

Research Article

A Comparison of Nicotine Biomarkers and Smoking Patterns in Daily and Nondaily Smokers

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Abstract

Background: Nondaily or intermittent smokers (ITS) are increasingly common, but how much nicotine, if any, ITS take in and how quickly they metabolize it has not yet been studied.

Methods: We compared carbon monoxide (CO), urinary cotinine, and nicotine metabolism [nicotine metabolite ratio (NMR): 3-hydroxycotinine:cotinine] in 224 ITS and 222 daily smokers (DS). Effects of gender and ethnicity were examined.

Results: DS had higher cotinine concentrations than ITS ($1,396 \pm 69$ vs. 478 ± 44 ng/mL), attributable to higher cigarettes per day (CPD). In both groups, cotinine rose more slowly as CPD increased. There were no differences in cotinine between White (WH) and African American (AA) DS; among ITS, AA cotinine was over twice that of WH. Among DS, CO was significantly higher among WH than AA smokers, but significantly lower among WH ITS than AA ITS. Although AA ITS smoked more than WH ITS (CPD: 4.13 ± 0.55 vs. 3.31 ± 0.41), this did not account for the observed cotinine nor CO differences. There were no differences in NMR by group or race, nor any gender effects.

Conclusions: At comparable CPD, DS' and ITS' intake of nicotine per cigarette was similar, as were their rates of nicotine metabolism. Among ITS, AA smokers smoke more and take in more nicotine per cigarette than WH ITS, consistent with the view of ITS as a heterogeneous group.

Impact: Differences in nicotine intake per cigarette and metabolism likely cannot account for differences in DS and ITS smoking. Future studies should explore ethnic differences in ITS smoking. *Cancer Epidemiol Biomarkers Prev*; 23(7); 1264–72. ©2014 AACR.

Introduction

Nicotine has long been implicated as the primary addictive agent in tobacco; people smoke to obtain nicotine. Among daily smokers (DS), smoking patterns are often viewed as reflecting a drive to maintain relatively stable levels of nicotine in the body (i.e., above a point at which nicotine withdrawal symptoms may emerge (1), thus requiring frequent smoking. However, this perspective is less suited to explaining the smoking patterns of nondaily smokers, an increasingly large proportion of the smoking population (2).

Nondaily, or intermittent smokers (ITS) now represent up to a third of adult smokers in the United States (3–5) and Europe (6, 7). Moreover, their numbers have grown rapidly in recent years [40% increase between 1995 and

2001 (8); although see ref. 9]. Nonetheless, ITS demonstrate some evidence of nicotine dependence (10), have considerable difficulty quitting (11), and suffer negative health consequences of smoking (12). Importantly, ITS' lighter smoking is not attributable to economic restraints that might keep them from smoking more: ITS actually have considerably higher incomes than DS, and say their smoking would not increase very much even if cigarettes were free (13).

One potential explanation for the observed differences in DS and ITS smoking behavior may be differences in nicotine intake per cigarette and/or rate of nicotine metabolism. In the extreme, ITS might not inhale and thus absorb almost no nicotine. Data showing increases in exhaled carbon monoxide (CO) after ITS smoke (14) make this unlikely. However, ITS might still take in relatively little nicotine per cigarette, perhaps below some threshold that protects them from developing more "dependent" smoking patterns (15). Alternatively, ITS may take in *more* nicotine per cigarette and thus may be able to smoke less than DS in order to obtain the same effect. Circulating nicotine levels are also determined by the rate of metabolism, and it has been shown that individuals who metabolize nicotine slowly, because of a genetic polymorphism, smoke less and are less dependent (16, 17). Thus, ITS might be distinguished by a lower rate of nicotine metabolism that perhaps makes increased

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smoking aversive. No research to date has empirically examined these questions.

In assessing nicotine intake and metabolism among ITS, it is important to consider that ITS are a heterogeneous group (13). Notably, about half of ITS have a history of prior daily smoking (11). These "converted" ITS (CITS) demonstrate heavier and more frequent consumption (13) and greater nicotine dependence (10) than "native" ITS (NITS) who have never smoked daily, and might also differ in nicotine intake and metabolism.

Other individual characteristics may also influence nicotine intake and metabolism. For example, women on average metabolize nicotine more rapidly than men (18, 19). It is not known how this gender difference might manifest itself among ITS. In addition, there are striking ethnic differences in the proportion of smokers who are ITS. National survey data have shown that, among adult smokers, ethnic minorities, including African American (AA), Hispanic and Asian smokers, are more likely to be ITS than non-Hispanic White (WH) smokers (23.8%, 35.7%, and 29.7%, respectively, vs. 16.6%; ref. 20). This could be related to other observed differences between WH and AA smokers. AA smokers tend to smoke less (21, 22), but demonstrate greater dependence at lower smoking rates (23). AA smokers also have been reported to metabolize nicotine more slowly than WH smokers (24, 25).

Cotinine, the primary metabolite of nicotine, is commonly used as a biomarker for daily nicotine intake among regular smokers (26). In addition, considering other metabolites, such as trans 3'-hydroxycotinine (3HC), can enhance precision in estimating nicotine intake (27). With regard to rate of metabolism, the ratio of 3HC to cotinine [a noninvasive marker of the rate of nicotine metabolism, also called the nicotine metabolite ratio (NMR)] is commonly used as an index of the rate of nicotine metabolism (26). It is thought to be more accurate than genetic analyses [e.g., variations in the genes controlling CYP2A6 (17)], because it considers the final phenotype, which seems to be under the control of multiple genes, some as yet unknown, as well as environmental factors (28). In this article, we quantify differences in nicotine intake and metabolism between DS and ITS, and among ITS, by history of daily smoking. Gender and ethnicity effects are also explored.

Materials and Methods

Participants

A total of 446 smokers (222 DS; 224 ITS: 131CITS, 67 NITS, and 26 ITS with unknown history of daily smoking) contributed data on smoking patterns and biomarkers of nicotine intake. All participants were volunteers enrolled in a larger study on smoking patterns, approved by the University of Pittsburgh. The current sample largely overlaps with that reported in Shiffman and colleagues (13). Briefly, criteria for participation included: ≥ 21 years old, report smoking for ≥ 3 years and at their current rate for ≥ 3 months, and no intention to quit within the next

month. DS had to report smoking daily, an average of 5 to 30 cigarettes per day (CPD); ITS had to report smoking 4 to 27 days per month, with no restrictions on CPD on smoking days. Two participants were excluded because of outlier values on cotinine, discrepant with their self-reported smoking. Twenty-one participants (all male) were excluded because they reported also using smokeless tobacco, which would have confounded the analyses of nicotine intake. AA smokers were oversampled to comprise approximately 30% of the sample.

Among DS ($n = 222$), 37.39% were AA, 41.11% were female, 39% earned $> \$25,000/\text{year}$, 62% had post-high school education, and the average age was 39.68 (SD = 11.63) years. Among ITS ($n = 224$), 34.82% were AA, 52.71% were female, 50% earned $> \$25,000/\text{year}$, 83% had post-high school education, and the average age was 35.18 (SD = 11.79) years. DS had smoked on average 23.84 (SD = 11.51) years, and currently smoked an average of 15.98 (SD = 5.94) CPD. ITS smoked for an average of 17.63 (SD = 12.06) years, averaged 19.83 (SD = 6.59) smoking days per month, and 3.24 (SD = 2.74) CPD on days in which they smoked. Similar proportions of DS (54%) and ITS (49%) smoked menthol cigarettes, but, as expected, more AA smokers (97%) than WH (43%) smoked menthol cigarettes.

Selection of biologic samples for assay

Subjects provided a urine sample on each of up to 8 laboratory visits. One sample per subject was selected for analysis, favoring sampling occasions when the subjects' smoking was most representative of their typical smoking (i.e., median CPD), as indicated by data collected in retrospect via Time-Line Follow-Back (TLFB; ref. 29) and/or recorded in real time using electronic diaries for ecologic momentary assessment (30). Exhaled CO readings were taken upon presentation to the laboratory for each visit (Vitalograph Inc.), and averaged for analysis.

Assays

Urine samples were assayed for unconjugated (free) cotinine and 3HC using liquid chromatography/tandem mass spectrometry (31). Nicotine intake was assessed using urinary cotinine (ng/mL), urinary cotinine corrected for creatinine, and the total molar sum of cotinine and 3HC. Creatinine-corrected urinary cotinine [i.e., cotinine (ng/mL) per unit creatinine (mg/mL)] data were only available for a subset of the sample (DS: $n = 179$; ITS: $n = 186$). Moreover, analyses suggested that creatinine-corrected data demonstrated greater variability (DS: coefficient of variation = 128.32 vs. 73.06 for uncorrected cotinine) and was more weakly correlated with smoking rates than uncorrected cotinine values (creatinine-corrected cotinine: $r = 0.40$ vs. uncorrected cotinine: $r = 0.50$). Total molar cotinine and 3HC demonstrated similarly higher variance (DS: coefficient of variation = 94.40) and a weaker correlation to smoking ($r = 0.42$) relative to uncorrected cotinine values. Consequently, to simplify reporting, only results for uncorrected cotinine values are presented, except in cases where the pattern of findings

substantively differed across outcomes. NMR was used to index the rate of nicotine metabolism. To correct for skew, analyses examined $\log(\text{NMR})$.

Self-reported cigarette consumption

To capture cigarette consumption before each lab visit, subjects completed TLFB reports in which they used a calendar to indicate retrospectively how many cigarettes they smoked on each day since their last visit (median recall period between sessions = 3 days). To analyze the relationship between cigarette consumption and nicotine metabolites, we used TLFB reports of mean consumption over the preceding 3 days, weighted to give greater weight to the most proximal days, as we expected most recent days to have the most influence on biomarkers (weights were 0.5, 1, and 2, respectively, for the 3 days prior). (Results were similar when we used unweighted averages of CPD across all days.) For CO analyses, we used overall average CPD from TLFB.

Analysis

Groups were contrasted using *t* tests and ANOVA methods (implemented via regression). All analyses, except those comparing WH and AA smokers, were weighted by race to account for oversampling of AA smokers. The relationship between cigarette consumption and cotinine is known to be curvilinear (32, 33), with the slope flattening at higher cigarette consumption. Accordingly, we included both linear and quadratic terms for CPD in regression models predicting cotinine and other outcomes from CPD. The ratio of cotinine to CPD was square-root-transformed to correct for skew.

Results

DS versus ITS

As expected, ITS had lower concentrations of all biomarkers of nicotine intake and smoke exposure, consistent

with their lower cigarette consumption. Figure 1 shows the relationship between CPD and cotinine, for each group. Consistent with population data, the overall trend reflects a curvilinear pattern in which cotinine initially rises steeply with increased CPD, but then levels off as CPD increases further. Indeed, adjusting for group, analyses show that the relationship of cotinine to CPD has significant curvilinear, as well as linear, components (linear: $B = 135.91$, $SE = 19.81$, $P < 0.0001$; quadratic: $B = -2.98$, $SE = 0.66$, $P < 0.0001$). Once these linear and quadratic effects of CPD are taken into account, the differences between ITS and DS in cotinine disappear ($P = 0.54$). As is also evident from the Figure, the curves (best-fit quadratic splines) seem to form a continuous curve, and lie on top of each other in the region from 5 CPD to 15 CPD, the range in which the groups' cigarette consumption overlaps. Indeed, among the subjects whose CPD was in this range (24% of ITS and 53% of DS), observed cotinine concentrations did not differ between ITS and DS (ITS: 1,123.51 ng/mL vs. DS: 1,320.64 ng/mL; $P = 0.20$). In other words, when smoking a similar number of cigarettes, ITS and DS take in similar amounts of nicotine.

However, Fig. 1 also shows that most ITS smoke less than 5 CPD, and thus lie on the steeper part of the cotinine-by-CPD curve, whereas most DS lie on the flatter part of the curve. Indeed, analysis confirms that, overall, ITS show a steeper linear increase in cotinine with increasing CPD (standardized $\beta = 0.47$ vs. $\beta = 0.26$ among DS), yielding a significant interaction in the linear term ($P < 0.01$), which estimates the slope of the regression line ($P < 0.01$). A simple index of cotinine-per-cigarette (square-root-transformed to account for skew) yielded significantly higher values for ITS than for DS ($P < 0.01$), again reflecting the fact that most ITS lie on the portion of the curve that slopes upward more steeply. There was no interaction in the quadratic term, reflecting similar curvature ($P = 0.20$).

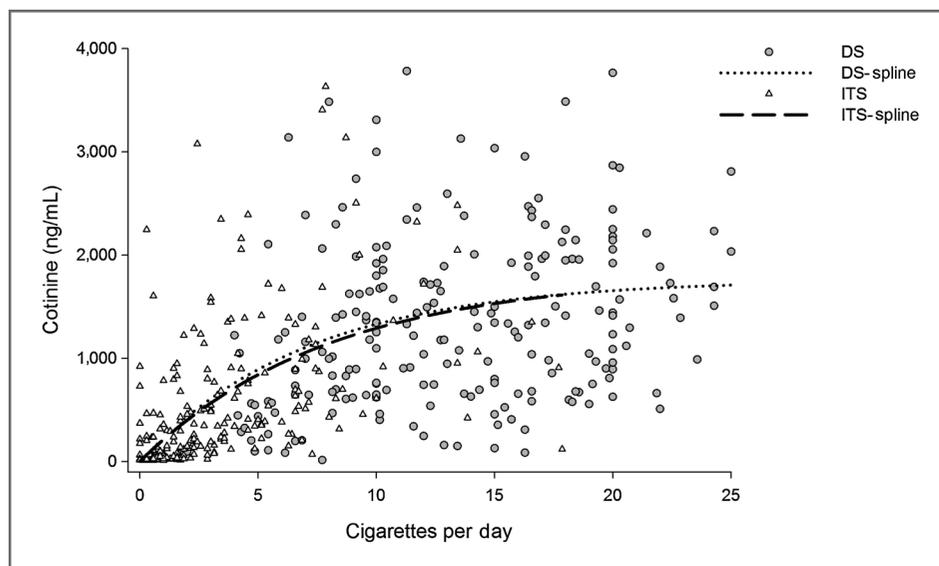


Figure 1. DS and ITS demonstrate similar relationships between cotinine and cigarettes per day. Scatter plot of DS' and ITS' uncorrected urinary cotinine values (ng/mL) and mean weighted CPD over the 3 days preceding the sample. Curves are smoothed quadratic spline fits, reflecting steep initial increase, and subsequent leveling off of cotinine values with increasing CPD.

Similar patterns were seen for creatinine-corrected cotinine, for 3H+Cotinine, and for CO, except that no significant quadratic effect of CPD nor group-by-CPD quadratic interaction on creatinine-corrected cotinine was observed ($P = 0.07$). For CO, there was a significant ITS/DS difference in the quadratic ($P = 0.04$), but not the linear term ($P = 0.07$). Controlling for linear (CPD) and quadratic (CPD²) effects of smoking rate, CO did not differ across groups.

There were no group differences in NMR, nor was NMR associated with CPD in either group.

CITS versus NITS

Comparisons of CITS versus NITS mirrored the patterns seen in the DS versus ITS comparisons (see Table 1). CITS demonstrated higher cotinine ($P < 0.01$) and total molar cotinine + 3HC ($P < 0.004$) compared with NITS, but differences were eliminated when statistically adjusting for CPD. Similarly, there were no differences in cotinine:CPD ratio (square-root-transformed values; $P = 0.48$). There were no differences between CITS and NITS in NMR.

Ethnicity

There were marked ethnic differences in CPD by smoker group: among DS, AA smoked less than WH; among ITS, this was reversed, such that AA smoked more than WH (Table 2). Cotinine values showed a different pattern, in which AA smokers had higher cotinine concentrations among both ITS and DS, although the difference was much greater among ITS, resulting in a group \times ethnicity interaction (Fig. 2A). After statistical adjustment for consumption (CPD and CPD²), the interaction became only marginally significant ($P = 0.05$), although AA smokers consistently demonstrated higher CPD-adjusted cotinine levels.

As was seen when comparing DS and ITS, curves of cotinine by CPD (based on best-fit quadratic splines), by smoker type and ethnicity, demonstrated differences by smoker type and ethnicity (Fig. 3). Among DS, the relationship was steeper for WH than AA; among ITS, the relationship was steeper for AA than for WH. Overall, the relationship between CPD and cotinine was steepest of any group among AA ITS (Fig. 3). Indeed, the steep increase among AA ITS seems to account for the observation, noted above in the DS versus ITS comparison, that cotinine increases more steeply with CPD among ITS; this steep increase was observed only among AA ITS, not among WH ITS.

As with uncorrected cotinine values, taking into account consumption (CPD and CPD²), the race by group interaction was marginally significant for creatinine-corrected cotinine ($P = 0.09$) but was significant for molar cotinine+3HC ($P < 0.01$). Across all biomarkers, the general pattern was the same: among DS, there was no difference between AA and WH. In contrast, among ITS, AA smokers had metabolite values at least two thirds higher than WH. Examining cotinine per cigarette

Table 1. Differences in average biomarker values across smoker groups

Biomarker	DS (n = 222)		ITS (n = 224)		ITS vs. DS		CITS (n = 131)		NITS (n = 67)		CITS vs. NITS	
	Mean (SE) [median]	Mean (SE) [median]	Mean (SE) [median]	Mean (SE) [median]	P	Mean (SE) [median]	Mean (SE) [median]	P	Mean (SE) [median]	Mean (SE) [median]	P	
CPD (weighted past 3 days)	14.67 (0.42) [14.71]	3.42 (0.23) [2.29]	<0.0001	3.74 (0.31) [2.71]	2.25 (0.29) [1.43]	<0.001	314.26 (66.44) [118.48]	446.22 (66.53)	<0.001	270.85 (134.20) [67.88]	4.89 (0.34) [4.24]	<0.01
Cotinine (ng/mL)	1395.50 (69.43) [1298.87]	478.12 (43.90) [219.71]	<0.001	562.81 (61.06) [340.74]	5.31 (0.65) [3.25]	<0.001	7.10 (0.69)	0.34	0.73 ^b	0.74	0.18	
Statistically adjusted for CPD ^a	968.35 (74.65)	890.66 (73.02)	0.53	180.69 (23.25) [83.96]	5.17 (0.42) [3.90]	<0.05 ^b	8.04 (0.65) [6.00]	0.74	0.74	0.74	0.18	
Cotinine/CPD	104.01 (5.33) [87.48]	202.30 (43.46) [78.90]	<0.05 ^b	5.10 (0.28) [3.98]	7.19 (0.47) [4.11]	<0.001	13.92 (0.83)	0.74	0.74	0.74	0.18	
NMR	5.09 (0.31) [3.70]	5.10 (0.28) [3.98]	0.25	8.04 (0.65) [6.00]	7.19 (0.47) [4.11]	<0.001	13.92 (0.83)	0.74	0.74	0.74	0.18	
CO (ppm)	21.06 (0.74) [20.33]	7.19 (0.47) [4.11]	<0.001	8.04 (0.65) [6.00]	7.19 (0.47) [4.11]	<0.001	13.92 (0.83)	0.74	0.74	0.74	0.18	
Statistically adjusted for CPD ^a	13.70 (0.86)	13.92 (0.83)	0.55	7.54 (0.50)	7.10 (0.69)	0.55	13.92 (0.83)	0.74	0.74	0.74	0.18	

NOTE: All descriptive statistics and *t* tests are weighted by race.

^aControlling for linear and quadratic CPD.

^bStatistical tests conducted on square-root-transformed values.

Table 2. Ethnic differences in average biomarker levels by smoker group

Biomarker	DS		ITS		<i>P</i> _{interaction}
	AA (<i>n</i> = 83)	WH (<i>n</i> = 132)	AA (<i>n</i> = 78)	WH (<i>n</i> = 139)	
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
CPD (weighted past 3 days)	12.44 (0.53)	15.10 (0.43)	4.13 (0.55)	3.31 (0.41)	<0.001
Cotinine (ng/mL)	1478.38 (96.13)	1383.16 (76.23)	964.52 (99.17)	358.37 (74.29)	<0.01
Statistically adjusted for CPD ^a	1137.62 (99.43)	946.10 (89.98)	1301.98 (101.36)	787.46 (86.94)	0.050
Cotinine/CPD	134.19 (46.63)	99.33 (37.11)	310.96 (49.72)	175.12 (36.97)	<0.01 ^b
NMR	4.89 (0.46)	5.25 (0.37)	5.08 (0.47)	5.07 (0.36)	0.59
CO (ppm)	16.52 (0.96)	21.62 (0.76)	10.43 (0.99)	6.51 (0.74)	<0.0001
Statistically adjusted for CPD ^a	12.41 (1.00)	14.95 (0.97)	15.42 (1.03)	12.50 (0.93)	<0.001

NOTE: All values are least-square group means from ANOVA.

^aControlling for linear and quadratic CPD.

^b*P* from statistical tests conducted on square-root-transformed values.

(square-root-transformed), there was a significant interaction between ethnicity and smoker group ($P < 0.01$), such that AA ITS had the highest cotinine-per-cigarette (see Table 2).

There were no ethnicity effects or ethnicity by group interaction effects on NMR.

As shown in Table 2, the data for CO also showed a significant smoker group by ethnicity interaction ($P < 0.001$) that paralleled the pattern for cotinine, such that—after controlling for CPD and CPD²—CO was significantly higher among WH DS than among AA DS, but significantly lower among WH ITS than AA ITS (see Fig. 2B).

Given that AA ITS were more likely to be CITS, we also examined whether history of daily smoking accounted for differences in AA and WH ITS. Controlling for CITS versus NITS did not affect the magnitude of ethnic differences, nor did CITS versus NITS interact with ethnicity to predict cotinine levels. Similarly, there was no interaction between ethnicity and prior history of daily smoking on the cotinine:CPD ratio.

We also examined whether or not ethnic differences we observed may have been accounted for by socioeconomic factors (i.e., average yearly income, years of education). Controlling for average yearly income or years of education had no effect on the pattern of results for any of the significant ethnicity by smoker group interactions (i.e., CPD, cotinine, cotinine:CPD, and CO; not shown).

Gender

There were no gender effects. Men and women did not differ in CPD, and there were no gender \times group interactions, including interactions with CPD. In other words, men and women did not differ in overall cotinine (or total molar cotinine + 3HC), in cotinine per cigarette, in the relationship of CPD to cotinine, or in NMR, and these null gender effects did not differ by smoker groups. However, there was a near-significant trend for an ethnicity by

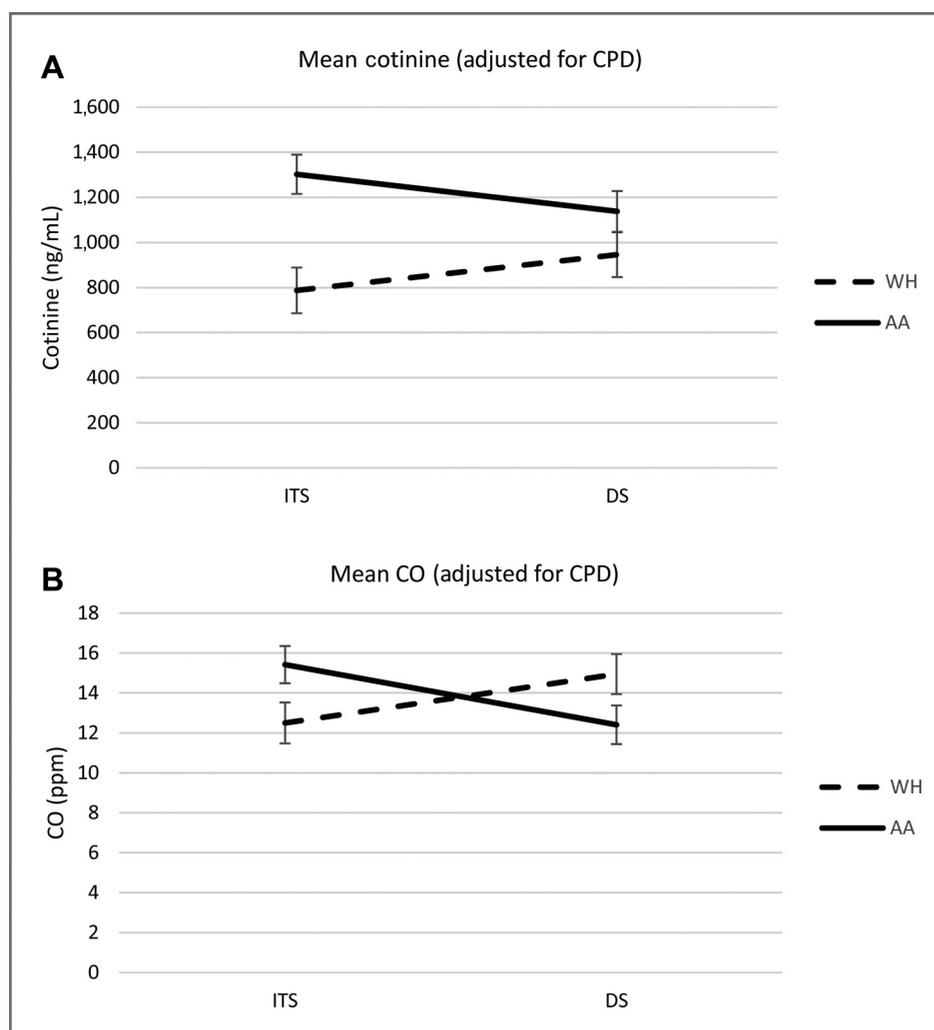
gender interaction on NMR ($P = 0.08$): among women, NMR tended to be higher for AA compared with WH; whereas among men, NMR tended to be higher for WH compared with AA.

Discussion

This was the first study to compare nicotine intake in relation to cigarette consumption in daily and nondaily smokers. Results suggest that, when smoking the same number of cigarettes per day, DS and ITS take in similar amounts of nicotine; that is, where the 2 groups overlap in cigarette consumption, the relationship of cotinine to CPD is remarkably similar between the groups, with curves for both groups showing a continuous curvilinear relationship between CPD and cotinine. However, this masks an important difference. As seen both in our data and in national probability samples (32), cotinine does not continue to rise at the same rate as CPD increases; as CPD rises above 15 to 20, the curve for cotinine flattens. Because DS in fact are much more likely to smoke heavily, and thus more likely to be on the flat end of the cotinine-by-CPD curve, DS actually take in *less* nicotine per cigarette overall. Thus, although ITS on average smoke 75% fewer cigarettes than DS, their cotinine levels were only 65% lower than those of DS. Still, the finding that the relationship of cotinine to CPD is not significantly different in the 2 groups, and the close resemblance of the curves for cotinine by cigarette consumption (Fig. 1) is very striking, suggesting that the 2 groups' extraction of nicotine from cigarettes at a given number of cigarettes smoked per day is fundamentally similar.

That we saw no differences between ITS and DS in the rate of nicotine metabolism has 2 important implications. First, it suggests that cotinine behaves similarly among ITS and DS as a marker of nicotine intake, making the above comparisons valid. Second, it indicates that ITS' atypical smoking behavior cannot be explained by hypotheses that posit that ITS metabolize nicotine so quickly

Figure 2. Ethnicity by smoker group interactions on cotinine (A) and CO (B). Plots depict significant ethnicity by smoker type interactions for uncorrected urinary cotinine (ng/mL; $P = 0.05$) and average predeprivation exhaled CO (ppm; $P < 0.001$) across study visits. Means and SEs reflect group least-square mean values, adjusted for cigarette consumption (CPD and CPD²). For cotinine, CPD was specified as mean weighted CPD in the 3 days preceding a urine sample; for CO, CPD was the mean CPD across the entire study period.



that it minimizes its effects, or conversely, metabolize it so slowly that they might achieve much greater effects from smaller nicotine intake than DS. Our results show that variations in the rate of nicotine metabolism do not explain nondaily smoking.

The finding that ITS take in "normal" amounts of nicotine when they smoke, and metabolize it "normally," makes it likely that they experience the acute effects of nicotine, and that their smoking is motivated and reinforced by these effects. Indeed, a recent study reported that ITS were more likely to try electronic nicotine-delivery devices and to persist in their use (34), suggesting that they seek nicotine and are reinforced by it. Because ITS are unlikely to seek nicotine in order to ward off nicotine withdrawal—they do not smoke steadily enough to maintain nicotine levels, and do not seem to suffer withdrawal when they stop—it is likely that nicotine serves the role of an acute positive reinforcer for ITS smoking. It has been suggested that nicotine can enhance cognitive function (35), reduce emotional distress (36), and make other reinforcers more reinforcing (37). These acute effects may be

sufficient to maintain intermittent smoking without the need to maintain steady levels of circulating nicotine. The fact that ITS actually take in more nicotine per cigarette may allow them to experience very salient, acute effects of nicotine from the small number of cigarettes they do smoke. Thus, in contrast to DS, who seem motivated to smoke to maintain nicotine levels above a withdrawal-suppression threshold (making them what Russell (38) called "trough maintainers"), ITS may be "peak-seekers" who seek direct nicotine effects in particular contexts, without the need for constant or regular nicotine intake.

Analyses of national data (11) showed that ITS have great difficulty quitting and fail in cessation almost as often as DS, despite their intermittent smoking pattern and low scores on traditional measures of dependence (10). Our finding that they take in nicotine from smoking, and that their nicotine intake for each cigarette is similar to that of DS, suggests that providing them with nicotine replacement might help them succeed in quitting. Given their very low overall nicotine exposure, and their intermittent dosing pattern, nicotine patches, which provide

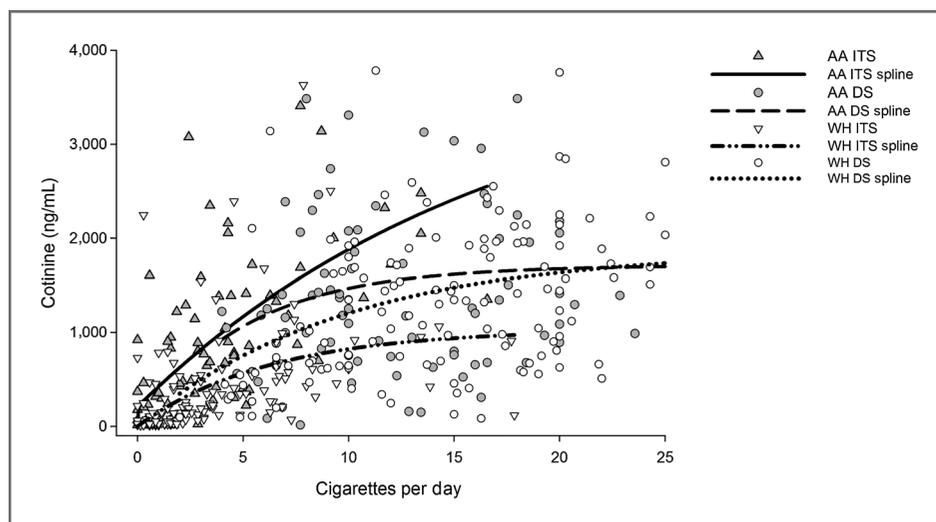


Figure 3. Ethnicity by smoker group differences in the relationship between cotinine and cigarettes per day. Scatter plot of uncorrected urinary cotinine values (ng/mL) and mean weighted CPD by ethnicity (WH, AA) and smoker group (DS, ITS). Curves are smoothed quadratic spline fits, and reflect differences in the curvilinear relationship between cotinine and CPD observed across groups.

nicotine at high levels throughout the day, would not be appropriate for this group. However, acute oral dosing forms such as nicotine gum or lozenge, which could be used at a frequency mirroring their smoking frequency, might increase their success in quitting. The efficacy of nicotine replacement in this population has not yet been demonstrated in clinical trials; we are currently conducting such a study, sponsored by the NIH.

We found no differences between CITS and NITS in per-cigarette nicotine intake or in nicotine metabolism. This suggests that past history of daily smoking does not carry over into different nicotine kinetics once a daily smoker becomes an intermittent one, despite the fact that differences in behavioral indicators of dependence do persist (13).

We found no effects of gender or gender interactions with smoking status, consistent with epidemiologic findings that both genders are equally represented among ITS (39). Although it has been suggested that men smoke for nicotine and women smoke in response to cues (40), we found no differences in nicotine intake or metabolism by gender in ITS or DS (and also found no differences in response to cues in a cue-reactivity paradigm; ref. 14). Our sample was unusual in that cigarette consumption was similar among men and women, which may reflect our exclusion of very heavy smokers, and inclusion of light smokers.

Our data suggest that the phenomenon of nondaily smoking may differ by race. AA ITS smoked more cigarettes than WH ITS, had higher CO values, and took in more nicotine per cigarette. As shown in Fig. 3, cotinine levels among AA ITS rose steeply with increased smoking, even as they were leveling off among WH ITS. This finding is consistent with previous studies of DS, which have suggested that AA DS take in more nicotine per cigarette than WH DS (41). As has been widely reported (22), among DS, the pattern seen in ITS reversed, with AAs smoking fewer cigarettes. When we controlled for these differences in CPD, the interaction between race and

smoker type on cotinine became only marginally significant, but remained significant for cotinine +3HC, in the same pattern. Among DS, AA and WH smokers demonstrated similar levels, whereas among ITS, AA smokers had higher levels of these nicotine metabolites and CO, even after controlling for CPD. This suggests that AA ITS may experience considerably greater nicotine exposure than WH ITS, which could suggest different dynamics for AA nondaily smoking. Differences in smoking behavior between WH and AA ITS should be further explored.

Some previous studies (e.g., 41, 42) have reported slower nicotine metabolism among AA smokers, whereas we observed no ethnic differences in NMR. It is not clear what explains this. Importantly, past findings have not been entirely consistent: for example, Kandel and colleagues (43) found that ethnic differences were found only among males. In our analyses, we found a near-significant ethnicity-by-gender interaction, although the details were not consistent with Kandel. This suggests that some as-yet-unidentified variables might influence or confound ethnic differences in NMR, making findings inconsistent. [Other studies (41, 42) have not examined whether gender modified ethnic differences.] It is also possible that the fact that we included light smokers and excluded very heavy smokers, which might overrepresent slow metabolizers, could have had an effect.

The study was subject to some limitations. The subjects were volunteers from a single city and may not be representative of the population. The analysis included only one biologic sample per subject; additional samples might have increased the reliability of the biomarker assessments, and perhaps yielded different results.

In conclusion, DS' and ITS' intake of nicotine at any given level of cigarette consumption is similar, although ITS smoke at lower rates, where the per-cigarette nicotine intake is somewhat higher. ITS and DS metabolize nicotine at the same rate. Thus, differences in nicotine intake and metabolism do not seem to account for observed differences in DS and ITS smoking patterns. Given their

low level of cigarette consumption, low daily levels of nicotine intake, and low level of dependence (10), it is striking that ITS have great difficulty quitting (11). If ITS are reinforced by acute nicotine administration, their behavior may represent an alternative persistent pattern of smoking and nicotine intake that is not attributable to dependence as traditionally conceived.

Among ITS, AA smokers seem to take in more nicotine per cigarette than do WH, consistent with the view of ITS as a heterogeneous group of smokers. Given the overrepresentation of minority groups in the nondaily smoking population, examining ethnic differences in ITS may be an important direction for future research, perhaps shedding light on broader ethnic variation in smoking patterns and motives.

Disclosure of Potential Conflicts of Interest

N.L. Benowitz is a consultant/advisory board member of Pfizer and GlaxoSmithKline. S. Shiffman consults to GlaxoSmithKline regarding nicotine replacement and smoking cessation, and is a partner in a firm developing nicotine replacement products. No potential conflicts of interest were disclosed by the other authors.

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Conception and design: S. Shiffman
Development of methodology: S. Shiffman
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Shiffman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Shiffman, M.S. Dunbar, N.L. Benowitz
Writing, review, and/or revision of the manuscript: S. Shiffman, M.S. Dunbar, N.L. Benowitz
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.S. Dunbar
Study supervision: S. Shiffman

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