Nicotine and Toxicant Exposure Among Cigarette Smokers Who Transition to Quitting, E-vapor, or Dual Use using PATH Wave 1 & Wave 2 Biomarker Data

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ABSTRACT

Significance: Changes in tobacco use behaviors (e.g., stopping all tobacco use, transitioning to e-vapor, or dual using cigarettes and e-vapor may impact exposure to nicotine and other smoke constituents. Using PATH data, we evaluated changes in urinary biomarkers of exposure among adult exclusive smokers (AES) who transitioned to e-vapor products (EVP) use or stopped smoking (SS). **Method:** We analyzed 18 urinary biomarkers of exposure to nicotine and other smoke constituents in 2,487 Wave 1 AES. By Wave 2, these AES had either SS, transitioned to exclusive use of EVP (EEVP), began dual using cigarettes and EVP (DU), or remained AES. Wave 1 to Wave 2 changes in biomarker levels of SS, EEVP, DU were compared to the changes in those that remained AES at Wave 2. The transition from smoking to DU was further explored to understand the impact of frequent (smoke on ≥20 days), or infrequent (≤19 days) smoking on biomarker levels of DU. Changes in the geometric mean of biomarkers were controlled for key demographics, BMI, and region. Dual use analysis was segmented for frequent or infrequent smoking at Wave 2 and controlled for use at Wave 1. **Results:** At Wave 2, 9% of Wave 1 AES stopped smoking, 1% switched to exclusive e-vapor, 9% were DU, 73% remained AES, and 8% other. AES who stopped smoking had significant reductions (p<.05) in 14 of 18 biomarkers compared to those that remained AES. AES who transitioned to EEVP use had significant reductions in 16 of 18 biomarkers compared to those that remained AES. AES who began dual use with e-vapor had significant reductions in 5 of 18 biomarkers. Among the DU, DU who smoked infrequently had significant reductions in 6 of 18 biomarkers compared to DU who smoked frequently. Other biomarker levels fluctuated (up or down) but did not reach statistical significance. **Conclusion:** AES who stopped smoking or switched to e-vapor had generally lower levels of biomarkers. DU who smoke infrequently had some lower biomarker levels than DU who smoked frequently. These results suggest that in DU, biomarker levels are driven by frequency of cigarette smoking and not all DU are the same. While quitting or complete switching is the optimum outcome, reduction in cigarette consumption reduces exposure to some cigarette smoke constituents.

METHODS

We performed a secondary analysis of 18 urinary biomarkers of exposure to nicotine and other smoke constituents in 2,487 PATH Wave 1 adult exclusive smokers. The sample included all adult exclusive smokers from the PATH Study sample who provided a Wave 1 and 2 urine sample with complete tobacco use and demographic data needed for this analysis. By Wave 2, these exclusive smokers either remained exclusive smokers, stopped all tobacco use, transitioned to exclusive use of e-vapor, began dual use of only cigarettes and e-vapor, or had some other behavior.

Wave 1 to Wave 2 changes in biomarker levels of those who stopped all tobacco use, transitioned to exclusive use of e-vapor, or began dual use of only cigarettes and e-vapor were compared to the changes in those that remained exclusive smokers at Wave 2, the reference condition. Other tobacco use states were omitted due to the uncertainty of interpretation or relevance.

The transition from smoking to dual use was further explored to understand the impact of frequent (≥20 days in the last 30), or infrequent (≤19 days in the last 30) smoking on biomarker levels of dual users.

Biomarker data were adjusted based on creatinine level and log transformed. The difference in biomarker levels was calculated between Waves and tobacco use groups were compared using exponentiated geometric mean ratios (implemented via regression). Urine analysis weights and the balanced repeated replication method was used during regression analysis as suggested by PATH[1]. We controlled for gender, age, race, education, BMI, and region when calculating changes in the biomarker geometric mean. Additionally, biomarker analysis for those who transitioned to dual use was segmented by frequency of smoking at Wave 2 and controlled for use at Wave 1.

Table 1: Tobacco Smoke Constituents Classification of Urinary Biomarkers of Exposure

Metabolite Group	Tobacco Smoke Constituents	Urinary Biomarker of Exposure	FDA Classification*
VOC	1,3-Butadiene	MHB3 (N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine)	CA, RT, RDT
	Acrolein	3HPMA (N-Acetyl-S-(3-hydroxypropyl)-L-cysteine), CEMA (N-Acetyl-S-(2-carboxyethyl)-L-cysteine)	RT, CT
	Acrylamide	AAMA (N-Acetyl-S-(2-carbamoylethyl)-l-cysteine)	CA
	Acrylonitrile	CYMA (N-Acetyl-S-(2cyanoethyl)-l-cysteine)	CA, RT
	Crotonaldehyde	HPMM (N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine)	CA
	Isoprene	IPM3 (N-Acetyl-S-(4-hydroxy-2-methyl-2-buten-1-yl)-L-cysteine)	CA
	Polycyclic Aromatic Hydrocarbons	2-FLU (2-Hydroxyfluorene), 3-FLU (3-Hydroxyfluorene), 1PYR (1-Hydroxypyrene)	CA, CT
	Propylene Oxide	2HPMA (N-Acetyl-S-(2-hydroxypropyl)-L-cysteine)	CA, RT
	Styrene	MADA (Mandelic acid), PHGA (Phenylglyoxylicacid)	CA
TSNA	Nicotine-derived nitrosamine ketone	NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol)	CA
	N'-Nitrosonornicotine	NNN (N'-Nitrosonornicotine)	CA
Nicotine	Nicotine	TNE-7 (Total Nicotine Equivalents – 7)	RDT, AD
Metals	Cadmium	Cadmium	CA, RT, RDT
	Lead	Lead	CA, CT, RDT

*FDA Classification: Carcinogen (CA), Respiratory Toxicant (RT), Cardiovascular Toxicant (CT), Reproductive or Developmental Toxicant (RDT), Addictive (AD)

1 US Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, and Food and Drug Administration, Center for Tobacco Products. PATH Study Biomarker Restricted Use Files User Guide. ICPSR36840, Inter-university Consortium for Political and Social Research [distributor], Ann Arbor, MI (2019 March 19).

RESULTS

Adult exclusive smokers who stopped all tobacco use had significant reductions (p<.05) in 14 of 18 biomarkers compared to those that remained exclusive smokers (Fig 1.2). Adult exclusive smokers who transitioned to exclusive use of e-vapor use had significant reductions in 16 of 18 biomarkers compared to those that remained exclusive smokers (Fig 1.3). Adult exclusive smokers who began dual use with e-vapor had significant reductions in 5 of 18 biomarkers (Fig 1.4).

Figure 1.1 Wave 1 and 2 Behaviors, Sample Size, and Biomarker Comparisons

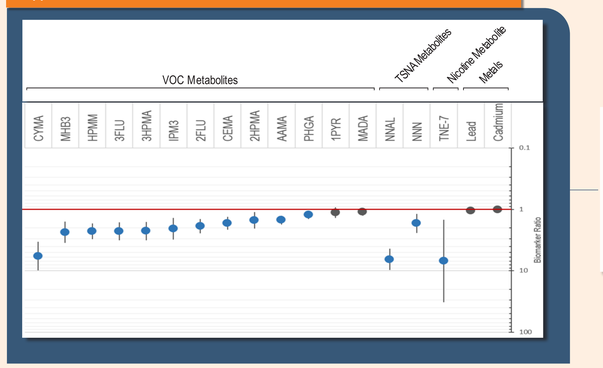
Wave 1 Behavior	Wave 2 Behavior	Sample Size, Wt. %	Biomarkers Reduced
Adult Exclusive Smoker	Continued Exclusive Smoker	1,771, 73%	*Ref.*
	Stopped All Tobacco Use	229, 9%	*14 of 18*
	Exclusive E-Vapor	37, 1%	*16 of 18*
	Dual Use: Cigarettes & E-Vapor	242, 9%	*5 of 18*
	Other (Omitted)	208, 8%	-

Among the dual users, dual users who smoked infrequently had significant reductions in 6 of 18 biomarkers compared to dual users who smoked frequently (Fig 2.2). Other biomarker levels fluctuated (up or down) but did not reach statistical significance.

Fig. 2.1. Wave 1 and 2 Behaviors, Sample Size and Biomarker Comparisons Among Dual Users

Wave 1 Behavior	Wave 2 Behavior	Sample Size, Wt. %	Biomarkers Reduced
Adult Exclusive Smoker	Dual Use: Frequent Cigarettes & E-Vapor	211, 8%	*Ref.*
	Dual Use: Infrequent Cigarettes & E-Vapor	31, 1%	*6 of 18*
	Other (Omitted)	2,245, 90%	-

Fig. 1.2. Biomarker Difference Between 1) Continued Smokers and 2) Those Who Stopped All Tobacco Use



Significantly Different From the Continued Smoker
Not Significantly Different
Red Line Represents No Change

Fig. 2.2. Biomarker Difference Between 1) Frequent Smokers/any E-vapor Dual Users and 2) Infrequent Smokers/any E-vapor Dual Users

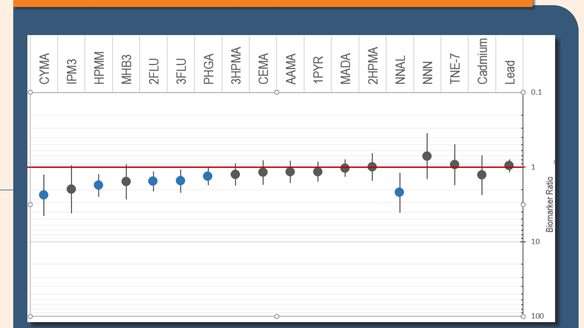


Fig. 1.3. Biomarker Difference Between 1) Continued Smokers and 2) Those Transitioned to Exclusive Use of E-vapor

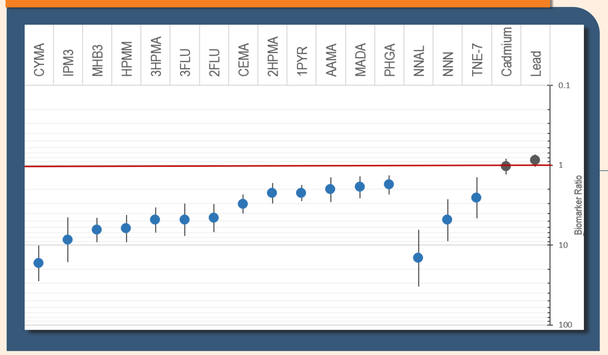
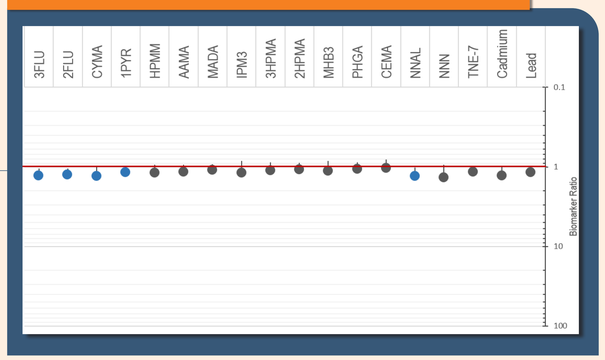


Fig. 1.4. Biomarker Difference Between 1) Continued Smokers and 2) Smoker/E-vapor Dual User



STRENGTHS AND LIMITATIONS

- This research provides an assessment of scientifically relevant biomarkers of exposure over time in the nationally representative PATH study.
- Tobacco use is based on self-reported product use with risks of misclassification bias.
- There was a change in e-cigarette/e-vapor classification between Wave 1 and Wave 2.

CONCLUSIONS

- Adult exclusive smokers who stopped all tobacco use or transitioned to exclusive use of e-vapor had generally lower levels of biomarkers than those remained exclusive smokers.
- Cigarette and e-vapor dual users who smoke infrequently had some lower biomarker levels than dual users who smoked frequently. These results suggest that in dual users, biomarker levels are driven by frequency of cigarette smoking and not all dual users are the same.
- While quitting or complete switching is the optimum outcome, reduction in cigarette consumption reduces exposure to some cigarette smoke constituents.