## Title

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## Publication Date

2022-05-01

## DOI

10.1016/j.addbeh.2022.107235

Peer reviewed

HHS Public Access

Author manuscript

*Addict Behav*. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

*Addict Behav*. 2022 May ; 128: 107235. doi:10.1016/j.addbeh.2022.107235.

# Biomarkers of Nicotine Exposure Correlate with the Hooked on Nicotine Checklist among Adolescents in California, United States

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## Abstract

**Background:** The Hooked on Nicotine Checklist (HONC) has been used to assess nicotine dependence (loss of autonomy over tobacco) among adolescents. Existing HONC validation studies for non-cigarette products, such as electronic cigarettes (e-cigarettes), have generally not considered biomarkers of nicotine exposure.

**Methods:** Within a cross-sectional sample of California (USA) high school students (total N=1396; mean age 15.2 years; 56% female; 54% Hispanic/Latinx), self-reported past 30-day users of any tobacco (including e-cigarettes) completed a modified 10-item HONC questionnaire and provided saliva samples (N=318 samples, including N=234 exclusive past 30-day e-cigarette users). Samples were analyzed for cotinine using liquid chromatography-tandem mass spectrometry (lower limit of quantification: 1.0 ng/mL).

**Results:** Across four categories of HONC score corresponding to an increasing number of reported dependence symptoms (scores: 0, 1, 2–4, 5–10), the prevalence of quantifiable salivary cotinine increased among past 30-day tobacco users (20%, 21%, 38%, 55%, respectively, *P*-for-trend<0.001) and among past 30-day exclusive e-cigarette users (15%, 22%, 31%, 42%, respectively, *P*-for-trend=0.001). Among participants with quantifiable cotinine levels, HONC total score and cotinine were positively correlated among past 30-day tobacco users (n=89; Spearman rho=0.449; *P*<0.001) and past 30-day exclusive e-cigarette users (n=49; Spearman rho=0.520; *P*<0.001). HONC score was also associated with past 30-day frequency of tobacco product use and reported use of tobacco within 30 minutes of waking.

**Conclusions:** These results support the validity of HONC to assess nicotine dependence among adolescents. Dependence symptoms may be experienced at low levels of nicotine exposure.

### Keywords

adolescents; nicotine dependence; biomarkers; measure validation

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## 1. Introduction

Among adolescents, nicotine dependence is associated with less successful smoking cessation (Horn, Fernandes, Dino, Massey, & Kalsekar, 2003) and with future sustained tobacco smoking, including among experimental or infrequent users (Dierker, Hedeker, Rose, Selya, & Mermelstein, 2015; Dierker & Mermelstein, 2010). The Hooked on Nicotine Checklist (HONC) was developed as a measure of nicotine dependence among adolescents with the theoretical grounding that dependence may manifest as loss of autonomy over tobacco use behavior (DiFranza et al., 2000; O'Loughlin, Tarasuk, Difranza, & Paradis, 2002). Previous research underpinning HONC validity showed that adolescents' loss of autonomy over tobacco may occur at low levels of cigarette smoking (MacPherson, Strong, & Myers, 2008; Ursprung & DiFranza, 2010) or at low levels of systemic nicotine exposure (DiFranza et al., 2007), including within days or weeks of inhaling their first cigarette (DiFranza et al., 2007). Detecting early symptoms of nicotine dependence is important because it may help identify individuals on trajectories toward heavier tobacco use (Lessov-Schlaggar et al., 2008).

Unlike previously developed nicotine dependence measures, for example, the Fagerström Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), which is comprised of measures more directly tied to cigarette consumption to assess physical dependence on tobacco, HONC assesses symptoms, such as cravings, irritability, and feeling like it's hard to quit. The focus on symptoms rather than product consumption provides at least two potential advantages. Symptoms may be more relevant than total consumption among adolescent tobacco users, who as a group, consume tobacco less frequently than adult tobacco users (DiFranza et al., 2000; McNeill, West, Jarvis, Jackson, & Bryant, 1986). Additionally, symptom-based questions allow flexibility in applying HONC to non-cigarette products, as has been done for adolescent users of tobacco waterpipe (Bahelah et al., 2016) and smokeless tobacco (DiFranza, Sweet, Savageau, & Ursprung, 2012).

Electronic cigarettes (e-cigarettes) are increasingly the primary product through which adolescents are exposed to nicotine (Wang et al., 2019), and multiple instruments to measure dependence among e-cigarette users, including adults, have been developed (Foulds et al., 2015; M. Morean, Krishnan-Sarin, & O' Malley, 2018; M. E. Morean, Krishnan-Sarin, & O' Malley, 2018; Rest, Mermelstein, & Hedeker, 2021; Vogel, Prochaska, & Rubinstein, 2020). Indeed, HONC has been adapted for adolescent e-cigarette users (Case et al., 2018; McKelvey, Baiocchi, & Halpern-Felsher, 2018; Tackett et al., 2021), and may predict persistent e-cigarette use over time (Vogel, Cho, McConnell, Barrington-Trimis, & Leventhal, 2020). While HONC total score has been positively correlated with salivary cotinine in adolescent cigarette smokers (Carpenter, Baker, Gray, & Upadhyaya, 2010; Huang, Cheng, Lin, & Lu, 2009), further studies are warranted that apply objective biomarkers of nicotine exposure to validate HONC among adolescent e-cigarette users.

### 1.1. Objectives

This study examines the relationship between biomarkers of nicotine exposure and HONC scores to assess further the validity of the HONC instrument, particularly among young e-cigarette users. Data are drawn from a sample of adolescent exclusive e-cigarette users and

other tobacco users in Northern California, United States. Specifically, across HONC score categories corresponding to increasingly more endorsed symptoms of loss of autonomy over tobacco, we examined the number of days of e-cigarette and other tobacco product use in the past 30 days, use of products within 30 minutes of waking, and levels of salivary nicotine metabolites (cotinine and 3-hydroxycotinine). A valid HONC instrument should yield a gradient of greater self-reported use and objectively measured nicotine exposure as HONC score increases.

## 2. Material and Methods

### 2.1. Participants

This cross-sectional assessment includes the baseline wave of an ongoing cohort of students (N=1423) attending 8 public high schools in Northern California, United States, as described elsewhere (Chaffee et al., 2020; Chaffee, Cheng, Couch, Hoeft, & Halpern-Felsher, 2021). Briefly, schools were located in municipalities with fewer than 50,000 residents and counties below 1000 persons/square-mile, reflecting a study focus on smaller communities where youth tobacco use has been high historically. All students in grades 9 or 10 at enrolled schools were eligible. School enrollment took place from March 2019 to February 2020. Baseline surveys were completed on tablet computers and same-day saliva samples were collected (see below). An Institutional Review Board at the University of California San Francisco approved all study procedures. Written informed parental consent and student assent were required. Participating students received a $10 gift card to an online retailer and participating schools received $300.

### 2.2 Survey Instruments

Tobacco use: Participants were asked whether they had ever used (yes/no) and number of days used (0–30) in the past 30 days separately for cigarettes, cigars, e-cigarettes, hookah, and smokeless (oral) tobacco via survey items with product images, brand names, and descriptions, including separate items for product sub-types (e.g., pod or mod e-cigarettes). Participants who reported use ≥1 day in the past 30 days for any of the above products (past 30-day tobacco users) were asked, “On the days you use the product(s) below, how soon after you wake up do you usually use them for the first time?” (options: within 5 minutes, 6–30 minutes, 31–60 minutes, more than 60 minutes) (Heatherton et al., 1991), later collapsed to within 30 minutes vs. later.

Hooked on Nicotine Checklist: All past 30-day tobacco users were presented a modified HONC instrument (Appendix Table A.1). Modifications consisted of expanding item prompts to include additional products; for example, asking “Have you ever had strong cravings to smoke, dip, vape, or use tobacco?” rather than “Did you ever have strong cravings to smoke?” (O’Loughlin et al., 2002). HONC prompt expansion has been performed previously to apply the instrument to other products (Bahelah et al., 2016; DiFranza et al., 2012; McKelvey et al., 2018; Vogel, Cho, et al., 2020). HONC total score was calculated as the number of items endorsed (out of 10). Thus, a higher score indicates greater loss of autonomy over tobacco.

### 2.3. Biomarkers

At the time of survey administration, participants rinsed their mouths with water, had the option to chew a small piece of wax to stimulate saliva, and provided approximately 3 mL of saliva into a barcode-labeled plastic screw-top vial. Samples were placed on ice and transported to the analysis facility within 48 hours. Saliva samples were analyzed for cotinine and 3-hydroxycotinine using liquid chromatography - tandem mass spectrometry (LC-MS/MS) (Jacob et al., 2011). Cotinine and 3-hydroxycotine are the most abundant metabolites of nicotine (N. Benowitz, Hukkanen, & Jacob, 2009); together, these metabolites provide a more complete assessment of total nicotine exposure than either alone (N. L. Benowitz, St Helen, Nardone, Cox, & Jacob, 2020). The lower limit of quantification was 1.0 ng/mL for each metabolite.

### 2.4. Statistical Analyses

Descriptive statistics (means, percentages) were reported for participant demographic characteristics. Given highly prevalent e-cigarette use among past 30-day tobacco users, a category of exclusive e-cigarette users was created, consisting of participants who reported using e-cigarettes ≥1 day in the past 30 days but used no other tobacco product in the past 30 days. Among past 30-day users, HONC psychometric properties were assessed.

Behavioral and biological measures of nicotine exposure consisted of the number of days of tobacco product use in the past 30 days, tobacco product use within 30 minutes of waking, the prevalence of nicotine metabolites in saliva (defined as the percentage of sample with cotinine and/or 3-hydroxycotinine levels at or above the quantification limit), and actual nicotine metabolite levels (among samples at or above the quantification limit and among all samples, assuming levels below quantification to be zero). The relatively low threshold defining the presence of nicotine metabolites (≥1 ng/mL) was chosen to allow potential identification of nicotine exposure among non-daily users. However, this threshold may be surpassed with passive (secondhand) tobacco smoke exposure; therefore, as a sensitivity check, the analysis of nicotine metabolite prevalence was repeated using recently defined thresholds to identify active cigarette smoking among adolescents (N. L. Benowitz, Bernert, et al., 2020). To our knowledge, no such thresholds have been proposed for adolescent e-cigarette use.

The eleven values of HONC score (0–10) resulted in some sparse cell sizes potentially susceptible to the influence of outlier values; thus, four ordered categories of HONC score were created, from lowest to highest level of dependence. The lowest category consisted of HONC score 0, under the precedent of separating score 0 from scores ≥1 to separate no loss of autonomy over tobacco from possible nicotine dependence (DiFranza et al., 2012; McKelvey et al., 2018; Vogel, Cho, et al., 2020). In this sample, score 1 included a sufficient number of participants to create a standalone category, and the remaining participants were divided into approximately equal-sized categories consisting of scores 2–4 and 5–10. In sensitivity checks (not shown), conclusions were robust to varying the category cut-points.

Linear trends in outcome variables over HONC score categories were tested by fitting bivariable regression models (test that coefficients do not equal zero). Spearman correlation

was examined between HONC total score and actual nicotine metabolite levels, including an exploratory analysis stratified by gender. P-values <0.05 were considered statistically significant.

## 3. Results

### 3.1. Participant Characteristics

The mean age of the study sample was 15 years (Table 1). Slightly more than half the sample identified as female (56%) and as Hispanic/Latinx (54%). Overall, 23% of the sample reported using at least one tobacco product in the past 30 days; 17% of the sample used e-cigarettes exclusively in the past 30 days; and 4% of the sample used more than one tobacco product. There was no statistically significant difference between past 30-day tobacco users and non-users in gender ($P$=0.58) or race/ethnicity ($P$=0.64), but the mean age of past 30-day tobacco users was slightly older ($P$=0.03). Among all past 30-day tobacco users, 92% used e-cigarettes in the past 30-days; all other products (cigars, cigarettes, smokeless tobacco, or hookah) were uncommonly used (Table 1). Most (74%) past 30-day tobacco users were exclusive e-cigarette users.

### 3.2. Nicotine Dependence Symptoms

Forty percent of past 30-day tobacco users endorsed ≥1 HONC item, contributing to a mean score of 1.5 and range of 0–10 (Appendix Table A.1). The most commonly endorsed item related to feeling strong cravings, and the least endorsed item related to using because quitting is hard (Appendix Table A.1). The HONC instrument had good internal consistency both among all tobacco users (Cronbach alpha=0.89) and exclusive e-cigarette users (Cronbach alpha=0.86).

### 3.2. Hooked on Nicotine Checklist Validation

**3.2.1 Monthly Use Frequency—**Participants reported using e-cigarettes a greater number of days in the past 30 days in each successively higher category of HONC score (Table 2). This statistically significant linear trend was observed both among all past 30-day e-cigarette users and exclusive e-cigarette users. In contrast, there was not a statistically significant linear trend for other tobacco products; however, the number of users of other products was small (Table 2). Among exclusive e-cigarette users, mean HONC score was higher in successive categories of more frequent past 30-day use (used 1 day: 0.3; 2–5 days: 0.9; 6–19 days: 1.6; ≥20 days: 2.5, $P$-for-linear trend<0.001).

**3.2.2 Use Soon After Waking—**Participants were more likely to report using e-cigarettes and using any tobacco product (including e-cigarettes) within 30 minutes of waking in each successively higher category of HONC score (Table 3). There was a statistically significant linear trend between using e-cigarettes soon after waking and HONC score category among all past 30-day e-cigarette users and exclusive e-cigarette users. As with use frequency, there was not a statistically significant linear trend for other tobacco products among the smaller numbers of participants who used those products (Table 3).

**3.2.3 Nicotine Metabolites—**The prevalence of quantifiable nicotine metabolites in saliva was greater in each successively higher category of HONC score (Table 4). A statistically significant linear trend was observed for cotinine, 3-hydroxycotinine, and the presence of either, both among past 30-day users of any tobacco product and exclusive e-cigarette users. Among past 30-day tobacco users, only in the category of HONC score ≥5 did the prevalence of quantifiable nicotine metabolites exceed 50% (Table 4). Associations between HONC score and metabolite prevalence were similar, but at a lower overall prevalence, when using a higher threshold to define metabolite prevalence (Appendix Table A.2).

Overall, levels of nicotine metabolites in saliva were positively correlated with HONC total score (Table 5), both among all past 30-day tobacco users (samples above quantification limit, cotinine Spearman rho: 0.46; $P<0.001$) and exclusive e-cigarette users (samples above quantification limit, cotinine Spearman rho: 0.54; $P<0.001$). There were not meaningful differences in correlation coefficients between female and male participants (Table 5). Among participants with quantifiable levels of nicotine metabolites, those levels were generally greater in each successive category of rising HONC score (Figure 1), although median metabolite levels were similar in the two highest HONC score categories.

## 4. Discussion

### 4.1 Overall Summary

In this sample of adolescent past 30-day tobacco users, symptoms of nicotine dependence measured using the Hooked on Nicotine Checklist were positively correlated both with e-cigarette use behaviors and with biomarkers of nicotine exposure. These findings are consistent with previous studies showing HONC is associated with e-cigarette use behaviors (Case et al., 2018; McKelvey et al., 2018; Tackett et al., 2021) and add further evidence from nicotine biomarkers. This analysis did not find convincing associations between HONC score and behaviors related to use of cigars, cigarettes, hookah, or smokeless tobacco. However, those products were used uncommonly in this sample, most often in dual-use with other products, impeding a straightforward interpretation.

### 4.2 Interpretation in the Context of Prior Research

Results align with an emerging literature showing correlations between nicotine exposure and other measures of nicotine dependence among adolescent e-cigarette users. In a small pilot study of e-cigarette users ages 12–21 (Boykan, Goniewicz, & Messina, 2019), those who at least one of five potential dependence items, particularly vaping on waking, had higher urinary cotinine levels than those who endorsed none. In another study of N=173 adolescent past 30-day e-cigarette users, the three measures of e-cigarette dependence tested were all positively correlated with salivary cotinine (Vogel, Prochaska, et al., 2020). Correlation coefficients reported in that study (Vogel, Prochaska, et al., 2020) were similar in magnitude to those observed for HONC in the present investigation. Biochemical validation of HONC is important, as HONC has also been shown to predict high school students' sustained e-cigarette use over time (Vogel, Cho, et al., 2020). HONC also has

the advantageous flexibility of wording that allows its use with multiple nicotine products, which makes it appealing for investigations of dual or poly-tobacco users.

Dependence symptoms were observed in the present study even at relatively low levels of nicotine exposure, whether assessed by questionnaire or salivary nicotine metabolites. Non-daily use of tobacco is common among adolescents, who may face barriers to obtaining tobacco (e.g., age-restricted sales, limited spending power, school- or parent-imposed rules) or who may only use under certain social circumstances, such as with friends. Given the relatively short half-life of cotinine as a marker of nicotine exposure, it is plausible that many non-daily tobacco users in this investigation cleared nicotine metabolites to non-quantifiable levels before providing a saliva sample. This result aligns with early HONC testing for cigarettes, which suggested that maintaining a consistently high level of systemic nicotine was not essential for developing dependence among youth (DiFranza et al., 2000; DiFranza et al., 2002). In an item-response theory analysis, HONC was found to capture more variability among young cigarette smokers experiencing lower levels of dependence, which may make HONC better suited than other measures to capture early dependence among adolescents (MacPherson et al., 2008).

### 4.3 Strengths and Limitations

A limitation of the present study is that potential nicotine exposure from household tobacco use by a parent or other family member was not taken into account in analysis. Salivary cotinine levels observed in this sample were often below thresholds used to differentiate active from passive smoking among adults, not unlike has been observed in other studies of infrequent adolescent smokers (DiFranza et al., 2007). Setting too high a bar to define “active” use in this sample would risk concealing actual exposure among legitimate intermittent users. Additionally, no consensus threshold is available for adolescent non-cigarette product users. Among other limitations, the cross-sectional nature of the study precluded any longitudinal assessment of the onset of dependence symptoms, particularly following tobacco product initiation. Also, the results from this sample of California adolescents may not necessarily generalize to other settings. Among study strengths, the sample size was larger than existing clinical or laboratory-based biomarker studies of adolescent e-cigarette users. Furthermore, assessing both behavioral and biological outcomes provided a novel validation data for applying HONC to e-cigarette use.

### 4.4 Conclusion

This investigation identified symptoms of loss of autonomy over tobacco among adolescent e-cigarette users, including at relatively low levels of nicotine exposure, suggesting risk for continuing and possibly accelerating product use in this age group. Biomarker findings support the validity of HONC to assess nicotine dependence among adolescents, particularly e-cigarette users, giving researchers and potentially tobacco regulators greater confidence in applying this flexible instrument to evaluate new and emerging tobacco and nicotine products.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments:

The authors thank Elizabeth Couch, Miranda Werts, and Janelle Urata of the University of California San Francisco and David Cash of Stanford University for support in data collection and study administration, Kristina Bello and Trisha Mao of the University of California San Francisco for analysis of biofluid samples, and Lisa Yu of the University of California San Francisco for supervising the analytical chemistry laboratory and preparation of reports. This research received support from US National Institutes of Health (grants U54HL147127, P30DA012393 and S10RR026437).

## Abbreviations:

| | |
|---|---|
| **HONC** | Hooked on Nicotine Checklist |
| **LC-MS/MS** | liquid chromatography - tandem mass spectrometry |

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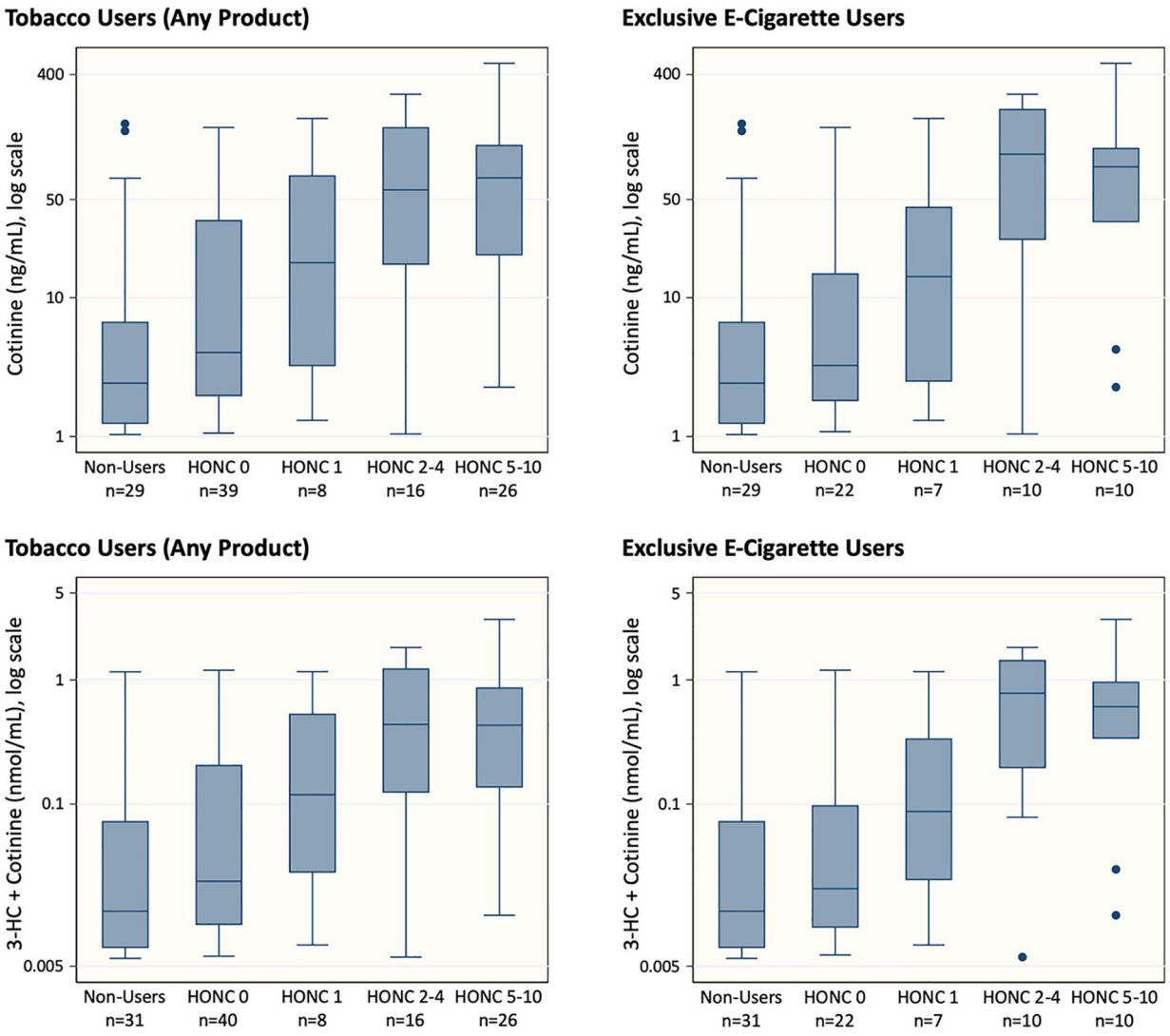


**Figure 1. Levels of Nicotine Metabolites in Saliva, by Hooked on Nicotine Checklist Score**

Box plots indicate levels of salivary nicotine metabolites among study participants with levels of cotinine or 3-hydroxycotinine above the limit of detection (1 ng/mL) according to Hooked on Nicotine Checklist score category (for past 30-day product users) and among past 30-day non-users. Tobacco users reported using ≥1 product (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) on ≥1 day in the past 30 days. Exclusive e-cigarette users reported using e-cigarettes ≥1 day in the past 30 days but used no other product in the past 30 days. Non-users reported no use of any tobacco products (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) in the past 30 days. Plotted boxes indicate the median and interquartile range; whiskers indicate the highest and lowest values not exceeding 1.5 the distance above and below the interquartile range, respectively. Abbreviations: 3-HC = 3-hydroxycotinine; HONC = Hooked on Nicotine Checklist

**Table 1.**

Characteristics of the Study Sample

| | Tobacco Users (Any Product)[1] n=318 | Exclusive E-Cigarette Users[2] n=234 | Past 30-Day Non-Users[3] n=1078 | Total Sample[4] n=1396 |
|---|---|---|---|---|
| Age in years, mean (SD) | 15.3 (0.7) | 15.3 (0.7) | 15.2 (0.8) | 15.2 (0.7) |
| Gender, % | | | | |
| Female | 57.2 | 61.5 | 56.1 | 56.4 |
| Male | 41.8 | 38.0 | 42.1 | 42.0 |
| Other, including missing | 0.9 | 0.4 | 1.8 | 1.6 |
| Race/Ethnicity, % | | | | |
| Hispanic/Latinx | 51.9 | 56.0 | 54.0 | 53.5 |
| Non-Hispanic White | 36.2 | 35.0 | 33.3 | 34.0 |
| Other, including missing | 11.9 | 9.0 | 12.7 | 12.5 |
| Ever (Any Lifetime) Use of: | | | | |
| Any Tobacco, % | 100 | 100 | 28.0 | 44.4 |
| E-cigarettes, % | 97.8 | 100 | 23.5 | 40.4 |
| Cigars, % | 26.1 | 15.4 | 3.2 | 8.5 |
| Cigarettes, % | 34.6 | 25.6 | 8.9 | 14.8 |
| Smokeless Tobacco, % | 19.5 | 11.1 | 4.2 | 7.7 |
| Hookah, % | 19.8 | 12.0 | 2.2 | 6.2 |
| Past 30-Day Use of: | | | | |
| Any Tobacco, % | 100 | 100 | 0 | 22.8 |
| E-cigarettes, % | 91.8 | 100 | 0 | 20.9 |
| Cigars, % | 11.0 | 0 | 0 | 2.5 |
| Cigarettes, % | 9.4 | 0 | 0 | 2.1 |
| Smokeless Tobacco, % | 9.1 | 0 | 0 | 2.1 |
| Hookah, % | 7.2 | 0 | 0 | 1.6 |

1. Reported using ≥1 product (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) on ≥1 day in the past 30 days; includes n=234 exclusive e-cigarette users

2. Reported using e-cigarettes ≥1 day in the past 30 days but used no other product in the past 30 days

3. Used no tobacco products (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) in the past 30 days; may have used ≥1 product prior to the past 30 days

4. Excluding individuals without a valid saliva sample (n=18) or past 30-day tobacco product users without a complete Hooked on Nicotine Checklist (n=9)

Abbreviation: SD = standard deviation

**Table 2.**

Days of Tobacco Product Use in the Past 30 Days, by Hooked on Nicotine Checklist Score

| | | | HONC Score Category | | | | |
|---|---|---|---|---|---|---|---|
| | | Total[1] N=318 | HONC 0 N=191 | HONC 1 N=38 | HONC 2–4 N=42 | HONC 5–10 N=47 | p-value[2] |
| Tobacco Users (Any Product) | | | | | | | |
| E-Cigarettes | n | 292 | 173 | 36 | 40 | 43 | <0.001 |
| | mean days[3] | 9.4 | 7.1 | 9.2 | 12.1 | 16.2 | |
| Cigars | n | 35 | 17 | 3 | 5 | 10 | 0.37 |
| | mean days[3] | 3.5 | 3.9 | 4.7 | 4.0 | 2.3 | |
| Cigarettes | n | 30 | 11 | 2 | 8 | 9 | 0.37 |
| | mean days[3] | 6.2 | 4.5 | 1.5 | 8.4 | 7.2 | |
| Smokeless Tobacco | n | 29 | 17 | 1 | 0 | 11 | 0.55 |
| | mean days[3] | 6.7 | 5.7 | 10 | --[4] | 8.0 | |
| Hookah | n | 23 | 11 | 3 | 4 | 5 | 0.54 |
| | mean days[3] | 4.0 | 4.0 | 7.3 | 3.3 | 2.4 | |
| Exclusive E-Cigarette Users | | | | | | | |
| E-Cigarettes | n | 234 | 146 | 32 | 32 | 24 | <0.001 |
| | mean days[3] | 8.4 | 6.3 | 9.1 | 11.3 | 16.3 | |

1. A total of 318 participants completed the Hooked on Nicotine Checklist, all of whom reported using ≥1 product (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) on ≥1 day in the past 30 days. Days of product use are shown only for past 30-day users of each product; thus, product-specific sample sizes are less than the total.

2. Test for linear trend over the four HONC score categories

3. Number of days using this product in the past 30 days, among past 30-day users of this product

4. There were no past 30-day smokeless tobacco users in this HONC score category

Abbreviation: HONC = Hooked on Nicotine Checklist

**Table 3.**

Tobacco Product Use within 30 Minutes of Waking, by Hooked on Nicotine Checklist Score

| | | | HONC Score Category | | | | |
|---|---|---|---|---|---|---|---|
| | | Total[1] | HONC 0 | HONC 1 | HONC 2–4 | HONC 5–10 | p-value[2] |
| Tobacco Users (Any Product) | | | | | | | |
| Any Product[3] | n | 303 | 179 | 38 | 41 | 45 | <0.001 |
| | < 30 min, % | 27.4 | 21.2 | 23.7 | 34.1 | 48.9 | |
| E-Cigarettes | n | 280 | 163 | 36 | 39 | 42 | <0.001 |
| | < 30 min, % | 25.0 | 19.0 | 22.2 | 28.2 | 47.6 | |
| Cigars | n | 30 | 15 | 2 | 4 | 9 | 0.73 |
| | < 30 min, % | 26.7 | 26.7 | 0 | 25.0 | 33.3 | |
| Cigarettes | n | 26 | 10 | 2 | 7 | 7 | 0.47 |
| | < 30 min, % | 34.6 | 30.0 | 0 | 42.9 | 42.9 | |
| Smokeless Tobacco | n | 27 | 16 | 1 | 0 | 10 | 0.33 |
| | < 30 min, % | 37.0 | 31.3 | 0 | --[4] | 50.0 | |
| Hookah | n | 19 | 9 | 3 | 3 | 4 | 0.06 |
| | < 30 min, % | 42.1 | 22.2 | 33.3 | 66.7 | 75.0 | |
| Exclusive E-Cigarette Users | | | | | | | |
| E-Cigarettes | n | 226 | 138 | 32 | 32 | 24 | 0.001 |
| | < 30 min, % | 19.5 | 13.8 | 18.8 | 28.1 | 41.7 | |

1. A total of 303 participants completed the Hooked on Nicotine Checklist and responded to items about tobacco use within 30 minutes of waking, all of whom reported using ≥1 product (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) on ≥1 day in the past 30 days. Use within 30 minutes of waking shown only for past 30-day users of each specific product; thus, sample sizes for each specific product are less than the total.

2. Test for linear trend over the four HONC score categories

3. Refers to use of any product (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) within 30 minutes of waking, among those who used ≥1 of these products in the past 30 days

4. There were no past 30-day smokeless tobacco users in this HONC score category

**Table 4.**

Prevalence of Nicotine Metabolites in Saliva, by Hooked on Nicotine Checklist Score

| | | HONC Score Category | | | | |
|---|---|---|---|---|---|---|
| | **Total**[1] | **HONC 0** | **HONC 1** | **HONC 2–4** | **HONC 5–10** | **p-value**[2] |
| Tobacco Users (Any Product) | | | | | | |
| n | 318 | 191 | 38 | 42 | 47 | |
| cotinine, % | 28.0 | 20.4 | 21.1 | 38.1 | 55.3 | <0.001 |
| 3-HC, % | 21.4 | 11.0 | 18.4 | 35.7 | 53.2 | <0.001 |
| cotinine and/or 3-HC, % | 28.3 | 20.9 | 21.1 | 38.1 | 55.3 | <0.001 |
| Exclusive E-Cigarette Users | | | | | | |
| n | 234 | 146 | 32 | 32 | 24 | |
| cotinine, % | 20.9 | 15.1 | 21.9 | 31.3 | 41.7 | 0.001 |
| 3-HC, % | 14.1 | 6.2 | 18.8 | 28.1 | 37.5 | <0.001 |
| cotinine and/or 3-HC, % | 20.9 | 15.1 | 21.9 | 31.3 | 41.7 | 0.001 |

[1] A total of 318 participants completed the Hooked on Nicotine Checklist and reported using ≥1 product (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) on ≥1 day in the past 30 days.

[2] Test for linear trend over the four HONC score categories

Additional notes: Prevalence of nicotine metabolites in saliva defined as the percentage of samples with cotinine and/or 3-hydroxycotinine above the limit of quantification (1 ng/mL).

Prevalence of nicotine metabolite in saliva among past 30-day tobacco non-users (N=1078): 2.7% for cotinine; 1.6% for 3-hydroxycotinine; 2.9% for either cotinine and/or 3-HC.

Abbreviation: 3-HC = 3-hydroxycotinine

**Table 5.**

Correlation Between Hooked on Nicotine Checklist Score and Levels of Nicotine Metabolites in Saliva

| | Spearman Correlation with HONC Score | | | | | |
|---|---|---|---|---|---|---|
| | All Samples[1] | | | Samples Above Limit of Quantification Only | | |
| | n | rho | p-value | n | rho | p-value |
| All Participants[2] | | | | | | |
| Tobacco Users (Any Product) | | | | | | |
| cotinine | 318 | 0.314 | <0.001 | 89 | 0.449 | <0.001 |
| 3-HC | 318 | 0.383 | <0.001 | 68 | 0.146 | 0.24 |
| molar sum 3-HC + cotinine | 318 | 0.310 | <0.001 | 90 | 0.459 | <0.001 |
| Exclusive E-Cigarette Users | | | | | | |
| cotinine | 234 | 0.256 | <0.001 | 49 | 0.520 | <0.001 |
| 3-HC | 234 | 0.344 | <0.001 | 33 | 0.478 | 0.005 |
| molar sum 3-HC + cotinine | 234 | 0.257 | <0.001 | 49 | 0.538 | <0.001 |
| Female Participants Only[3] | | | | | | |
| Tobacco Users (Any Product) | | | | | | |
| cotinine | 182 | 0.332 | <0.001 | 38 | 0.504 | 0.001 |
| 3-HC | 182 | 0.399 | <0.001 | 29 | 0.217 | 0.26 |
| molar sum 3-HC + cotinine | 182 | 0.322 | <0.001 | 39 | 0.540 | <0.001 |
| Exclusive E-Cigarette Users | | | | | | |
| cotinine | 144 | 0.311 | <0.001 | 25 | 0.593 | 0.002 |
| 3-HC | 144 | 0.404 | <0.001 | 17 | 0.471 | 0.06 |
| molar sum 3-HC + cotinine | 144 | 0.312 | <0.001 | 25 | 0.627 | <0.001 |
| Male Participants Only[3] | | | | | | |
| Tobacco Users (Any Product) | | | | | | |
| cotinine | 133 | 0.316 | <0.001 | 49 | 0.452 | 0.001 |
| 3-HC | 133 | 0.378 | <0.001 | 37 | 0.126 | 0.46 |
| molar sum 3-HC + cotinine | 133 | 0.318 | <0.001 | 49 | 0.460 | <0.001 |
| Exclusive E-Cigarette Users | | | | | | |
| cotinine | 89 | 0.221 | 0.03 | 24 | 0.497 | 0.01 |
| 3-HC | 89 | 0.302 | 0.004 | 16 | 0.569 | 0.02 |
| molar sum 3-HC + cotinine | 89 | 0.224 | 0.03 | 24 | 0.522 | 0.009 |

1. Samples below quantification limit (1 ng/mL) assigned a value of 0

2. A total of 318 participants (including those missing gender data) completed the Hooked on Nicotine Checklist and reported using ≥1 product (e-cigarettes, cigars, cigarettes, smokeless tobacco, or hookah) on ≥1 day in the past 30 days.

3. The number of female and male participants adds to less than the total due to missing responses for gender

Abbreviation: 3-HC = 3-hydroxycotinine