



## Brief Report

# Harm Reduction Associated with Dual Use of Cigarettes and e-Cigarettes in Black and Latino Smokers: Secondary Analyses from a Randomized Controlled e-Cigarette Switching Trial

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## Abstract

**Introduction:** Most adult cigarette smokers who use e-cigarettes are dual cigarette and e-cigarette (CC-EC) users, yet little is known about relative consumption of cigarettes to e-cigarettes and any associated harm reduction.

**Methods:** Rate of substitution from cigarettes to e-cigarettes at week 6 and change in biomarkers of exposure and potential harm were examined among dual dual cigarette and e-cigarette users [64/114 (56%); 35 Black, 29 Latino] in an e-cigarette switching randomized trial.

**Results:** Dual users averaged 79% substitution of cigarettes for e-cigarettes at week 6, resulting in a reduction from baseline of  $70.0 \pm 54.1$  cigarettes per week ( $p < .001$ ). Total nicotine consumption remained stable (baseline:  $1160.5 \pm 1042.1$  pg/mL of cotinine, week 6:  $1312.5 \pm 1725.9$  pg/mL of cotinine,  $p = .47$ ), while significant reductions were seen in the potent lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) ( $-55.9 \pm 88.6$  ng/ml,  $p < .001$ ), carbon monoxide ( $-6.3 \pm 8.6$  ppm,  $p < .001$ ), and self-reported respiratory symptoms ( $-3.3 \pm 8.0$ ,  $p = .002$ ). No significant changes were found in blood pressure or spirometry. Greater substitution from cigarettes to e-cigarettes was associated with larger reductions in NNAL ( $r = -.29$ ,  $p = .02$ ).

**Conclusions:** The predominant dual-use pattern was characterized by regular e-cigarette and intermittent cigarette use. Findings demonstrate the short-term harm reduction potential of this dual-use pattern in Black and Latino smokers and suggest that the greatest benefit, aside from cessation of both products, is achieved by higher substitution of e-cigarettes for cigarettes. Findings need confirmation in a larger sample with longer follow-up in dual users with greater variability in the rate of substitution.

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**Implications:** Findings suggest short-term harm reduction potential of dual cigarette-e-cigarette use for Black and Latino smokers. Results also demonstrate the heterogeneity of dual-use, with the greatest harm reduction seen in dual users with higher rates of substitution from cigarettes to e-cigarettes. Study results should be confirmed in a full clinical trial with long-term follow-up to evaluate maintenance of dual-use patterns and associated harm reduction potential over time.

One in six US adult cigarette smokers report trying electronic cigarettes (e-cigarettes), the majority of whom are dual users of combustible cigarettes and e-cigarettes (dual cigarette and e-cigarette [CC-EC]).<sup>1</sup> While evidence suggests that e-cigarettes may pose less risk than cigarettes and represent an effective harm reduction strategy among adult cigarette smokers who switch exclusively, the literature on dual CC-EC use is mixed,<sup>2</sup> with some studies finding that dual CC-EC use results in higher biomarkers of exposure and/or potential harm over cigarettes alone<sup>3</sup> while other studies have found evidence of harm reduction for dual CC-EC use.<sup>4,5</sup> To date, studies have treated dual CC-EC users as a homogeneous group. This is a notable gap given that different patterns of dual-use exist—e.g., primary EC with intermittent CC, primary CC with intermittent EC, similar use of both EC and CC – and the extent of harm reduction is likely associated with relative consumption of cigarettes to e-cigarettes.<sup>6</sup>

Non-Hispanic Blacks (Blacks) and Latinos are the two largest minority groups in the United States and are disproportionately burdened by tobacco-related disease and death.<sup>7,8</sup> These groups are less likely than non-Hispanic Whites to try e-cigarettes and, when they do, are more likely to become dual users.<sup>9</sup> Dual CC-EC use may be of particular concern for Black and Latino smokers given that the majority smoke  $\leq 10$  cigarettes per day (CPD).<sup>10,11</sup> Dual CC-EC use in lighter smokers may increase nicotine exposure and associated harm in terms of biomarkers over cigarettes alone but, to our knowledge, has not been examined.

This study examined changes in biomarkers of exposure (BOE; e.g., cotinine, carbon monoxide, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol [NNAL]) and potential harm (BOPH; e.g., respiratory symptoms, blood pressure) in Black and Latino smokers who were dual CC-EC users at the conclusion of a randomized e-cigarette switching trial. We focused on nicotine salt pod-based e-cigarettes because they are the leading class of e-cigarettes (>75% e-cigarette market share).<sup>12</sup> These devices contain higher nicotine concentrations than other e-cigarettes (5% nicotine by weight, equivalent to ~59 mg/ml nicotine per pod versus 0–36 mg/ml in other e-cigarettes) and when used in combination with cigarettes, may lead to increased consumption of nicotine especially in lighter smokers.<sup>13</sup> We hypothesized that nicotine exposure would remain the same and that the harm reduction potential of dual CC-EC use would be driven by the rate of substitution from cigarettes to e-cigarettes. Specifically, those with higher rates of substitution (i.e., a larger reduction in cigarettes) would experience the greatest reductions in BOE and BOPH.

## Methods

Study methods and procedures are described in detail elsewhere.<sup>13</sup> In brief, Latino ( $n = 94$ ) and Black ( $n = 92$ ) smokers who were interested in switching to e-cigarettes were randomized 2:1–6 weeks of JUUL e-cigarettes (5% nicotine) in their choice of mint, menthol, Virginia tobacco, or mango flavor pods or 6 weeks of

cigarettes as usual. JUUL pods were provided free of charge, and participants were instructed not to purchase additional pods. All used and unused pods were returned for weighing. Eligible participants were adult ( $\geq 21$  years) daily smokers who smoked 5 or more CPD for  $\geq 6$  months and were interested in switching to e-cigarettes. Participants were excluded if they were e-cigarette users ( $\geq 4$  of the previous 30 days), primary users of noncigarette tobacco products (e.g. cigarillos), or had medical contraindications to e-cigarette use (e.g., hospitalized for a heart-related event in the previous 30 days, pregnant). Recruitment occurred from May 2018 through March 2019, with follow-up completed by May 2019.

Those randomized to e-cigarettes received JUUL (5% nicotine) along with brief education, training, and action planning for making a complete switch to e-cigarettes. Allocation of pods was one pod per pack of cigarettes based on baseline cigarette consumption. Used, partial, and unused pods were returned at week 6 for weighing.

## Measures

Demographic and tobacco use history variables were assessed at baseline.

Individuals were categorized as dual CC-EC users at week 6 based on the 7-day Timeline Follow Back interview of the number of any cigarettes and any e-cigarettes used each day over the previous 7 days. Dual-use was defined as concurrent self-reported use of cigarettes and e-cigarettes in the previous 7 days. Those who reported exclusive e-cigarette use but who had an exhaled carbon monoxide (CO) of  $\geq 6$  ppm (determined *a priori*) were also classified as dual users.<sup>14</sup> Self-reported maintenance of cigarette and e-cigarette use patterns were examined at month 6.

E-cigarette consumption was derived by taking the weight of returned JUUL pods and converting grams of e-liquid into cigarette equivalents (one pod = .57 grams and is equivalent to 20 cigarettes). All (100%) pods were returned at week 6 for weighing. No additional pods were returned, suggesting that participants used only study provided pods throughout the duration of the study. The rate of substitution from cigarettes to e-cigarettes was calculated by dividing the total amount of e-cigarettes consumed in the past 7 days at week 6 by the sum of total cigarette and e-cigarette consumption (e-cig / cig + e-cig). Cigarette consumption was quantified as cigarettes per week based on the 7-day Timeline Follow Back interview.

Urine samples were collected at baseline and week 6 to test NNAL concentration, a potent lung carcinogen, and cotinine, the primary metabolite of nicotine, via ultra-performance liquid chromatography—tandem mass spectrometry and normalized for creatinine.<sup>15,16</sup> NNAL was selected above other biomarkers of carcinogen exposure because it is widely regarded as the primary causative agent in lung cancer and can be easily measured in urine.<sup>17,18</sup> Limits of quantification were 30 pg/mL and 1 ng/ml for NNAL and cotinine, respectively. CO levels were measured using a Micro+

coVita Smokerlyzer device. Pulmonary functioning was measured using a Discovery-2 SpiroVision spirometer to evaluate a series of spirometry values (i.e., FEF25-75). Systolic and diastolic blood pressure was measured using an Omron® BP742N 5 Series digital blood pressure cuff. Respiratory symptoms were measured using self-reported responses to the American Thoracic Society Questionnaire, calculated on a scale from 0 to 32 in which higher scores indicate more respiratory symptoms.<sup>19</sup>

### Statistical Analyses

Continuous variables were summarized with means and standard deviations. Categorical variables were summarized with frequency and percentages. Dual-use patterns were examined by assessing the rate of substitution from cigarettes to e-cigarettes at week 6. Change in BOE and BOPH from baseline to week 6 were compared using two-sided t-tests. Pearson correlation was used to examine the association between substitution from cigarettes to e-cigarettes and reduction in NNAL, CO, and respiratory symptoms at week 6.

### Results

Of the 125 participants who were randomized to e-cigarettes, 114 (91%) returned at week 6, and 64 of those who returned were dual CC-EC users (56%), representing the final analytic sample.

The 64 dual CC-EC users were predominantly Black (55%) and male (59.4%) with an average age of 43.9 (SD = 13.1) and household income of \$26,642 (SD = 24,883). Most had low educational attainment (89.1% less than college graduate). At baseline, the average CPD was 12.3 (SD = 8.0), 64.1% smoked menthol cigarettes and 70.3% smoked their first cigarette within 30 minutes of waking up.

The majority (84.5%) substituted  $\geq 50\%$  of their cigarettes for e-cigarettes at week 6 (Supplemental Figure 1). This translated into an average of 79% of cigarettes being substituted for e-cigarettes at week 6 and resulted in a reduction of  $70.0 \pm 54.1$  cigarettes per week ( $p < .001$ ) (Table 1). Total nicotine consumption remained unchanged (baseline:  $1160.5 \pm 1042.1$  pg/mL of cotinine, week 6:  $1312.5 \pm 1725.9$  pg/mL of cotinine,  $p = .47$ ), while significant reductions were seen in NNAL ( $-55.9 \pm 88.6$  ng/ml,  $p < .001$ ), CO ( $-6.3 \pm 8.6$  ppm,  $p < .001$ ), and respiratory symptoms ( $-3.3 \pm 8.0$ ,  $p = .002$ ) (Table 2). No changes were seen in blood pressure or spirometry. Greater substitution of cigarettes for e-cigarettes was correlated with significant reductions in NNAL ( $r = -.29$ ,  $p = .02$ ) and respiratory symptoms ( $r = -.33$ ,  $p = .008$ ), but not in cotinine ( $r = .16$ ,  $p = .21$ ) or CO ( $r = -.07$ ,  $p = .61$ ) (Supplemental Table 1). Per self-report among the 55 week 6 dual CC-EC users who completed the month 6 follow-up (telephone only, no biologicals), 35.9% remained dual CC-EC users, 28.1% transitioned to exclusive e-cigarette use, 12.5% reverted back to exclusive cigarette use, and 9.4% reported no use of cigarettes or e-cigarettes.

**Table 1.** Cigarette, E-cigarette, and Total Consumption<sup>a</sup> among Dual E-cigarette/Cigarette Users ( $n = 64$ )<sup>b</sup>

Categories	Baseline mean (SD)	Week 6 mean (SD)	$\Delta$ (Week 6–BL) Mean (SD)	<i>p</i> -value
Cigarettes, past 7 days	84.7 (56.3)	14.7 (23.2)	-70.0 (54.1)	< .001
E-cigarettes, past 7 days <sup>c</sup>		75.7 (62.1)		
Total consumption in cig equivalents (cig + e-cig)		90.5 (61.0)	5.8 (69.3)	.51
Rate of substitution from cig to e-cig <sup>d</sup>		79% (29%)		

<sup>a</sup> Calculated as the number of cigarettes reported in the previous week in the Timeline Follow-Back plus the cigarette equivalent in e-cigarette pods (one JUUL pod = 20 cigarettes, one pod = .57g) returned at the visit

<sup>b</sup> Of the 114 participants in the e-cigarette group that completed the week 6 visit (60 in KC, 54 in SD), 64 qualified as dual CC-EC users (35 in KC, 29 in SD) and were categorized separately from e-cigarette only and cigarette only participants at week 6

<sup>c</sup> Represented as cig equivalents. Participants returned JUUL pods at each follow-up visit. Returned pods were weighed and summed to derive the total grams of e-liquid consumed. From this, a calculation (one pod = .57 grams and is equivalent to 20 cigarettes) was applied to convert grams of e-liquid consumed into cigarette equivalents. 100% of pods distributed were returned

<sup>d</sup> Rate of substitution from cigarettes to e-cigarettes (i.e., conversion rate) represents the proportion of cigarettes that were replaced by e-cigarettes at Week 6, or in other words, the total proportion of total cigarette equivalents made up of e-cigarettes. For example, a conversion rate of 79% means that for dual users overall, 79% of their total consumption at Week 6 was derived from e-cigarettes

**Table 2.** Analyses of Biomarkers of Exposure and Potential Harm among Dual E-cigarette/Cigarette Users ( $n = 64$ )<sup>a</sup>

Categories	Baseline mean (SD)	Week 6 mean (SD)	$\Delta$ (Week 6–BL) Mean (SD)	<i>p</i> -value (two-sided <i>t</i> -test)
NNAL (ng/mL) <sup>b</sup>	130.4 (99.2)	74.6 (71.8)	-55.9 (88.6)	< .001
Cotinine (pg/mL) <sup>b</sup>	1160.5 (1042.1)	1312.5 (1725.9)	152.0 (1672.8)	.47
Carbon monoxide (CO, ppm)	16.8 (8.7)	10.6 (6.4)	-6.3 (8.6)	< .001
BP-systolic (mmHg)	129.9 (17.2)	130.4 (18.2)	0.5 (15.6)	.81
BP-diastolic (mmHg)	81.9 (9.8)	81.9 (10.6)	0.0 (9.3)	.99
FEF25-75 <sup>c</sup>	3.1 (1.5)	3.0 (1.6)	-0.1 (1.2)	.49
Respiratory symptoms <sup>a,d</sup>	12.7 (8.2)	9.4 (7.7)	-3.3 (8.0)	.002

<sup>a</sup> Of the 114 participants in the e-cigarette group that completed the week 6 visit (60 in KC, 54 in SD), 64 qualified as dual CC-EC users (35 in KC, 29 in SD) and were categorized separately from e-cigarette only and cigarette only participants at week 6.

<sup>b</sup> Normalized for creatinine.

<sup>c</sup> Defined as the average flow from the point at which 25% of the forced vital capacity (FVC) has been exhaled to the point at which 75% of the FVC has been exhaled.

<sup>d</sup> Respiratory symptoms were asked at the baseline, week 2 and week 6 visits using the American Thoracic Society Questionnaire. Participants responded to 8 statements with 0 (never), 1 (less than once per week), 2 (1–2 times per week), 3 (several times per week), or 4 (daily) for a total summed respiratory symptoms scale ranging from 0 to 32.

## Discussion

To our knowledge, this is the first study to characterize the harm reduction potential of dual CC-EC use in Black and Latino smokers switching to a nicotine salt-based pod system. Among this sample of dual users, we found high rates of substitution, resulting in significant reductions in cigarettes (~12 CPD at baseline to ~2 CPD at week 6) and maintenance of nicotine exposure. Most participants (68.8%) substituted 75% or more of their cigarettes for e-cigarettes at week 6. Conversely, a relatively small percentage (10.9%) substituted <25% of their cigarettes for e-cigarettes. For most dual users in our sample, their primary source of nicotine at week 6 was e-cigarettes, indicating a pattern of primary e-cigarette use with intermittent cigarettes.<sup>6</sup> Findings conflict with prior studies where dual-use has been predominately characterized by a primary cigarette with occasional e-cigarette use or primary use of both e-cigarettes and cigarettes.<sup>20</sup> Notably, prior studies have a longer follow-up, which influences the rate of substitution. Prior studies were conducted with older first-, second-, or third-generation e-cigarettes. The fourth-generation e-cigarette used in this study contain higher nicotine concentrations, closely mimic the nicotine delivery and “boost” of cigarettes, and are comprised of nicotine salts, which deliver highly nicotinized vapor with less inhalation irritation.<sup>21</sup> These factors more closely emulate the experience of smoking, are more satisfying to the user and may have contributed to higher rates of substitution in our sample and self-reported maintenance of these patterns over time, although this should be confirmed in future studies.

Dual users experienced significant reductions in carcinogen exposure, carbon monoxide, and respiratory symptoms. As hypothesized, the greatest reductions in carcinogen exposure and respiratory symptoms were seen in dual users with higher rates of substitution from cigarettes to e-cigarettes. The lack of association between the rate of substitution and carbon monoxide is likely due to the fact that CO measures cigarette consumption in the last ~8 hours. Associations between CO and cigarette consumption are strongest after a cigarette is consumed and diminish over time.<sup>22</sup> By week 6, individuals were smoking, on average, two cigarettes per week, which may partially explain the low and insignificant correlation between CO change and rate of substitution. Findings confirm prior studies that have shown reduced harm in dual CC-EC users<sup>4,5</sup> but should be confirmed in a larger study with longer follow-up. The small number of participants with low rates of substitution limited our ability to conduct subgroup analyses examining change in BOPH and BOE in dual users with greater variability in dual CC-EC use—e.g., primary cigarette with an intermittent e-cigarette, the primary use of both CC-EC. These patterns should also be examined in future studies.

Recruitment was conducted in a single Midwestern city for Black participants and a single West Coast city for Latino participants, limiting generalizability. The brief, 6-week time period limits any conclusions about maintenance of dual-use patterns over time and long-term effects of different patterns of use. Further, the 6-week time period was likely not long enough to capture change in spirometry and blood pressure. Finally, this is a post hoc secondary analysis from an e-cigarette switching randomized trial and was not powered to examine differences in dual-use type.

In conclusion, findings demonstrate the importance of recognizing dual CC-EC users as a heterogeneous group classified by different patterns of cigarette to e-cigarette use and highlight the harm reduction potential of dual CC-EC use in Black and Latino users with high rates of substitution. Findings should be confirmed in a fully powered trial with long-term follow up in order to characterize

sustained change and effects over time. Finally, in order to maximize the harm reduction potential, interventions to support dual CC-EC users in fully transitioning to e-cigarettes or off of both products are needed.

## Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

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## Declaration of Interests

Dr. Ahluwalia serves as a consultant to Lucy Goods, a manufacturer of nicotine gum.

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