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Original Investigation

Validation of the Wave 1 and Wave 2 Population Assessment of Tobacco and Health (PATH) Study Indicators of Tobacco Dependence Using Biomarkers of Nicotine Exposure Across Tobacco Products

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Abstract

Introduction: This study examined the predictive relationships between biomarkers of nicotine exposure and 16-item self-reported level of tobacco dependence (TD) and subsequent tobacco use outcomes.

Aims and Methods: The Population Assessment of Tobacco and Health (PATH) Study surveyed adult current established tobacco users who provided urine biospecimens at Wave 1 (September 2013–December 2014) and completed the Wave 2 (October 2014–October 2015) interview ($n = 6872$). Mutually exclusive user groups at Wave 1 included: Cigarette Only, E-cigarette Only, Cigar Only, Hookah Only, Smokeless Tobacco Only, Cigarette Plus E-cigarette, multiple tobacco product users who smoked cigarettes, and multiple tobacco product users who did not smoke cigarettes. Total Nicotine Equivalents (TNE-2) and TD were measured at Wave 1. Approximate one-year outcomes included frequency/quantity used, quitting, and adding/switching to different tobacco products.

Results: For Cigarette Only smokers and multiple tobacco product users who smoked cigarettes, higher TD and TNE-2 were associated with: a tendency to smoke more, smoking more frequently over time, decreased likelihood of switching away from cigarettes, and decreased probability of quitting after one year. For other product user groups, Wave 1 TD and/or TNE-2 were less consistently related to changes in quantity and frequency of product use, or for adding or switching products, but higher TNE-2 was more consistently predictive of decreased probability of quitting.
Conclusions: Self-reported TD and nicotine exposure assess common and independent aspects of dependence in relation to tobacco use behaviors for cigarette smokers. For other product user groups, nicotine exposure is a more consistent predictor of quitting than self-reported TD.
Implications: This study suggests that smoking cigarettes leads to the most coherent pattern of associations consistent with a syndrome of TD. Because cigarettes continue to be prevalent and harmful, efforts to decrease their use may be accelerated via conventional means (eg, smoking cessation interventions and treatments), but also perhaps by decreasing their dependence potential. The implications for noncombustible tobacco products are less clear as the stability of tobacco use patterns that include products such as e-cigarettes continue to evolve. TD, nicotine exposure measures, and consumption could be used in studies that attempt to understand and predict product-specific tobacco use behavioral outcomes.

Introduction

Exposure to nicotine and tobacco is both a cause and consequence of tobacco dependence (TD).[1,2] As physiological and psychological adaptations to repeated exposures accumulate, behaviors that support tobacco use are reinforced and facilitate persistent use.[2] Primary indicators of TD constitute a syndrome that typically includes withdrawal symptoms upon cessation, difficulty quitting or inhibiting use, tolerance, persistent use despite negative consequences, craving, and other related indicators that have been described in various diagnostic systems (eg, ICD-11, DSM-5).[3]

Existing schemas were not designed to measure TD to more than one tobacco product.[4–6] Tobacco products differ in nicotine pharmacokinetics, typical patterns of use, and varying social constraints.[2,5,7–9] Certain indicators of TD such as tolerance, withdrawal, and craving, may be sufficiently robust across different tobacco products to identify common symptoms reflective of TD.[10] Data from the Population Assessment of Tobacco and Health (PATH) Study were previously used to develop a reliable single primary latent construct underlying responses to TD indicators for cigarettes, e-cigarettes, cigars, hookah, and smokeless tobacco products.[10] Concurrent validity of this unidimensional TD measure has been established via positive associations between TD and product use frequency.

Previous studies have demonstrated positive associations between TD, typically for cigarette smoking, and biomarkers of nicotine exposure.[11,12] Some correlation between TD and biomarkers of nicotine exposure is expected, given the association between TD and frequency/quantity of product use. In the Total Exposure Study,[13] Fagerstrom Test for Nicotine Dependence (FTND) scores were positively correlated with biomarkers of nicotine and cigarette smoke exposure, including 24-hour urine nicotine equivalents, serum cotinine (primary metabolite of nicotine), and blood carboxyhemoglobin.[14] Associations between FTND scores and biomarkers were attenuated but still significant after taking into account cigarettes smoked per day, indicating that some aspects of TD explain nicotine exposure beyond quantity and frequency measures.

Urine samples from a subsample of Wave 1 of the PATH Study respondents were analyzed permitting quantitation of biomarkers of nicotine exposure via total nicotine equivalents (TNE).[15] TNE is the molar sum concentrations of nicotine and its various metabolites present in urine (eg, total cotinine + total trans-3-hydroxycotinine [3HC] in the present study).[6,16] Inclusion of both TD and biomarkers of nicotine exposure provides the additional opportunity to concurrently validate a previously developed measure of TD.[10] We hypothesized that higher levels of TD at Wave 1 would be associated with higher levels of self-reported tobacco product consumption and correspondingly higher levels of TNE-2.

The analyses presented in this paper examined the independent and combined additive predictive relationships between biomarkers of nicotine exposure and TD, measured at Wave 1, and other tobacco use outcomes including product-specific frequency/quantity used, quitting, and adding or switching to different tobacco products, measured approximately one year later at Wave 2.

Methods

Data Source

The National Institutes of Health (NIH), through the National Institute on Drug Abuse (NIDA), partnered with the Food and Drug Administration's (FDA) Center for Tobacco Products to conduct the PATH Study under a contract with Westat. The PATH Study is a nationally representative, longitudinal cohort study of 45 971 adults and youth in the United States, ages 12 years and older. This study used data from a subset of the 32 320 adult (18 years and older) interviews in Wave 1, conducted from September 12, 2013 to December 14, 2014. Adult tobacco users, young adults ages 18–24, and African Americans were oversampled relative to population proportions.[15] The weighted response rate for the household screener at Wave 1 was 54.0%. Among households that were screened, the overall weighted response rate was 74.0% for the Wave 1 adult interview. At Wave 2 (10/2014–10/2015), the overall weighted response rate conditioned on participation at Wave 1 was 83.2% for the Adult Interview.

The selected biomarkers presented here were collected from a subsample of adults who agreed to provide biospecimens. Population weights accounted for differences between the full set of adult interview respondents and the set of adults with analyzed biospecimens.

Weighted estimates are representative of never, current, and recent former (within 12 months) users of tobacco products in the US civilian, noninstitutionalized adult population at the time of Wave 1. Further details regarding the PATH Study design and methods are published elsewhere.[15,16] Details on interview procedures, questionnaires, sampling, weighting, and information on accessing the data and the Biomarker Restricted-Use Files User Guide are available at https://doi.org/10.3886/Series606. The study was conducted by Westat and approved by the Westat Institutional Review Board. All adult participants (age 18 and older) provided informed consent, and adult participants who agreed to give biospecimens provided separate informed consent.

Of the total adults enrolled in the PATH Study at Wave 1 (n = 32 320) 14 287 provided a urine specimen that was analyzed for cotinine and 3HC, and 11 615 were also interviewed at Wave 2, of which, 6872 were adult tobacco users (n = 3 had some panels but no data on TNE-2). A current established cigarette user was defined as an adult who has smoked at least 100 cigarettes in his/her lifetime and now smokes every day or some days. For all other tobacco products, a current established user was defined as an adult who has ever used the product 'fairly regularly' and now uses it every day or some days. Mutually exclusive current established tobacco-user groups included: Cigarette Only users (n = 3625), E-cigarette Only users (n = 259), Cigar Only (traditional, cigarillo, or filtered) users (n = 393), Hookah Only users (n = 252), and Smokeless Tobacco Only (smokeless or snus pouches) users (n = 508). Users of multiple tobacco products were classified into those who reported only Cigarette + E-cigarette use (n = 422), other multiple product users who smoked cigarettes as one of the products (Multiple Product-Cigarettes; n = 1233), or multiple product users who did not smoke cigarettes (Multiple Product-No Cigarettes; n = 180).

Self-reported Measures

Tobacco Use Outcomes

We indexed daily (30 of the past 30 days) or non-daily (<30 of the past 30 days) frequency of product use in the past 30 days and the average quantity of a given product on use days during Wave 1 and Wave 2. For Hookah Only users, we assessed the frequency of use in multivariable models using the number of days used in the past 30 days. Quit attempts were defined by reports of either '…tried to quit completely' or '…tried to quit by reducing or cutting back' in the past 12 months. Quitting success was defined by reports of no tobacco use for 6 months prior to the Wave 2 interview. Additional tobacco product use outcomes were defined at Wave 2: (1) No change (continued current use (some days/every day) of same product(s) and did not add current established use of any other product), (2) Any switching (stopped use of any product and added current established use of any other product), (4) Any adding (continued current use of same product(s) and added current established use of any other product), and (5) Total quitting (stopped use of all products and did not add current established use of any product).

Indicators of TD at Wave 1

The PATH Study adult interview included 16 TD symptoms derived from the Wisconsin Inventory of Smoking Dependence Motives or WISDM (11 items),[17] Nicotine Dependence Syndrome Scale (four items),[18] and Diagnostic and Statistical Manual (DSM) Criteria (one item),[3] that can be used as the common instrument to assess TD across different kinds of tobacco product users.[10] Items were scaled to produce TD scores ranging from 0 to 100.

Other Independent Variables

We also assessed demographic characteristics at Wave 1: sex (male/female), age groups (18–24, 25+), and race/ethnicity (Non-Hispanic White, Other Groups).

Biospecimen Collection

All adult interview respondents were asked to provide urine biospecimens. Full-void urine specimens were self-collected by 21 801 (67.5%) consenting participants in a 500 mL polypropylene container (PN 6542, Globe Scientific). All containers, pipet tips, and vials that came in direct contact with the urine sample were prescreened by the National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) Laboratories and determined not to have amounts of metal contamination that would adversely influence the analytical measurements. For more information on sample collection and the aliquots created from the urine biospecimens, please see the PATH Study Wave 1 Biospecimen Urine Collection Procedures.[19] All biomarker results reported by CDC met the requirements of the quality control/quality assurance program of the CDC National Center for Environmental Health, Division of Laboratory Sciences.[20]

Biomarkers of TD: Nicotine Metabolites

Total urinary nicotine metabolites, including the free and glucuronide conjugated forms, were measured by two separate isotope dilution high-performance liquid chromatography/tandem mass spectrometric (HPLC-MS/MS) methods based on the cotinine cutoff value of 20 ng/mL. For samples with cotinine concentrations ≥20 ng/mL, anatabine, anabasine, and nicotine plus its six major metabolites were measured; for samples with cotinine concentration <20 ng/mL, only cotinine and trans-3′-hydroxycotinine were measured.[21] TNE-2 was calculated for all samples – by taking the molar sum of cotinine and trans-3′-hydroxycotinine.

Study Analysis

Correlational measures of association and covariate-adjusted linear and logistic regression models were used to concurrently validate Wave 1 TD scores against TNE-2. Covariate-adjusted linear, logistic and multinomial regression models were used to explore the relative independent predictive relationship between self-reported TD and TNE-2 on product-specific changes in the frequency of use, changes in quantity of use, as well as quitting, and adding or switching to different tobacco products at Wave 2. For Hookah Only users, quasi-Poisson regression was used to evaluate associations with the number of days of past 30-day use given the low numbers of daily users at Wave 2 (n = 8). Planned covariates for all primary aims included Wave 1 age, sex, and race-ethnicity. We used covariate-adjusted models to estimate the individual effects of TD and TNE-2, separately. In a third covariate-adjusted model we simultaneously evaluated the two measures' independent relationship with the primary outcomes. Levels of TD were scaled to a mean of 0 and Standard Deviation (SD) of 1 for assessing relationships with outcomes within each Wave 1 tobacco user group. Levels of TNE-2 were log transformed.

The Wave 1 Restricted Use Files (RUF) and Urine Weights of the Biomarker Restricted Use Files (BRUF) from the PATH Study were used to make estimates nationally representative of the never, current, and recent former tobacco using population at the time of Wave 1. The Balanced Repeated Replication (BRR) method with Fay

adjustment (eg, Fay = 0.3) was used when conducting weighted analyses with the survey package[22] in R.[23] Missing data on age, sex, race, and Hispanic ethnicity at Wave 1 were imputed as described in the Restricted-Use Files User Guide.[16]

Results

Descriptive Analyses

Weighted demographic characteristics (sex, age, and race/ethnicity) of Wave 1 current established users of each tobacco product group who were also assessed at Wave 2 are presented in Table 1.

Concurrent Association of Biomarkers of Nicotine Exposure (TNE-2) and TD

Weighted correlations showed low to moderate relationships between TD and TNE-2 which ranged from $r = 0.13$ among E-cigarette Only users, $r = 0.45$ among Cigarette Only users and $r = 0.50$ among Cigar Only users. Levels of TD ($F(8,91) = 418.2$, $p < .001$) and TNE-2 at Wave 1 ($F(8,91) = 225.6$, $p < .001$) were significantly different among the eight product user groups. E-Cigarette Only (mean (se) = 25.4 (1.7); sd (se) = 25.8 (8.0)), Hookah Only (mean (se) = 8.4 (0.7); sd (se) = 13.1 (6.3)), Cigar Only (mean (se) = 18.0 (1.9); sd (se) = 24.6 (9.1)), and Smokeless Only (mean (se) = 48.3 (1.5); sd (se) = 28.1 (5.8)) users scored significantly lower on TD than Cigarette Only (mean (se) = 54.8 (0.8); sd (se) = 28.0 (4.8)) users, and all but Smokeless Only users also had lower TNE-2. Cigarette + E-cigarette (mean (se) = 63.1 (1.4); sd (se) = 24.0 (6.8)) users scored higher on TD and TNE-2 than Cigarette Only users (ps < .01). Smokeless Only users had higher TNE-2 ($p < .01$) than Cigarette Only users. Multiple Product-Cigarette (mean (se) = 32.3 (2.7); sd (se) = 29.5 (9.9)) users did not differ significantly from Cigarette Only users on TD ($p > .05$) or TNE-2 ($p > .46$). Multiple Product-No Cigarette users scored lower on TD ($p < .01$) and had lower TNE-2 ($p < .01$) than Cigarette Only users.

Associations With Wave 1 Concurrent Quantity of Tobacco Use

Both Wave 1 TD and TNE-2 had significant positive relationships with quantity of tobacco use (Table 2) among each of the examined product user groups (ie, Hookah Only and Multiple Product-No Cigarette users were not examined due to difficulty quantifying units of use uniformly for all products). One exception was a non-significant association between TD ($p = .14$) or TNE-2 ($p = .07$) with quantity of use among E-cigarette Only users. When assessed together in covariate-adjusted regression models, TD and TNE-2 had independent associations with average quantity of tobacco product use among Cigarette Only, Smokeless Only, and for cigarettes among Cigarette + E-cigarette users (see Table 2). Among Cigar Only users (use of traditional ($n = 140$), cigarillo ($n = 190$), and filtered cigars ($n = 57$) were assessed separately), combined evaluation suggested that TD and TNE-2 were associated independently with quantity of cigarillos smoked. TNE-2 alone was independently associated with quantity of traditional cigar use and TD alone was associated independently with filtered cigar use.

Associations With Wave 1 Daily Tobacco Use

Both Wave 1 TD and TNE-2 also were associated significantly (Table 2) with Wave 1 daily use of each product (or products) in their respective use group (eg, cigarettes among Cigarette Only users). Significant relationships remained when Wave 1 TD and TNE-2 were assessed for their independent associations with Wave 1 daily tobacco use for all but one user group. Wave 1 TNE-2, but not TD retained a significant association with Wave 1 daily use among E-cigarette Only users.

Association of Biomarkers of Nicotine Exposure (TNE-2) and TD With Predicted Change in Wave 2 Quantity of Tobacco Use

Levels of TD and TNE-2 at Wave 1 individually, were each significantly predictive of the average quantity of product used at Wave 2 for Cigarette Only, Smokeless Only, and Cigarette + E-cigarette user groups after adjusting for Wave 1 quantity of each corresponding product used (all $p < .01$; Table 3). TD ($p < .01$) but not TNE-2 ($p = .07$) were associated with Wave 2 quantity among Multiple Product-Cigarette users. TD and TNE-2 at Wave 1 were independently predictive of quantity of Wave 2 use among Cigarette Only and Cigarette + E-cigarette users. Within Cigar Only users, Wave 1 TD was associated with quantity of cigarillos and TNE-2 was associated with Wave 2 quantity of filtered cigars ($p < .05$) when combined in the same model. The quantity of e-cigarette use at Wave 2 was not predicted by Wave 1 indices of TD ($p = .75$) or TNE-2 ($p = .89$) among E-cigarette Only users in the individual models.

Association With Predicted Change in Wave 2 Frequency of Tobacco Use

Rates of daily tobacco use at Wave 1 were highest for Cigarette + E-cigarette Only, Multiple Product-Cigarette, and Cigarette Only user groups (Table 3). Wave 2 rates of daily use were lowest among Hookah Only and Cigar Only users, with 3% and 28% using daily, respectively. In individual evaluations, higher levels of Wave 1 TD were predictive of Wave 2 daily use of products among Cigarette Only ($p < .01$), Cigarette + E-cigarette ($p < .01$), Multiple Product-Cigarette ($p < .01$) users with adjustment for planned covariates and daily use of corresponding products at Wave 1. We did not observe a significant relationship between Wave 1 TD and change in Wave 2 daily use among E-cigarette Only ($p = .88$), Cigar Only ($p = .64$), Hookah Only ($p = .51$), Smokeless Only ($p = .21$) or Multiple Product-No Cigarette ($p = .08$) user groups. In individual evaluations, higher Wave 1 levels of TNE-2 were predictive of Wave 2 daily use among Cigarette Only ($p < .01$), E-cigarette Only ($p < .05$), Cigar Only ($p = .01$), Smokeless Only ($p < .01$), Cigarette + E-cigarette ($p < .01$), Multiple Product-Cigarette ($p < .01$), and Multiple Product-No Cigarette ($p < .05$). Wave 1 TD ($p = .51$) and TNE-2 ($p = .95$) were not predictive of Wave 2 daily use among Hookah Only users.

In combined models, higher levels of Wave 1 TD (ps < .05) and TNE-2 (ps < .01) both independently predicted Wave 2 daily use among Cigarette Only, Cigarette + E-cigarette, and Multiple Product-Cigarette users. Wave 1 TNE-2 also maintained significant independent associations with Wave 2 daily use among E-cigarette Only, Cigar Only, and Smokeless Only users ($p < .05$). Wave 1 TD and TNE-2 were not predictive of Wave 2 daily use among Hookah Only or Multiple Product-No Cigarette users.

Association With Predicted Successful Quitting Among Those Who Attempted to Quit

Rates of successful quitting (Table 4) were quite variable across product use groups, ranging from 3.1% among Multiple

Table 1. Weighted Demographic Characteristics of Wave 1 Current Established Users of Each Tobacco Product Group at Wave 2

	Cigarette (*n* = 3625)		E-cigarette (*n* = 259)		Cigar (*n* = 393)		Hookah *n* = 252)		Smokeless (*n* = 508)		Cigarette + E-cigarette (*n* = 422)		Multiple products: cigarette (*n* = 1233)		Multiple Products: No Cigarette (*n* = 180)	
Demographic characteristics	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Sex																
Male	1655	47.3% (1.4%)	111	44.1% (3.8%)	286	79.0% (2.5%)	133	54.6% (3.5%)	482	95.6% (1.0%)	171	38.3% 3.0%	925	79.1% (1.7%)	140	84.2% (2.5%)
Female	1970	52.7% (1.4%)	148	55.9% (3.8%)	107	21.0% (2.5%)	119	45.4% (3.5%)	26	4.4% (1.0%)	251	61.7% (3.0%)	308	20.9% (1.7%)	40	15.8% (2.5%)
Age group																
18–24	683	10.5% (0.7%)	65	16.3% (2.5%)	159	22.1% (2.6%)	192	66.6% (4.2%)	96	10.0% (1.2%)	81	11.1% (1.6%)	500	27.0% (1.8%)	97	41.9% (4.8%)
25+	2942	89.5% (0.7%)	194	83.7% (2.5%)	234	77.9% (2.6%)	60	33.4% (4.2%)	412	90.0% (1.2%)	341	88.9% (1.6%)	733	73.0% (1.8%)	83	58.1% (4.8%)
Racial/ethnic group																
Non-Hispanic White	2328	68.3% (1.4%)	195	76.9% (3.2%)	175	52.4% (3.9%)	116	46.9% (3.7%)	431	87.7% (1.7%)	323	81.8% (2.2%)	794	65.1% (3.1%)	103	60.1% (5.1%)
Other groups	1297	31.7% (1.4%)	64	23.1% (3.2%)	218	47.6% (3.9%)	136	53.1% (3.7%)	77	12.3% (1.7%)	99	18.2% (2.2%)	439	34.9% (3.1%)	77	39.9% (5.1%)

Values for numbers of cases (*N*) are unweighted. All percentages (%) are weighted estimates and include standard errors (se).

Table 2. Associations of Biomarkers of Nicotine Exposure (TNE-2) and TD With Wave 1 Quantity of Tobacco Use and Wave 1 Rates of Daily Use Among Wave 1 Users

	Individual relationships			Individual relationships			Combined relationships					
	TNE-2			TD scale			TNE-2			TD scale		
Tobacco use group	*b*	se	*p*	*b*	se	*p*	*b*	se	*p*	b	se	*p*
Quantity of use												
Cigarette Only	0.30	0.02	<.01	0.71	0.03	<.01	0.17	0.01	<.01	0.58	0.03	<.01
E-cigarette Only	0.05	0.03	.07	0.10	0.07	.14	0.05	0.02	.06	0.09	0.06	.16
Cigar Only: Traditional	0.08	0.02	<.01	0.27	0.13	.05	0.05	0.02	<.01	0.17	0.13	.19
Cigar Only: Cigarillo	0.11	0.02	<.01	0.42	0.10	<.01	0.06	0.02	<.01	0.36	0.10	<.01
Cigar Only: Filtered	0.14	0.04	<.01	0.64	0.15	<.01	0.05	0.04	.22	0.58	0.19	<.01
Hookah Only												
Smokeless Only	0.15	0.02	<.01	0.40	0.05	<.01	0.09	0.02	<.01	0.34	0.06	<.01
Cigarette + E-cigarette	0.21	0.04	<.01	0.56	0.06	<.01	0.11	0.04	<.01	0.52	0.06	<.01
Multiple Products: Cigarette	0.25	0.05	<.01	0.91	0.08	<.01	0.08	0.06	.18	0.86	0.13	<.01
Multiple Products: No Cigarette												
Rates of daily use												
Cigarette Only	0.78	0.08	<.01	2.00	0.12	<.01	0.54	0.07	<.01	1.62	0.12	<.01
E-cigarette Only	0.41	0.07	<.01	0.56	0.22	.01	0.38	0.07	<.01	0.46	0.25	.06
Cigar Only	0.62	0.12	<.01	1.44	0.30	<.01	0.45	0.11	<.01	0.91	0.26	<.01
Hookah Only	0.13	0.02	<.01	0.24	0.06	<.01	0.08	0.03	<.01	0.20	0.05	<.01
Smokeless Only	0.65	0.13	<.01	1.50	0.17	<.01	0.50	0.12	<.01	1.22	0.18	<.01
Cigarette + E-Cigarette	0.54	0.15	<.01	1.27	0.24	<.01	0.43	0.15	.01	1.07	0.25	<.01
Multiple Products: Cigarette	0.62	0.09	<.01	1.78	0.22	<.01	0.49	0.09	<.01	1.46	0.23	<.01
Multiple Products: No Cigarette	0.55	0.13	<.01	1.59	0.52	<.01	0.43	0.12	<.01	0.99	0.44	.03

Estimates (*b*) adjusted for gender, age, and racial/ethnic group. se = standard error. Estimates are scaled within each user group to reflect increases in standard deviations for TD Scale and log transformed values of TNE-2. All estimates from linear regression for quantity and logistic regression for daily use are weighted to reflect the survey design. Cells for Hookah Only and Multiple Product: No Cigarette users are empty as no estimates of quantity were evaluated for these product types. E-cigarette quantity assessed with number of e-cigarettes for disposable/non-rechargeable users or e-cigarette cartridges each day if using rechargeable or refillable product.

Table 3. Association of Biomarkers of Nicotine Exposure (TNE-2) and TD With Predicted Change in Wave 2 Quantity of Tobacco Use and Rates of Daily Use

					Individual relationships			Individual relationships			Combined relationships					
					TNE-2			TD			TNE-2			TD		
Tobacco use group	W1	se	W2	se	*b*	se	*p*	*b*	se	*p*	*b*	se	*p*	*b*	se	*p*
Quantity of use																
Cigarette Only	14.19	0.29	13.50	0.29	0.12	0.01	<.01	0.24	0.03	<.01	0.09	0.01	<.01	0.20	0.03	<.01
E-cigarette Only	2.20	0.31	3.62	0.44	0.01	0.05	.89	−0.03	0.09	.75	0.01	0.05	.87	−0.03	0.09	.74
Cigar Only: Traditional	2.07	0.31	1.48	0.20												
Cigar Only: Cigarillo	3.32	0.42	2.60	0.48	0.06	0.03	.09	0.29	0.11	.01	0.04	0.03	.24	0.27	0.10	.01
Cigar Only: Filtered	8.22	1.34	5.77	0.96	0.11	0.05	.04	−0.30	0.29	.30	0.16	0.06	<.01	−0.47	0.28	.10
Hookah Only																
Smokeless Only	7.15	0.29	7.06	0.30	0.05	0.03	.04	0.15	0.04	<.01	0.03	0.03	.19	0.14	0.04	<.01
Cigarette + E-cigarette	13.95	0.64	13.87	0.59	0.19	0.04	<.01	0.36	0.08	<.01	0.15	0.04	<.01	0.33	0.08	<.01
Multiple Products: Cigarette	14.07	0.50	12.60	0.49	0.11	0.06	.07	0.45	0.07	<.01	0.05	0.06	.46	0.42	0.10	<.01
Multiple Products: No Cigarette																
Rates of daily use																
Cigarette Only	86%	0.9%	83%	1.2%	0.29	0.04	<.01	0.59	0.12	<.01	0.24	0.04	<.01	0.51	0.12	<.01
E-cigarette Only	78%	3.0%	76%	3.0%	0.31	0.14	.03	−0.04	0.29	.88	0.33	0.14	.03	−0.17	0.23	.47
Cigar Only	32%	3.8%	28%	4.0%	0.38	0.14	.01	0.17	0.37	.64	0.39	0.15	.01	−0.06	0.37	.88
Hookah Only	6%	1.5%	3%	1.0%	0.00	0.05	.95	0.07	0.11	.51	0.00	0.05	.98	0.07	0.10	.49
Smokeless Only	81%	2.4%	72%	2.5%	0.32	0.11	<.01	0.18	0.15	.21	0.32	0.11	<.01	0.10	0.14	.49
Cigarette + E-cigarette	95%	0.9%	89%	1.5%	0.44	0.11	<.01	0.42	0.09	<.01	0.40	0.11	<.01	0.55	0.26	.04
Multiple Products: Cigarette	93%	1.0%	88%	1.3%	0.42	0.09	<.01	0.79	0.18	<.01	0.38	0.08	<.01	0.71	0.17	<.01
Multiple Products: No Cigarette	65%	4.8%	62%	5.8%	0.29	0.13	.03	1.05	0.59	.08	0.22	0.13	.09	0.81	0.57	.16

W1 and W2 columns reflect survey weighted estimates of mean quantity of use or rates of daily use at Wave 1 (W1) and Wave 2 (W2). Estimates (*b*) from linear regression for quantity and logistic regression for daily use are weighted to reflect the survey design and were adjusted for gender, age, and racial/ethnic group. Estimates are scaled within each user group to reflect increases in standard deviations for Tobacco Dependence (TD) Scale and log transformed values of Total Nicotine Equivalents-2 (TNE-2). se = standard error. For Hookah Only users Poisson regression models evaluated the number of days used (not dichotomous daily use). Cells for Hookah Only and Multiple Product: No Cigarette users are empty as no estimates of quantity were evaluated for these product types. Cells for Cigar Only: Traditional are empty given poor convergence of linear regression models. E-cigarette quantity assessed with number of e-cigarettes for disposable/non-rechargeable users or e-cigarette cartridges each day if using rechargeable or refillable product.

Table 4. Association of Biomarkers of Nicotine Exposure (TNE-2) and TD With Odds of Quit Success between Wave 1 and Wave 2 Interviews

			Individual relationships						Combined relationships					
	W2 past year quit attempt		TNE-2			TD			TNE-2			TD		
Tobacco use group	%	se	OR	L95	U95	OR	L95	U95	OR	L95	U95	OR	L95	U95
Quit Success														
Cigarette Only	5.0%	1.1%	0.74	0.67	0.82	0.58	0.33	1.02	0.76	0.67	0.85	0.87	0.48	1.60
E-Cigarette Only	13.4%	3.5%	0.77	0.61	0.97	0.86	0.46	1.60	0.78	0.62	0.98	0.92	0.46	1.83
Cigar Only	16.3%	3.1%	0.85	0.73	0.99	0.72	0.32	1.62	0.85	0.72	1.01	0.96	0.42	2.18
Hookah Only	32.8%	5.1%	0.92	0.79	1.08	0.72	0.43	1.18	0.97	0.82	1.15	0.71	0.40	1.26
Smokeless Only	11.8%	2.8%	0.77	0.64	0.92	0.77	0.46	1.30	0.76	0.61	0.93	1.10	0.67	1.80
Cigarette + E-cigarette	3.3%	1.5%	0.75	0.42	1.33	1.10	0.43	2.85	0.69	0.31	1.52	1.38	0.42	4.61
Multiple Products: Cigarette	3.1%	0.7%	0.63	0.52	0.76	0.37	0.20	0.68	0.66	0.55	0.79	0.66	0.35	1.26
Multiple Products: No Cigarette[a]	12.6%	6.0%	0.68	0.32	1.43	0.48	0.09	2.72						

Estimates from logistic regression models are weighted to account for survey design and adjusted for gender, age, and racial/ethnic group. Estimates are scaled within each user group to reflect increases in standard deviations for Tobacco Dependence (TD) Scale and log transformed values of Total Nicotine Equivalents-2 (TNE-2). L95 = lower 95th%ile, OR = odds ratio; se = standard error, U95 = upper 95th%ile.

[a]Estimates not reported given poor convergence of regression models.

Product-Cigarette users and 3.3% among Cigarette + E-cigarette users to 32.8% among Hookah Only users. In adjusted logistic regression models, higher levels of Wave 1 TD were significantly predictive of a lower odds of successful quitting at Wave 2 among Multiple Product-Cigarette users (OR = 0.37; $p < .01$). Wave 1 TD was not significantly predictive of successful quitting among other user groups (all $p > .10$). Wave 1 TNE-2 was predictive of decreased odds of quitting success among Cigarette Only (OR = 0.74, $p < .01$), E-cigarette Only (OR = 0.77, $p < .05$), Cigar Only (OR = 0.85, $p < .05$), Smokeless Only (OR = 0.77, $p < .01$) and Multiple Product-Cigarette users (OR = 0.63; $p < .01$). We did not observe significant relationships between levels of TD or TNE-2 and successful quitting among Hookah Only or Cigarette+E-cigarette users (all $p > .10$).

In combined models, TNE-2 retained independent significant relationships with lower odds of Wave 2 quitting success among Cigarette Only, E-cigarette Only, Smokeless Only, and Multiple Product-Cigarette users ($p < .05$). In models with TNE-2, Wave 1 TD was no longer a significant predictor of quitting success among Multiple Product-Cigarette user groups.

Association of Biomarkers of Nicotine Exposure (TNE-2) and TD With Changes in Patterns of Tobacco Product Use

Rates of maintaining the 'Same' pattern of use varied from a high of 66.1% among Cigarette Only to 25.7% among Hookah Only users (Supplemental Table 1). While rates of 'Adding' a product ranged consistently from 20.3 to 27.9% across Wave 1 product users, rates of 'Switching' ranged from a high of 19.2% among Hookah Only to a low of 3.0% among Cigarette Only users. Rates of 'Quit' also varied with a high of 31.2% among Hookah Only to a low of 5.9% among Cigarette Only users. In individual multinomial models, higher levels of TD were associated ($p < .01$) with lower odds of 'Switching' relative to staying the 'Same' among Cigarette Only ($p < .01$), higher odds of switching among Cigar Only ($p < .01$) and were not associated with 'Switching' in other user groups (ps > .05). Higher levels of TD were associated with having lower odds of having 'Quit' relative to staying the 'Same' among Cigarette Only ($p < .01$) users. Levels of Wave 1 TD were not associated with having 'Quit' among E-cigarette Only, Cigar Only, Hookah Only, or Smokeless Only users (ps > .10). Wave 1 levels of TNE-2 were associated with lower odds of 'Switching' among Cigarette Only ($p < .01$) and Smokeless Only ($p < .05$) users; lower odds of quitting among Cigarette Only ($p < .01$), E-cigarette Only ($p < .01$), and Smokeless Only ($p < .01$) users. Wave 1 TD and TNE-2 were not associated with 'Adding' among any user group ($p > .05$).

In combined models, both Wave 1 TD and TNE-2 were associated with reduced odds of being 'Quit' relative to staying the 'Same' at Wave 2 among Cigarette Only users. Among Smokeless Only users TNE-2 remained predictive of lower odds of having 'Quit' at Wave 2 ($p < .01$). Among Cigar Only users, Wave 1 TD was independently associated with higher odds of 'Switching' relative to staying the 'Same'. Wave 1 TNE-2 was not associated with transitions among Cigar Only or Hookah Only users. Wave 1 TD was not associated with transitions among Hookah Only or Smokeless Only users.

Discussion

Concurrent, positive associations between the TD scores and nicotine exposure assessed via TNE-2 were found for almost all single

and multiple combinations of tobacco product use. Concurrent quantity and frequency of product use were also generally and positively associated with TD scores and TNE-2, particularly among Cigarette Only and Smokeless Only users. The highest levels of TNE-2 concentrations and TD also were observed among cigarette smokers and among Smokeless Only users, groups with a high proportion of daily users.

For Cigarette Only smokers, TD and TNE-2 were associated with a pattern of outcomes consistent with higher dependence: a tendency to smoke more and more frequently over time, decreased likelihood of switching away from cigarettes, and decreased probability of quitting after one year. Both TD and TNE-2 predicted changes in quantity and frequency of cigarette use for Cigarette Only users. Although on average, the quantity of cigarettes consumed did not change significantly over one year, both TD and TNE-2 were predictive of changes in cigarettes per day. The same was true for frequency of use. Wave 1 TD and TNE-2 were associated with staying or becoming a daily smoker. Wave 1 TD and TNE-2 were also inversely associated with switching patterns of tobacco product use and with quitting at the one-year follow-up. Similar findings for changes in quantity and frequency consumed, and successful quitting (adding and switching were not assessed) were found in the Multiple Product-Cigarette user group, indicating possibly that coherence across multiple tobacco use behavioral outcomes is influenced primarily by smoking cigarettes.

For other product user groups, Wave 1 TD and/or TNE-2 were less consistently related to changes in quantity and frequency of product use, or for adding or switching products. Attenuated relationships relative to Cigarette Only users likely arise from challenges in assessing quantity and frequency of use for other products and potential less uniform patterns of use over time. Among E-cigarette Only users, TD and TNE-2 had significant relationships with concurrent frequency of use but not with quantity of use, or transitions to other products. TNE-2 but not TD, however, predicted Wave 2 daily use among E-cigarette Only and Smokeless Only users. Thus, relationships between TNE-2 and TD, and tobacco use outcomes, were consistently stronger for cigarette users than for users of other products. However, with an evolving marketplace generating new electronic nicotine delivery products and e-liquid formulations (eg, nicotine salts), the strength of associations between TD, TNE-2, and use of e-cigarette products will require continued surveillance.

Results of this study further elucidate complex relationships among measures of TD, nicotine exposure, and product-specific behavioral outcomes, and suggest that smoking cigarettes leads to the most coherent pattern of associations consistent with a syndrome of TD. Because cigarettes continue to be prevalent, popular and harmful,[9,24] efforts to decrease their use may be accelerated via conventional means (eg, smoking cessation interventions and treatments), but also perhaps by decreasing their dependence potential, for example, by considering a reduced nicotine product standard.[21] The implications for noncombustible tobacco products are less clear. In the present study, higher TD and TNE-2 for smokeless and e-cigarette product users were also associated with increased product consumption and less quitting, but certain formulations of these products may be perceived to be less harmful than cigarettes.[25] It is also possible that some proportion of smokeless and e-cigarette product users were using these products instead of smoking cigarettes.[8]

The findings reported here should also be interpreted taking into consideration possible study limitations. Although the TD unidimensional measure was found to be psychometrically sound and consistent across products,[10] additional items that might tap product-specific aspects of TD may have been excluded. Research on product-specific aspects of TD will help us understand associations with behavioral outcomes. Impacts from the frequency of measured outcomes could also be explored; for example, by increasing assessments of temporal patterns of consumption and abstinence, which may be fairly dynamic for some individuals. We also did not take into account reasons for quitting, whether or not tobacco users used nicotine replacement therapy or other methods to quit and did not consider experimental use of other products when forming tobacco user groups. The definition of some tobacco user groups was broad and did not take into account differences in product characteristics (eg, e-cigarette device type; ease of use; satisfaction) that could influence nicotine delivery as well as absorption, and frequency and quantity of product use.[26,27] We also did not account for individual differences in biological factors such as the rate of nicotine metabolism, which could have influenced observed levels of nicotine exposure.[28,29]

In summary, TD and nicotine exposure (measured by TNE-2) assess some common and independent aspects of dependence in relation to tobacco use behaviors. For cigarette smokers, both factors are related to changes (or lack thereof) in levels of tobacco consumption, adding/switching products, and quitting. For other product user groups, nicotine exposure is a more consistent predictor of quitting. Wherever possible, TD, nicotine exposure measures, and consumption could be used in studies that attempt to understand and predict product-specific tobacco use behavioral outcomes.

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Data Availability

Data are available in a public, open-access repository, the National Addiction and HIV Data Archive: https://www.icpsr.umich.edu/web/NAHDAP/studies/36498.

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