Not All Dual Use of Cigarettes and E-vapor Products is the Same: Biomarkers and Tobacco Use Behavior in Subpopulations of Dual Users from the PATH Wave 1 Data

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ABSTRACT

Significance: Dual users (DU) of cigarettes (CIG) and e-vapor products (EVP) are often considered a single group. We assessed biomarkers of exposure (BoE) to Harmful and Potentially Harmful Constituents (HPHCs) and biomarkers of potential harm (BoPH) to better understand levels of exposure among subgroups of dual users.
Methods: We segmented DU (n=970) in the PATH Study Wave 1 (2013-2014) into four major subgroups based on the number of days they used each product in the past 30 days – Frequent DU of both products (use each product ≥20 days), Smokers who Vape (smoke on ≥20 days, vape on ≤19 days), Vapers who Smoke (vape on ≥20 days, smoke on ≤19 days), and Infrequent DU of both products (use each product on ≤19 days). Biological samples were analyzed for BoEs including tobacco specific nitrosamines (NNAL, NNN), nicotine (TNE-7), cadmium, lead, 2-hydroxyfluorene, 3-hydroxyfluorene, pyrene (1-hydroxypyrene), and eight mercapturic acid metabolites of gas-phase HPHCs. We also analyzed BoPHs, including high-sensitivity c-reactive protein (hs-CRP), interleukin-6 (IL-6), soluble intercellular adhesion molecule (sICAM) and fibrinogen. The statistical comparisons were made within DU groups and versus exclusive daily CIG smokers (n=2,442).
Results: The proportions in each subgroup were: Smokers who Vape (n=678; 69.2%); Frequent DU (n=169; 18.1%); Infrequent DU (n=66; 6.9%) and Vapers who Smoke (n=57; 5.8%). Within the DU groups, Smokers who Vape showed statistically significant ($p<0.05$) higher levels of 8/18 BoEs compared to Frequent DU. Vapers who Smoke and Infrequent DU showed statistically significant lower levels of 16/18 BoEs than Smokers Who Vape and Frequent DU. Infrequent DU had the lowest biomarker levels among all DUs. Both Vapers Who Smoke and Infrequent DU groups exhibited significantly lower levels of BoEs 15/18 and 17/18, respectively, as well as lower levels of BoPHs IL-6 and sICAM, respectively, compared to exclusive CIG smokers.
Conclusions: Biomarker levels in DU overall are driven by frequency of cigarette smoking and not by frequency of e-cigarette use suggesting not all dual users are the same.

METHODS

The PATH Study Wave 1 included data from 32,320 adults (18+ years) collected from September 2013 to December 2014. All adult participants were asked to provide urine and blood samples. Biospecimens from 11,522 adult respondents who provided a urine sample, of which, 7,159 provided a blood sample were selected for biomarker analyses to evaluate whether the levels of selected BoE and BoPH differ among DU versus CIG and EVP.

We segmented DU (n=970) into four major subgroups based on the number of days they had used each product in past 30 days – Frequent DU of both products (use each product ≥20 days), Smokers who Vape (smoke on ≥20 days, vape on ≤19 days), Vapers who Smoke (vape on ≥20 days, smoke on ≤19 days), and Infrequent DU of both products (use each product on ≤19 days).

Biological samples were examined for BoEs including tobacco specific nitrosamines (NNAL, NNN), nicotine (TNE-7), cadmium, lead, 2-hydroxyfluorene, 3-hydroxyfluorene, pyrene (1-hydroxypyrene), and eight mercapturic acid metabolites of gas-phase HPHCs. We also examined BoPHs, including high-sensitivity c-reactive protein (hs-CRP), interleukin-6 (IL-6), soluble intercellular adhesion molecule (sICAM) and fibrinogen. A linear regression model was used to estimate biomarker levels for each of the groups, while adjusting for sex, age, race/ethnicity, region, education and BMI. Appropriate sampling weights and replicate weights were applied to adjust for complex survey design. The statistical comparisons were made between DU groups, and DU groups were also compared to CIG smokers (n=2,442). The never tobacco user group (n=1,700) was used as a reference group to illustrate relative comparison of tobacco exposure.

REFERENCES

1-Guidance for Industry, Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act (3/2012).
2-Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products (5/10/2016).
3-American Academy of Pediatrics v. FDA, No. PWG-18-883, 2019 U.S. Dist. Westlaw 3067492 D. Md. (7/7/19).
4-S.A. Baig, D.P. Giovenco, Behavioral heterogeneity among cigarette and e-cigarette dual users and associations with future tobacco use: Findings from the Population Assessment of Tobacco and Health Study, Addictive Behaviors (2019)

RESULTS

Table 1: Notable characteristics of subpopulations of dual users with urinary biomarker data

Dual User Subgroup	Sample Size, weighted %	Notable Characteristics
Frequent Duals	N=169, 18.0%	More likely to be White, non-Hispanic (87.7%)
Smokers who Vape	N=678, 69.2%	Smoke more cigarettes per day (15.7) than any other dual use subgroup (4.8-15.0)
Vapers who Smoke	N=57, 6.9%	More likely to have Body Mass Index less than 25
Infrequent Duals	N=66, 6.9%	More likely to be younger than 25 years old

Table 2: Tobacco smoke constituents classification of urinary biomarkers of exposure

Tobacco Smoke Constituents	Urinary Biomarker of Exposure	FDA Classification
1,3-Butadiene	MHB3 (N-Acetyl-S-(4-hydroxy-2-methyl-2-buten-1-yl)-L-cysteine)	CA, RT, RDT
Acrolein	3-HPMA (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
Metals	Cadmium, Lead	CA, CT, RDT
Nicotine-derived nitrosamine ketone	NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol)	CA
N'-Nitrosonornicotine	NNN (N'-Nitrosonornicotine)	CA
Nicotine	TNE-7 (Total Nicotine Equivalents – 7)	RDT, AD
Polycyclic Aromatic Hydrocarbons	2-Hydroxyfluorene, 3-Hydroxyfluorene, 1-Hydroxypyrene	CA, CT
Propylene Oxide	2-HPMA (2-Hydroxypropylmercapturic acid)	CA, RT
Styrene	MADA (Mandelic acid),PHGA (Phenylglyoxylicacid)	CA

BIOMARKERS OF EXPOSURE

Difference in Biomarkers of Exposure Relative to Exclusive Cigarette Smoking by Dual User Segment

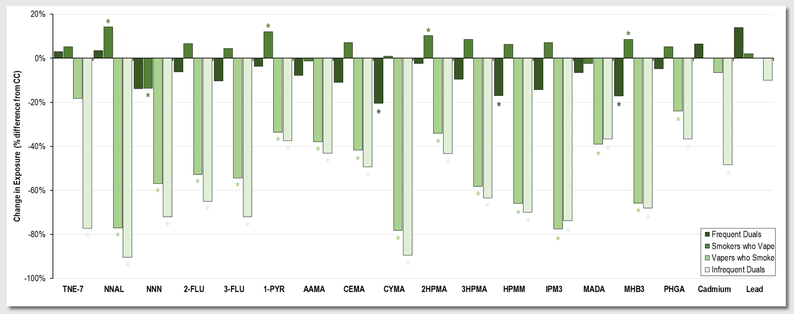

Figure 1: Both Vapers who Smoke and Infrequent Duals had significantly lower levels in the majority of biomarkers than daily Exclusive Cigarette Smokers. In contrast, among Smokers who Vape, there were significantly higher levels of NNAL, 1-PYR, 2-HPMA and MHB3 than exclusive cigarette smokers. (% difference from exclusive daily cigarette smokers, error bars not displayed for clarity, *p < 0.05). Model was adjusted for sex, age, race/ethnicity, region, education and BMI.

BIOMARKERS OF POTENTIAL HARM

Difference in Biomarkers of Potential Harm Relative to Exclusive Cigarette Smoking by Dual User Segment

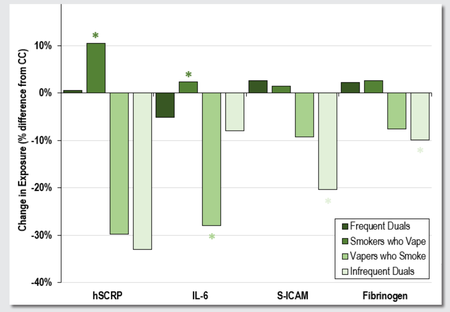

Figure 3: We observed higher levels of hs-CRP and IL-6 among Smokers who Vape whereas both Vapers who Smoke and Infrequent Duals had lower levels (% difference from exclusive daily cigarette smokers, error bars not displayed for clarity, *p < 0.05). Model was adjusted for sex, age, race/ethnicity, region, education and BMI.

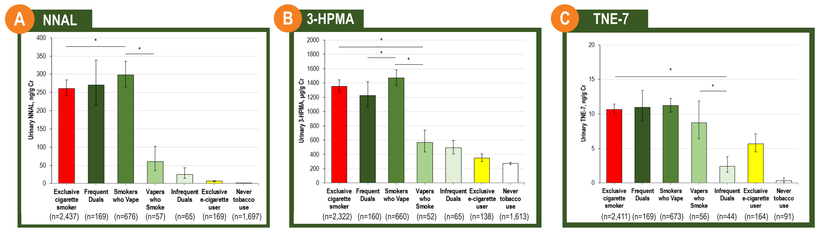

Figure 2: We observed higher levels of (A) NNAL and (B) 3-HPMA among Smokes who Vape than any other tobacco product user group; (C) TNE-7 levels were similar with an exception among Infrequent Duals, where they were significantly lower. (GM ± 95% CL, *p < 0.05)

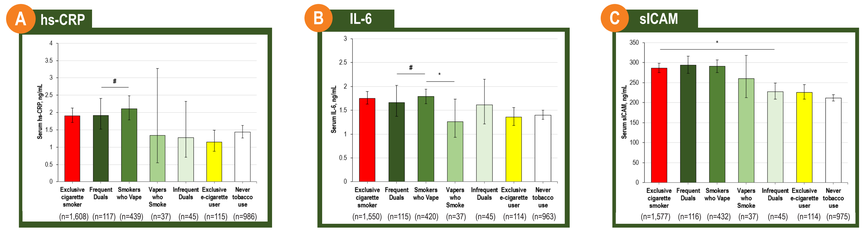

Figure 4: We observed higher levels of (A) high-sensitivity C-reactive protein (hs-CRP) and (B) interleukin-6 (IL-6) among Smokers who Vape relative to other groups; (C) sICAM levels remained consistent across groups with significantly lower levels among Infrequent Duals. (GM ± 95% CL, *p < 0.05, #p = 0.05)

CONCLUSIONS

- In general, groups reporting lower levels of cigarette consumption largely had lower levels of BoEs compared to groups with higher cigarette consumption.
- We observed a continuum of exposure reduction driven by cigarette consumption, where the highest exposure was among smokers who vape and the lowest exposure was among the exclusive e-vapor user group.
- All dual users should not be considered as a monolithic group as there are distinct differences in biomarker exposure levels.

STRENGTHS AND LIMITATIONS

- This research provides a comprehensive cross-sectional assessment of BoE and BoPHs in the nationally representative PATH Study Wave 1.
- The results indicate real-world evidence based on self-reported product use behavior.
- The PATH survey questionnaire does not differentiate between first-, second-, or later generation e-cigarette devices as the exposure to nicotine and other toxicants may be different.
- The self-reported tobacco use consumption behavior may be subject to reporting bias.