First Cigarette (min)	-0.29	0.032	-0.000007	0.034
Years smoked	4.07	<0.01	0.00011	<0.01
Roll Your Own Cigarette	-57.70	<0.01	-0.0016	<0.01

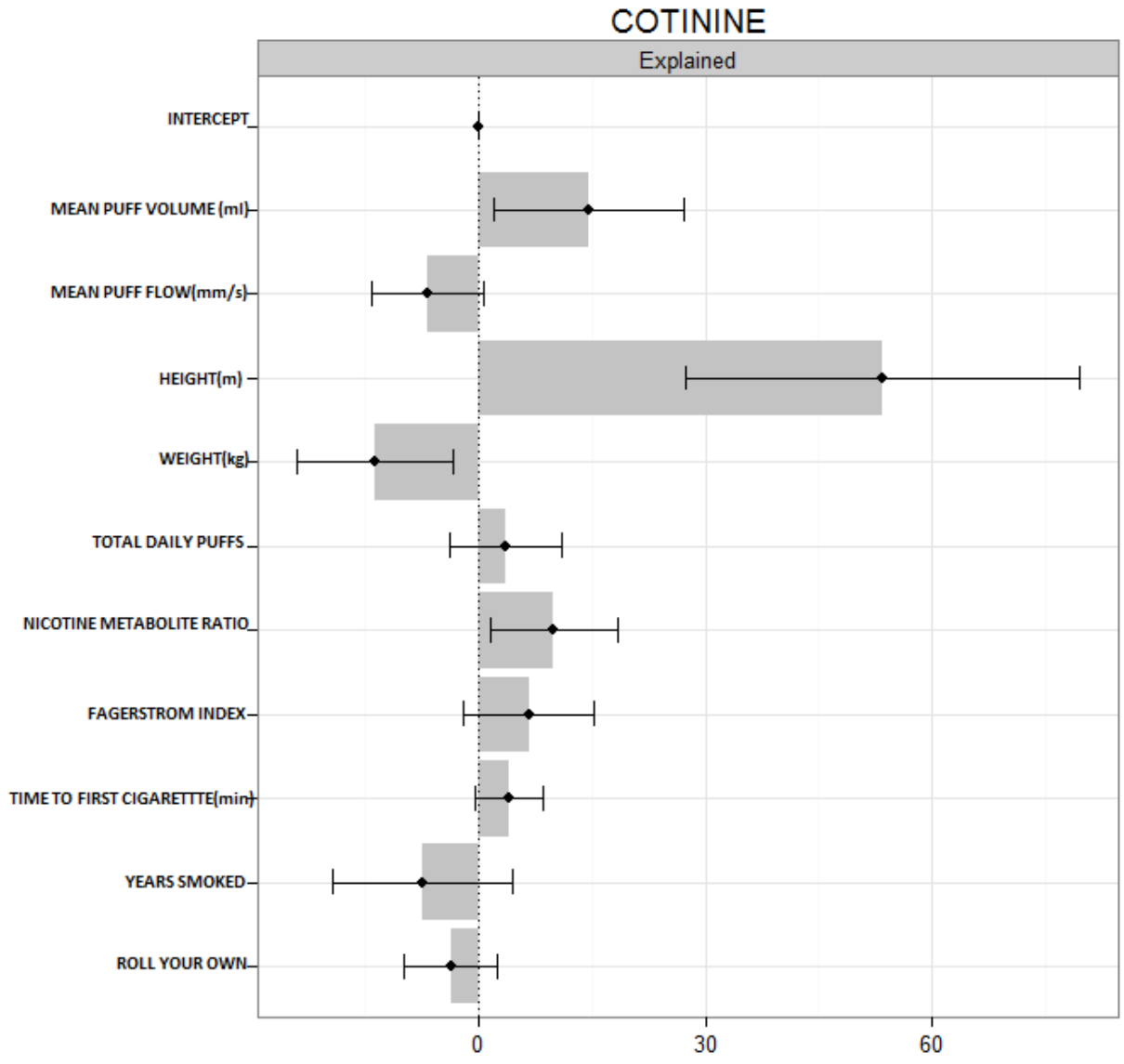
The Blinder-Oaxaca decomposition in Table 6 shows that smokers' MPV, height, weight, and NMR are the driving factors behind the univariate differences in COT and TSNM. A total of 83.39% of the differences can be attributed to the predictors, while the remainder is attributed to the coefficients for COT. Likewise, 63.5% of TSNM can be explained by the differences in the predictors between females and males. There was a 65.91 difference in COT between men and women, 54.97 can be explained by the chosen model, while 10.94 remains unexplained. Of the 54.97, MPV favors men and contributes 14.45 to the gap in COT between men and women; likewise, NMR contributes 9.79 and height contributes 47.34 to this gap. Weight is also a significant predictor of differences, but contributes by shrinking the difference and decreasing the gender gap by 13.29. The coefficients of the predictors in Table 3 are the expected difference of the outcome that is explained by the predictor calculated using difference between males and females in expected value of each predictor. The sum of the coefficients of the individual predictors equals the total explained differences.

Table 6: Blinder-Oaxaca Decomposition of Gender Differences Model of COT and TSNM

	COT		95% Conf Interval		TSNM		95% Conf Interval	
Predictor	Coefficient	P-value	Lower	Upper	Coefficient	P-value	Lower	Upper
Difference	65.91	<0.01	31.53	100.29	0.0118	0.01	0.0028	0.0209
Explained**	54.97	<0.01	16.31	93.62	0.00075	0.04	-0.0026	0.0176
Unexplained	10.94	0.61	-30.84	52.74	0.00043	0.44	-0.0066	0.0153
Mean Puff Volume (mL)*	14.45	0.01	3	25.9	0.0036	0.01	0.00075	0.0065
Mean Puff Velocity (mm/s)	-6.69	0.07	-13.36	0.519	-0.0016	0.07	-0.0032	0.0001
Height*	47.34	<0.01	12.72	81.96	0.0101	0.02	0.0015	0.0187
Weight*	-13.29	0.01	-22.96	-3.62	-0.0035	0.01	-0.006	-0.001
Total Daily Puffs	3.57	0.31	-3.26	10.4	0.001	0.34	-0.001	0.0031
Nicotine Metabolite Ratio*	9.79	0.02	1.65	17.93	0.0014	0.05	0.0001	0.0029
Fagerstrom Index	6.72	0.13	-1.88	15.32	0.0021	0.12	-0.0005	0.0048
Time to First Cigarette (min)	4.08	0.13	-1.26	9.42	0.00006	0.73	-0.0003	0.0004
Years smoked	-7.38	0.21	-18.86	4.11	-0.002	0.19	-0.005	0.001
Roll Your Own Cigarette	-3.64	0.22	-9.5	2.22	-0.001	0.21	-0.0026	0.0006

Figure 2 provides a visual comparison of the contributions of each of the covariates analyzed for COT. The coefficient estimates and confidence limits correspond to those shown in Table 6. As seen below, height is the biggest driving factor of gender differences in COT, followed by MPV, weight, and NMR. Everything else that was significant for the ANCOVA, in Table 5, does not appear to be significant here.

Figure 2: Contributions to Gender Differences in COT



DISCUSSION

The study of men and women smokers in a naturalistic setting and their differences in smoking behaviors and nicotine uptake enforces the idea that smoking topography, in addition to height and weight, plays an important role in explaining nicotine metabolite levels, even more so than metabolism (NMR). Studies have shown that gender plays an important role in adolescent smoking behavior and cessation [5]. While gender differences in smoking behavior has been explored, there is a gap on possible differences in puffing topography and nicotine metabolites. In a laboratory-based study of 69 subjects smoking ad lib, women took smaller and shorter puffs than men [10]. Another ad lib smoking study also found that women took smaller and shorter puffs but drew more puffs per cigarette [4]. In the National Health and Nutrition Examination Surveys (1999-2002) and other studies, women had lower cotinine levels than men [6]. The PASS is the first study to capture smoking behavior in a naturalistic setting, using portable puff flow analyzers, and identify these smoking behaviors as explanations for observed gender differences in nicotine metabolites.

In our study, we were able to explain ~83% of the differences in COT and ~64% of the differences in TSNM between males and females. Figure 1 shows the effect sizes of the variables that impact the difference in nicotine metabolites between men and women. The difference in height is the greatest contributor to the differences between sexes in COT and TSNM. Women's lower nicotine intake appears to be mostly due to their smaller stature. This seems to be confirmed by the difference in mean puff volume between men and women contributing towards the difference in nicotine metabolites, which has been found in laboratory settings in the past [4]. Similar studies have found that level of physical activity has a mediating influence, particularly for men, on their acute metabolism of nicotine [15]. The difference in nicotine metabolism rate also contributes to the differences in nicotine metabolites between men and women.

It is well known that smoking is associated with lower body weight [16, 17]. Studies have also recorded permanent weight gain during cessation attempts [18]. In our study, we find that body weight is a significant factor in reducing the differences between men and women. Lighter women tend to consume much more nicotine than heavier women, but this relationship is not true for men. Some studies suggest that smoking reduces desires to eat and leads to drastic weight-control methods in women [19], thus reducing body weight, and other studies have shown that dieting during a cessation attempt can increase women's success rate in quitting smoking [20].

In fact, height and weight have been shown to be a confounding factor with gender in smoking [21], with males and females having differing magnitudes and direction of effects. We have shown that these two factors, along with NMR and MPV, account for the majority of the differences in nicotine uptake between men and women. Future research should further examine these associations between MPV, height, weight, and NMR with cotinine levels and gender.

The limitations of the PASS study include its population demographics, which may not be generalizable to smokers across the country. We sampled from the population of smokers in Central Pennsylvania, who are predominately white. Previous research[22, 23] has shown that there are significant race, gender, and race-gender interactions, differences in smoking patterns, and differences in nicotine uptake and metabolism. Blacks tend to be lighter smokers than whites, and a much greater proportion of blacks smoke menthol cigarettes when compared with whites. In our study, only 8% (n=23) participants were black and 22 of them smoked menthol cigarettes. Future research should be conducted to explore the race-gender differences in a more balanced design. In addition, research is needed to understand why there exist differences in NMR between genders. The levels of 3HC between males and females were almost identical, but COT and TSNM are significantly different between genders. We did not measure sex hormones or pathways [24], nor observe any interactions of hormones with nicotine [25]. Overall, our data and analyses are robust and have an advantage over laboratory smoking findings, since we captured the smokers' behaviors in their natural environment where they are most comfortable.

In conclusion, males and females have significantly different levels of nicotine uptake, individual characteristics, and smoking profiles, and, when accounted for, the effect of gender in nicotine uptake becomes superficial. Differences in height, MPV, and NMR contribute to the differences in nicotine uptake between men and women, while differences in weight abridge the nicotine gap between genders. These findings underscore the important role that inherent characteristics have in nicotine cigarette consumption and are relevant to tobacco regulatory policy and science, providing regulators insight on the differences between male and female smokers.

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APPENDIX: BLINDER OAXACA DECOMPOSITION

The decomposition is based on modeling separate regression equations for males and females:

$$Y_M = \alpha_M + \beta_M X_M + \epsilon_M$$

$$Y_F = \alpha_F + \beta_F X_F + \epsilon_F$$

The next step is to construct a counterfactual equation, predicting female nicotine metabolites with the intercept and coefficients from the men's equation:

$$Y'_F = \alpha_M + \beta_M X_F + \epsilon_F$$

To investigate the differences between genders, we want to model the differences between the expected outcomes between males and females:

$$\bar{Y}_M - \bar{Y}_F = \bar{Y}_M + (\bar{Y}'_F - \bar{Y}'_F) - \bar{Y}_F = (\bar{Y}_M - \bar{Y}'_F) + (\bar{Y}'_F - \bar{Y}_F)$$

The characteristics effect, or the explained component due to the differences in the levels of the predictors between genders, is:

$$\bar{Y}_M - \bar{Y}'_F = \beta_M(\bar{X}_M - \overline{X_F})$$

The coefficients effect, or the unexplained component due to the differences in the intercepts and coefficients of the predictors between genders, is:

$$\bar{Y}'_F - \bar{Y}_F = (\alpha_M - \alpha_F) + (\beta_M - \beta_F)X_M$$

This technique was used to explore the causes of gender differences and compared the explained difference attributed to individual predictors. The Blinder-Oaxaca is able to detect response-predictor group-level trends that an ANCOVA cannot summarize.