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Biochemical validation of dependence on JUUL and other e-cigarettes among youth

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Abbreviations: PATH= Population Assessment of Tobacco and Health; ENP=Electronic Nicotine Product; ED scale =ENP dependence scale; WISDM=Wisconsin Inventory of Smoking Dependence Motives; 3HC = trans-3'-hydroxycotinine; nmol/mL=nanomoles per milliliter.

Contributors Statement Page:

Dr Pierce conceptualized this project, obtained access to the data, drafted the initial manuscript and reviewed and revised the manuscript.

Dr Leas conducted all analyses for this paper and critically reviewed the manuscript for important intellectual content

Dr Strong conceptualized and designed the study and critically reviewed the manuscript for important intellectual content

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

INTRODUCTION

The Population Assessment of Tobacco and Health (PATH) is a large, longitudinal, nationally representative Study,¹ that queries all tobacco users with a self-reported, psychometrically-validated dependence scale.²⁻⁴ Among 2013-14 adult exclusive e-cigarette users, this scale was weakly associated with urinary nicotine ($r=0.13$) although the dependence scale had a better correlation among exclusive cigarette smokers ($r=0.45$).⁵ However, the e-cigarette market changed and, in 2019, the high-nicotine JUUL e-cigarette captured 56% market share among under 21 years old e-cigarette users.⁶ In that year, the self-reported e-cigarette dependence (ED) levels among adolescents appeared similar in magnitude to dependence levels in same age cigarette smokers.⁶ The recent availability of urinary nicotine biomarkers for the 2019 PATH survey enables us to assess the correlation between the ED scale and nicotine biomarker in 2019.

METHODS

Sample: In 2019, PATH collected urine biospecimens on respondents over age 14 years and analyzed total nicotine equivalents (TNE-2) [molar sum of cotinine and trans-3'-hydroxycotinine (3HC)] are publicly available on a sub-sample.⁷ We identified 124 adolescents and 325 young adults who were either: a) aged 18-34 years, self-defined “fairly regular” and current (past 3 days) exclusive users of electronic nicotine products (ENPs), or b) aged 14-17 years, current 30-day (including past 3 days) exclusive ENP vapers. We also required the ED scale to be completed (final $n=432$). Participants were asked their usual brand of use.

Tobacco Dependence scores: The PATH Study uses the WISDM framework⁸ to query domains for ED on both the adolescent and the adult questionnaires: I find myself reaching for ENP without thinking about; I frequently crave an ENP; my ENP use is out of control; I usually want

to use an ENP right after I wake up; using an ENP really helps me feel better if I've been feeling down; using an ENP helps me think better; I would feel alone without my ENP. Response options ranged from 1 ("Not true of me at all") to 5 ("Extremely true of me"), so the summed ED scale ranged from 7 to 35. We correlated the individual's continuous ED score with the urinary biomarker for both JUUL and other brands.

Laboratory Analyses: The PATH Study provides quality-controlled assessments of urinary TNE-2s (nmol/mL) using liquid chromatography, tandem mass spectrometry methods.⁹

Statistical Analyses: We report unweighted spearman correlation coefficients as well as weighted linear models comparing ED to TNE-2 for those reporting any ENP use as well as by brand. Due to their skewedness, values of TNE-2 were log-transformed to improve model fit in the weighted linear models.

RESULTS

The Spearman's correlations between ED scores and TNE-2 levels suggested a moderate correlation for the JUUL subgroup ($r=0.46$) and a weak correlation for the non-JUUL subgroup ($r=0.25$). Using the weighted linear model, we estimated the percent increase in TNE2 per unit increase in e-cigarette dependence score for any e-cigarette used ($n=449$), separately for JUUL e-cigarettes ($n=132$) and for any other named brand ($n=139$). The R^2 for each model was low with JUUL model ($R^2=0.21$) having a slightly better fit than other e-cigarettes ($R^2=0.13$). In each model, coefficients represent the percentage increase in TNE2 per 1 unit increase in e-cigarette dependence scores and these are estimated from a weighted linear model. The coefficient was significantly different from zero in each model tested indicating a linear association between

TNE2 and ED scores (p 's <0.05), although the association was stronger for JUUL ($\beta=14.4$, 95% CI: 5.9,23.6) than for other e-cigarettes ($\beta=7.2$, 95% CI: 1.6,13.1).

DISCUSSION

In 2019, the correlation between self-reported e-cigarette dependence scores and urinary nicotine metabolites among exclusive e-cigarette users was much higher than that reported in 2013-14.⁴ Correlations for JUUL users were equivalent to those previously seen for exclusive cigarette smokers ($r\sim 0.46$). In this study population, the JUUL correlation appears higher than that for other e-cigarettes which may reflect its fixed higher-dose nicotine concentrations, or, alternatively, that other e-cigarettes were more diverse in their nicotine concentrations and formulations.

CONCLUSION

The correlation for JUUL vapers, majority of whom were under 21 years, was equivalent to that previously reported for cigarette smokers. This suggests that the introduction of high nicotine e-cigarettes is associated with increased nicotine addiction in US youth.

1

2 Table 1: Models comparing the association between Total Nicotine Equivalents (TNE2) and e-cigarette dependence among exclusive
3 past 4-day users of e-cigarette at Wave 5 of PATH Study

Type of e-cigarette used	n	β	95% CI		p-value	R ²
all types of e-cigarette	449	10.2	3.8	17.0	0.002	0.13
JUUL brands	132	14.4	5.9	23.6	0.0001	0.21
Other E-cigarette brands	139	7.2	1.6	13.1	0.012	0.10

4 *Total Nicotine Equivalents (TNE2) is equal to the molar sum of urine values of cotinine and trans 3' hydroxycotinine (3HC)

5 Note: 178 participants did not name the brand of their most recent e-cigarette product, so JUUL + Other e-cigarettes does not total to
6 All e-cigarette vapers.

7 Coefficients represent the percentage increase in TNE2 per 1 unit increase in e-cigarette dependence scores and are estimated from a
8 weighted linear model.

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