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Pulmonary and Other Health Effects of Electronic Cigarette Use Among Adult Smokers Participating in a Randomized Controlled Smoking Reduction Trial

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Abstract

Background: There is limited evidence about the effects of dual electronic cigarette (e-cig) and combustible cigarette use on lung health or other health outcomes. Studies that have evaluated these outcomes have not included estimates of e-cig or cigarette exposure in the analyses.

Materials and Methods: Data analyzed were from 263 smokers participating in a randomized controlled trial designed to encourage participants to reduce their combustible cigarette use by substituting with an e-cig or a non-electronic cigarette substitute (cig-sub). T-tests were used to evaluate changes from baseline at 1 month and 3 months in lung function, blood pressure, pulse, exhaled carbon monoxide, and weight. Linear mixed effects models were used to test associations between health outcomes and study product group, including exposure to the study products (e-cig and cig-sub times used and days used in the past 7 days) and cigarettes per day (CPD).

Results: There were few significant differences between the groups for lung function indices at any time point in the unadjusted analyses. There were significant reductions in diastolic blood pressure and pulse at 1 month in the unadjusted analyses for those in the e-cig group compared to the cig-sub group. CPD decreased significantly more for the e-cig group than for the cig-sub group at both time points. There were no significant associations between any measured health outcomes and group in the linear mixed effects models.

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Conflict of Interest: JF has done paid consulting for pharmaceutical companies involved in producing smoking cessation medications, including GSK, Pfizer, Novartis, J&J, and Cypress Bioscience. TE is a paid consultant in litigation against the tobacco industry and is named on a patent application for a device that measures the puffing behavior of electronic cigarette users. There are no competing interests to declare for other authors.

Conclusion: E-cig use did not contribute to significant changes in health outcome markers as compared with use of a non-electronic cig-sub.

Keywords

Electronic cigarettes; Health Effects; Smoking Reduction; Lung Function

Introduction

In August of 2016, the U. S. Food and Drug Administration (FDA) finalized a deeming rule that brought electronic cigarettes (e-cigs) under its regulatory authority (Food and Drug Administration, 2016). E-cigs are a class of tobacco products that use a battery to heat and aerosolize liquid (often containing nicotine) that is inhaled by the user (Hajek, Etter, Benowitz, Eissenberg, & McRobbie, 2014). Though e-cig aerosol contains fewer toxicants than smoke from combustible tobacco cigarettes, there is much that remains unknown about these products (National Academies of Sciences, 2018). As the FDA begins to formulate a regulatory plan for e-cigs, the agency must evaluate evidence about the harms and benefits of e-cigs and their influence on public health.

Both the potential harms and benefits of e-cigs have been a topic of debate in the field of tobacco control for some time (Abrams, 2014; Bhatnagar et al., 2014; Foulds & Veldheer, 2011; Grana, Benowitz, & Glantz, 2014; Nutt et al., 2014; Zeller & Hatsukami, 2009). Of particular concern are the effects of e-cig use on lung function (e.g., forced expiratory volume in 1 second [FEV1]) and other health markers (e.g., blood pressure, pulse, exhaled carbon monoxide [CO], and weight). Data has begun to emerge demonstrating the short term impact of e-cig use using clinical measures (National Academies of Sciences, 2018). For instance, Flouris et al. (2013) found that there was no significant change in lung function indices after acute exposure to active e-cig use (e.g., a range between 3 and 14 puffs over 30 minutes) or passive e-cig exposure (1 hour) (Flouris et al., 2013). Similarly, longer studies of e-cig use have found either no change or some improvement in both lung function and other health outcomes (blood pressure) among those who use an e-cig to quit or reduce smoking (Cibella et al., 2016; Cravo et al., 2016; Farsalinos et al., 2016; Polosa, Morjaria, Caponnetto, Caruso, et al., 2014). Several studies have measured changes in exhaled CO among e-cig users and they have consistently demonstrated that e-cig use is associated with lower CO levels because of reduced cigarette smoke exposure (Cravo et al., 2016; McRobbie et al., 2015; Polosa, Morjaria, Caponnetto, Campagna, et al., 2014). Finally, at the cellular level, more recent evidence has demonstrated that there may be harms caused by e-cig use that are not measured by typical clinical indices (Chaumont et al., 2018; Ghosh et al., 2018; Reidel et al., 2018).

The interpretation of these studies in terms of harm is complicated by the fact that most previous analyses did not take into account estimates of e-cig aerosol or combustible cigarette exposure during the course of the studies. For instance, Cravo et al. (2016) reported on differences in lung function test parameters during a 12-week randomized controlled trial for smokers randomized to conventional cigarettes or an e-cig. Importantly, the analysis did

not take into account the number of cigarettes smoked, e-cig puffs, or any other measures of tobacco exposure needed to fully understand the influence of e-cig use on lung function.

Evaluating lung function and other health outcomes without including measures of the amount of exposure to cigarettes and e-cig use leaves investigators with inadequate evidence with which to settle the debate about the impact of e-cig use for harm reduction. The current study aims to provide data relevant to lung health (spirometry) effects and other health effects (blood pressure, CO, weight) of e-cig use in smokers who were attempting to reduce their combustible cigarettes consumption using an e-cig or a non-aerosol producing, non-nicotine containing cigarette substitute (cig-sub, QuitSmart). In particular, exposure levels to both combustible cigarettes and e-cig aerosol are included as a focal point of the analysis. Participants in this study are part of a larger trial designed to characterize the influence of e-cigs on toxicants, biomarkers, health indicators, and health risk (Lopez et al., 2016).

Materials and Methods

Main trial design.

Data for this study was taken from a larger two-site (Virginia Commonwealth University, Richmond, VA and Penn State College of Medicine, Hershey, PA), four arm, parallel-group randomized controlled trial designed to examine the influence of e-cig use on toxicant exposure, health indicators and combustible tobacco product use. Details of the trial can be found elsewhere (Lopez et al., 2016). Briefly, 520 adults aged 21–65 who smoked at least 10 cigarettes per day (CPD) and were interested in reducing their combustible cigarette consumption were enrolled in the 9 month trial. After an assessment visit (V1), participants returned approximately 1 week later and were randomized to one of four arms. Arm 1 was a cigsub and arms 2, 3, and 4 were one of three e-cig conditions (with 0, 8, or 36 mg/mL nicotine concentration). During the randomization phase of the study, participants were then encouraged to reduce their combustible cigarette smoking by 50% for 2 weeks, then by 75% for 2 weeks, and then to maintain 75% reduction and continue to try to reduce for the remainder of the trial.

Participant selection for this analysis.

Between October 2015 and May 2017, at the time of this report, 403 participants were randomized to one of the 4 arms of the study (e-cig nicotine concentration remains double-blinded) and were eligible to attend the 3-month follow up. Participants were included in this analysis only if they provided spirometry data at randomization (V2) and completed this measurement at the 1-month (V5) and 3-month follow-up visit (V7). Of those randomized, 140 did not provide spirometry data at all 3 time points and therefore 263 participants were included for analysis; 72 randomized to a cig-sub and 191 randomized to one of the three e-cig arms. A schema of the study visits, time between visits and measurements collected at each time point is presented in Figure 1. At each visit after randomization, participants received brief counseling including a discussion of their CPD reduction goals and they were encouraged to use their assigned study product as a substitute for combustible cigarettes.

Demographics, subjective and clinical measures.

Demographic information, including age, race, and gender, was self-reported and collected at V1. The Penn State Cigarette Dependence Index (PSCDI) was collected at each visit, and the timing and frequency of the clinical biomarkers is outlined in Figure 1. Blood pressure (BP) was collected using an electronic sphygmomanometer after participants were seated quietly for at least 5 minutes. Weight was collected on digital scales that were calibrated according to the manufacturer's specifications. Exhaled CO was collected using the Vitalograph BreathCO carbon monoxide monitor (Vitalograph, Inc., Lenexa, KS). Spirometry measurements were performed without a bronchodilator using the CareFusion SpiroUSB spirometer (Basingstoke, UK). Indices measured include forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio (FEV1/FVC%), forced expiratory flow 25–75% of FVC (FEF25–75), and forced expiratory time (FET).

Study products.

The study products used included an e-cig and a cig-sub. The e-cig consisted of a 3.3–4.1 volt, 1100 mAh rechargeable battery and a 1.5 Ohm, dual-coil, 510-style cartomizer (SmokTech, Shenzhen, China). The e-cig battery has a button that, when pressed by the user, activates the battery to heat the coil and produce an aerosol that is inhaled. In addition, each time the button is pressed for longer than 1 second, an automatic, digital puff counter on the battery records a puff. The puff counter can be reset by connecting the battery to the charging cord. The cig-sub (QuitSmart, Inc., NC) is a plastic tube that resembles a cigarette. It has an adjustable draw, but it does not have any electronic parts and it does not contain nicotine or emit any aerosol. Specific details of these products and the procedures for dispensing blinded, randomized nicotine concentration doses to participants, have been previously published.

Measures of cigarette and study product exposure.

At V2, participants were given paper logs to record their daily study product (cig sub and e-cig) and cigarette use for the duration of the randomized phase of the study. Data collected from the logs was used to create the following 3 exposure variables.

1. Cigarettes per day (CPD) – All participants were asked to log the total number of cigarettes smoked per day (CPD) in their diary and this was collected at each visit. CPD was calculated by averaging the total number of cigarettes smoked over the past 7 days. The change in CPD was calculated by subtracting the baseline CPD from the mean past 7 day CPD value at either the 1 month or 3 month time points.
2. Study product times used (e-cig or cig-sub times used) – All participants were asked to log their study product use in their log.
  - a. Those randomized to the cig-sub condition were asked to record each “time” they used their product and were instructed to consider a period of use, or one “use time”, as equivalent to about 15 puffs or 10 minutes. The number of times used was calculated by averaging the total number

of times used over the past 7 days prior to the study visit (cig-sub times used).

- b. Those randomized to an e-cig condition were asked to record the total number of puffs taken per day as measured on the automatic puff counter. The mean number of puffs per day was calculated by averaging the total puffs taken over the past 7 days (mean puffs/day). Because puffs per day is not equivalent measure to times used per day, we used data from the Penn State Electronic Cigarette Dependence Index (PSECDI) development report (Foulds et al., 2015) and assumed that 15 e-cig puffs was equal to one e-cig “time”. Thus, we created a times used variable for e-cig users by dividing the mean e-cig puffs by 15 (e-cig times used).
3. Study product days used (days used) – Using log data, we averaged the number of days that participants reported using their study product in the past 7 days (range 0–7).

Statistical methods.

Data were analyzed using R version 3.4.2 (<https://www.r-project.org/>). Because the three e-cig arms are still blinded, participants in each of the 4 trial arms were re-grouped into two conditions (cig-sub or an e-cig). Summary statistics were calculated for baseline demographic and cigarette characteristics. Chi-square tests and two-tailed t-tests were used to determine differences in changes from baseline for lung function and other health outcomes. The change from baseline to 1 month and to 3 months for each of the health indicators (CO, systolic BP, diastolic BP, pulse, weight) and spirometry indices (FEV1, FVC, FEV1/FVC%, FEF25–75, and FET) were modeled on randomization group (e-cig vs. cig-sub), change from baseline in CPD, days used the study product, e-cig or cig-sub use times, and demographics (age, race, gender, education level) using 10 linear mixed effects models (one for each health outcome of interest). To account for the varying effect of CPD and e-cig or cig-sub times used for each group at each visit, two three-way interaction terms were included in all models (change in CPD*randomization group*visit and times used*randomization group*visit). Model selection was done using backward elimination method. The final model was checked as adequate based on elaborate residual analyses. Adjusted means and p-values from these models were then calculated using a Wald test. Assuming unequal variance between the two groups, this study had 80% power to detect a 0.3 L difference in FEV1 and 64% power to detect a 0.25 L difference in FEV1 between the e-cig and cig-sub groups at Visit 7 based on a two-sided t-test. Two-tailed p-values of less than 0.05 were considered statistically significant. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data collection tools (Harris et al., 2009).

Results

An overview of baseline study participant demographics, cigarette characteristics, spirometry indices, and other health indicators by study product are presented in Table 1.

Overall, the sample was 60% female, 65% white, had a mean age of 47 years (SD: 11.3), and smoked a mean CPD of 18.4 (SD: 6.7). At the 3 month time point, the majority of the participants were dual users (69.2%, e-cig or cig-sub and combustible cigarettes) or smoking only combustible cigarettes (26.6%). Only a small proportion were exclusively using their study product (2.7%, n=6 e-cig and n=1 cig-sub) or had stopped using their study product and combustible cigarettes (1.1%, n=3). Those in the e-cig group logged an average of 80 and 66 ecig puffs per day at 1 month and 3 months, respectively. Between groups data for participants' product exposure including the mean number of days used the e-cig or cig-sub, mean number of cig-sub and e-cig times per day, and the mean CPD smoked are presented in Figure 2. Those in the e-cig group used their product significantly more times and decreased their CPD significantly more than those in the cig-sub group at both time points. Between groups, adjusted mean cigarette dependence, as measured by the PSCDI, decreased significantly more for the e-cig group than for the cig-sub group at 1 month (-3.1 e-cig v. -1.3 cig-sub, $p<0.001$) and at 3 months (-3.9 e-cig v. -1.9 cig-sub, $p<0.001$). Within the groups, CPD, CO, and PSCDI decreased significantly from baseline to both time points for participants in both groups (data not shown, all $p<0.007$).

Unadjusted changes in CO, spirometry indices, blood pressure and weight from baseline to the 1-month and 3-month follow-up are presented in Figure 3. There were no significant differences in these changes between the e-cig and cig-sub group at any time point with the exception of FET (at 3 months), diastolic BP (at 1 month), and pulse (at 1 month). For BP and pulse, both decreased significantly more in the e-cig group than in the cig-sub group at the 1-month follow-up ($p=0.02$ and $p=0.03$, respectively) and neither of these outcomes remained significantly different at the 3-month follow up.

In addition, in the linear mixed effects models, after adjusting for demographics and the three product exposure variables (e-cig or cig-sub times used, e-cig or cig-sub days used, and CPD), there were no significant associations between the group variable (e-cig or cig-sub) and any of the measured health outcomes. Furthermore, based on the results of the interaction terms between the visits and the randomization groups, there were no significant differences between the groups for changes in any of the outcomes at 1 month or 3 months; including pulse and BP pressure, and FET. In order to demonstrate how the quantity of exposure to either the cig-sub or the e-cig influenced health indicators, Table 2 presents results from the linear mixed effects models by group and at each time point (1 month and 3 months). There were no significant associations between e-cig times used and any of the measured health outcomes including CO. At 3 months, there was a significant decrease in FVC as cig-sub use increased. Furthermore, in the CO model, there was a significant positive association between CO and CPD meaning that as CPD decreased, CO also decreased. This relationship was significant for both the e-cig and cigsub groups at both time points (data not shown, $p<0.02$ for both products at both time points).

Discussion

This study examined the influence of e-cig use versus use of a non-electronic, non-aerosol-producing cigarette substitute product on pulmonary health and other health markers in smokers who were attempting to reduce their combustible cigarette consumption. Unique to

this study were measures of exposure to these products and cigarettes that have not been included in previous reports. Based on the outcomes measured, the data suggest that exposure to e-cigs while attempting to reduce cigarette consumption does not contribute to additional harms over 3 months. Though there were some potential benefits seen in the e-cig group due to decreases in pulse and diastolic BP (at 1 month) and an increase in FET (at 3 months), these differences between the groups did not remain significant after adjusting for demographic characteristics and exposure to cigarettes and e-cigs.

This study is in agreement with other studies that provided participants with e-cigs and found no clinically relevant changes in lung function after three months of e-cig use (Cibella et al., 2016; Cravo et al., 2016; Flouris et al., 2013). This is also the case for longer follow up periods. For instance, in a randomized controlled trial (RCT) design in which participants were assigned to 1 of 3 nicotine cartridge doses, Cibella et al. (2016) presented a stratified analysis at 24 weeks and 52 weeks for participants who reduced their combustible cigarette use by >50%, those who were biochemically verified as combustible cigarette quitters, and continuing smokers (e.g., those who continued to smoke at a similar rate as at baseline). In this analysis, there were no significant group differences in the percent predicted for FEV1, FVC, FEV1/FVC% between the groups at either 24 or 52 weeks.

Though the findings from this study are consistent with those that used similar clinical measures previously, missing from both the Cibella et al (2016) and the Cravo et al. (2016) studies is an adjustment for the amount of exposure participants had to e-cigs. As is common for RCT study designs, analyses are focused on understanding group level differences in outcomes, but when the question at hand is related to whether the amount of exposure may contribute to health outcomes, this method makes it difficult to disentangle the impact of e-cig aerosol exposure from changes in cigarette smoke exposure.

The present study was undertaken using the assumption that, if exposure were measured in a more detailed way, this greater detail may shed further light on the issue of whether e-cig exposure contributes to harm. In effect, there were no statistical differences in any of the pulmonary function outcomes measured at 1 month and only one difference at 3 months (FET) in the unadjusted results. Furthermore, there were no differences between the groups in the adjusted models. In the unadjusted results, there were some decreases in diastolic BP and pulse at 1 month among those using the e-cig compared to those in the cig-sub group. While it is possible that these measurements changed due to e-cig aerosol exposure, a more plausible mechanism for these improvements is a possible decrease in nicotine exposure among those in the e-cig group as opposed to the cig-sub group. Even though some of those in the e-cig group were using an e-cig with 8 mg or 36 mg nicotine concentration liquid, participants in this group decreased their CPD significantly more than those in the cig-sub group which may have contributed to an overall decrease in their nicotine exposure. In addition, the change in FET at 3 months may be related to a familiarity with spirometry testing rather than a clinically relevant improvement (Tsai, Christie, Gaughan, Palma, & Margolis, 2006).

The observation that there were not differences between the groups for the lung function indices in the adjusted models is potentially reassuring to those who may be concerned

about an acute response to either initiating e-cig use (Sommerfeld, Weiner, Nowalk, & Larkin, 2018) or dual e-cig/cigarette use. We did not find that dual use of cigarettes and e-cigs caused any measurable additional harm in the short-term regardless of the number of puffs participants took on their e-cig or on the number of cigarettes they smoked. In the absence of an acute response to e-cig initiation, lung function changes slowly which may make longer-term studies (>1 year) necessary (Kerstjens, Rijcken, Schouten, & Postma, 1997; Samet & Lange, 1996).

Importantly, on average, smokers in both groups reduced their CPD, CO, and cigarette dependence significantly from baseline, and those in the e-cig group decreased their CPD and combustible cigarette dependence significantly more than those in the cig-sub group. So, while concerns may remain about the long term effects of e-cig use in the context of continued dual use, in this short-term study, using e-cigs to reduce cigarette consumption led to decreased cigarette consumption with no additional signs of harms to health on the measures detailed here, as compared with use of a cig-sub that produces no aerosol.

We should note that our findings are in contrast to studies that have measured cellular changes in the lung and found that e-cigs induced harm in the pulmonary epithelia (Ghosh et al., 2018), defense proteins (Reidel et al., 2018), and that they caused tissue hypoxia (Chaumont et al., 2018). These differences could possibly be explained by limitations in the level of sensitivity that clinical measures such as spirometry and blood pressure may have. It is possible that e-cigs are causing harm at the cellular level before they can be detected by the clinical measures presented here, and this possibility should be considered in future studies. Further, changes in pulmonary function may be more meaningful among those with existing obstructive lung disease, however, participants with serious obstructive lung disease (e.g., on oxygen, or multiple exacerbations requiring hospitalization in the past year) were excluded from participation in this study.

In addition, other markers of toxicant exposure (e.g., cotinine, NNAL, 1-hydroxypyrene) would add further to the assessment of potential harm. This study is limited in that, since data collection is ongoing, the investigators remain blind to nicotine concentration condition. Results may be influenced when the blind is broken. Furthermore, the data presented here represent half of the overall target sample for the trial, and a larger sample would provide greater power with which to detect statistically significant differences between the groups. Finally, because this study is ongoing, the analysis was limited to a 3-month follow up period. Studies with longer follow-ups, in addition to those that include estimates of cumulative exposure to e-cig aerosol over time, will provide more insight into whether exposure to e-cig aerosol has positive or negative impacts on health outcomes. One could argue that this report should not have been pursued until all participants in this trial had completed all measures and the blind could be broken. However, given the intensity of the debate about the potential harms or benefits of ecigs, and the limited state of the existing literature on this topic, we believe that dissemination of the results of this analysis adds much needed data to the ongoing discussion.

Conclusion:

There was no evidence that e-cig use for 3 months while trying to reduce combustible cigarette use contributed to additional harms when compared to puffing on a cigarette substitute as indexed by measures of lung function, blood pressure, or weight. Conversely, CO, CPD, and cigarette dependence decreased significantly from baseline regardless of group. In addition, between the groups, CPD and cigarette dependence decreased significantly more in the e-cig group than in the cig-sub group.

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References

- Abrams DB (2014). Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? *JAMA*, 311(2), 135–136. doi:10.1001/jama.2013.285347 [PubMed: 24399548]
- Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, ... Outcomes, Research. (2014). Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*, 130(16), 1418–1436. doi:10.1161/CIR.000000000000107 [PubMed: 25156991]
- Chaumont M, Bernard A, Pochet S, Melot C, El Khattabi C, Reye F, ... van de Borne P (2018). High Wattage E-cigarettes Induce Tissue Hypoxia and Lower Airway Injury: A Randomized Trial. *American Journal of Respiratory and Critical Care Medicine*. doi:10.1164/rccm.201711-2198LE
- Cibella F, Campagna D, Caponnetto P, Amaradio MD, Caruso M, Russo C, ... Polosa R (2016). Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clinical Science (London, England: 1979)*, 130(21), 1929–1937. doi:10.1042/CS20160268
- Cravo AS, Bush J, Sharma G, Savioz R, Martin C, Craige S, & Walele T (2016). A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. *Regulatory Toxicology and Pharmacology*, 81 Suppl 1, S1–S14. doi:10.1016/j.yrtph.2016.10.003 [PubMed: 27769828]
- Farsalinos K, Cibella F, Caponnetto P, Campagna D, Morjaria JB, Battaglia E, ... Polosa R (2016). Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Internal and Emergency Medicine*, 11(1), 85–94. doi:10.1007/s11739-015-1361-y [PubMed: 26749533]
- Flouris AD, Chorti MS, Poulaniiti KP, Jamurtas AZ, Kostikas K, Tzatzarakis MN, ... Koutedakis Y (2013). Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhalation Toxicology*, 25(2), 91–101. doi:10.3109/08958378.2012.758197 [PubMed: 23363041]
- Deeming Tobacco Products To Be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act, 21 CFR 1100 C.F.R. (2016).
- Foulds J, & Veldheer S (2011). Commentary on Etter & Bullen (2011): could E-cigs become the ultimate nicotine maintenance device? *Addiction*, 106(11), 2029–2030. doi:10.1111/j.1360-0443.2011.03532.x [PubMed: 21978314]
- Foulds J, Veldheer S, Yingst J, Hrabovsky S, Wilson SJ, Nichols TT, & Eissenberg TT (2015). Development of a questionnaire to assess dependence on electronic cigarettes in a large sample of ex-smoking e-cig users. *Nicotine Tob Res*. doi:10.1093/ntr/ntu204

- Ghosh A, Coakley RC, Mascenik T, Rowell TR, Davis ES, Rogers K, ... Tarran R (2018). Chronic E-cigarette Exposure Alters the Human Bronchial Epithelial Proteome. *American Journal of Respiratory and Critical Care Medicine*. doi:10.1164/rccm.201710-2033OC
- Grana R, Benowitz N, & Glantz SA (2014). E-cigarettes: a scientific review. *Circulation*, 129(19), 1972–1986. doi:10.1161/CIRCULATIONAHA.114.007667 [PubMed: 24821826]
- Hajek P, Etter JF, Benowitz N, Eissenberg T, & McRobbie H (2014). Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction*, 109(11), 1801–1810. doi:10.1111/add.12659 [PubMed: 25078252]
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, & Conde JG (2009). Research electronic data capture (REDCap)--A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, 42(2), 377–381. doi:10.1016/j.jbi.2008.08.010 [PubMed: 18929686]
- Kerstjens HA, Rijcken B, Schouten JP, & Postma DS (1997). Decline of FEV1 by age and smoking status: facts, figures, and fallacies. *Thorax*, 52(9), 820–827. [PubMed: 9371217]
- Lopez AA, Cobb CO, Yingst JM, Veldheer S, Hrabovsky S, Yen MS, ... Eissenberg T (2016). A transdisciplinary model to inform randomized clinical trial methods for electronic cigarette evaluation. *BMC Public Health*, 16, 217. doi:10.1186/s12889-016-2792-8 [PubMed: 26941050]
- McRobbie H, Phillips A, Goniewicz ML, Smith KM, Knight-West O, Przulj D, & Hajek P (2015). Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein. *Cancer Prevention Research (Philadelphia, Pa.)*, 8(9), 873–878. doi:10.1158/1940-6207.CAPR-15-0058
- National Academies of Sciences, Engineering, and Medicine,.. (2018). Public health consequences of e-cigarettes. Washington, DC: The National Academies Press.
- Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, Foulds J, ... Sweanor D (2014). Estimating the harms of nicotine-containing products using the MCDA approach. *European Addiction Research*, 20(5), 218–225. doi:10.1159/000360220 [PubMed: 24714502]
- Polosa R, Morjaria JB, Caponnetto P, Campagna D, Russo C, Alamo A, ... Fisichella A (2014). Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Internal and Emergency Medicine*, 9(5), 537–546. doi:10.1007/s11739-013-0977-z [PubMed: 23873169]
- Polosa R, Morjaria J, Caponnetto P, Caruso M, Strano S, Battaglia E, & Russo C (2014). Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *International Journal of Environmental Research and Public Health*, 11(5), 4965–4977. doi:10.3390/ijerph110504965 [PubMed: 24814944]
- Reidel B, Radicioni G, Clapp PW, Ford AA, Abdelwahab S, Rebuli ME, ... Kesimer M (2018). E-Cigarette Use Causes a Unique Innate Immune Response in the Lung, Involving Increased Neutrophilic Activation and Altered Mucin Secretion. *American Journal of Respiratory and Critical Care Medicine*, 197(4), 492–501. doi:10.1164/rccm.201708-1590OC [PubMed: 29053025]
- Samet JM, & Lange P (1996). Longitudinal studies of active and passive smoking. *American Journal of Respiratory and Critical Care Medicine*, 154(6 Pt 2), S257–265. doi:10.1164/ajrccm/154.6_Pt_2.S257 [PubMed: 8970398]
- Sommerfeld CG, Weiner DJ, Nowalk A, & Larkin A (2018). Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome From E-Cigarette Use. *Pediatrics*, 141(6). doi:10.1542/peds.2016-3927
- Tsai AG, Christie JD, Gaughan CA, Palma WR, Jr., & Margolis ML (2006). Change in forced expiratory time and spirometric performance during a single pulmonary function testing session. *Respiratory Care*, 51(3), 246–251. [PubMed: 16533413]
- Zeller M, & Hatsukami D (2009). The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. *Tobacco Control*, 18(4), 324–332. doi:10.1136/tc.2008.027318 [PubMed: 19240228]

Highlights

- E-cigs can be used as an aid to reduce combustible cigarette consumption
- Some short term health benefits were observed for those in the e-cig group but did not remain after adjusting for other factors
- E-cig use along with combustible cigarette use does not contribute to additional harms in the short term

Figure 1:

Schema of study visits and measurements taken

*Abbreviations: CO=Exhaled carbon monoxide, PSCDI= Penn State Cigarette Dependence Index

Figure 2:

Mean days used e-cig or cig-sub (a), mean times used e-cig or cig-sub (b), and mean change from baseline in cigarettes per day (CPD) by group at the 1-month and 3-month follow-up (c) (* indicates significant difference between groups, $p<0.05$)

Figure 3†:

Unadjusted change from baseline in exhaled carbon monoxide, select spirometry indices, blood pressure, and weight by group at 1-month and 3-month follow up (* indicates significant difference between groups, p-values <0.05).

†In the linear mixed effects models, based on the results of the interaction terms for the randomization group and visit, after adjusting for demographics and change in CPD, e-cig or cig-sub times used, and days used the e-cig or cig-sub, there were no significant differences between the groups. Abbreviations: E-cig=Electronic cigarette, Cig-sub=Cigarette substitute, CO=Exhaled carbon monoxide, FEV1=Forced expiratory volume in 1 second; FVC=Forced

vital capacity, FEV1/FVC%=FEV1/FVCratio, FEF 25–75=Forced expiratory flow at 25–75% of FVC, FET=Forced expiratory time, BP=Blood pressure.

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Table 1:

Baseline characteristics of study sample by group (n=263)

Baseline characteristic	Cigarette substitute group (Cig-sub) (n=72)	Electronic cigarette group (E-cig) (n=191)	p-value
% (n) female	61.1 (44)	56.5 (108)	0.61
Mean Age in years (SD)	48.4 (11.0)	46.5 (11.4)	0.22
% (n) White	65.3 (47)	68.1 (130)	0.14
% (n) Black	26.4 (19)	29.8 (57)	
% (n) Other	8.3 (6)	2.1 (4)	
% (n) with more than a high school degree	59.7 (43)	63.9 (122)	0.99
% (n) who smoke menthol	63.9 (46)	62.8 (120)	0.99
Mean baseline cigarettes per day (SD)	19.1 (7.2)	18.1 (6.5)	0.30
Median baseline cigarettes per day (n)	18.0 (72)	17.0 (191)	0.37
Mean PSCDI (SD)	13.7 (3.6)	13.3 (3.4)	0.37
Mean CO in ppm (SD)	22.8 (11.6)	21.5 (10.7)	0.29
Median CO in ppm (n)	20.5 (72)	20.0 (191)	0.33
Mean FEV1 in liters (SD)	2.48 (0.7)	2.7 (0.9)	0.21
Mean FEV1% predicted (SD)	76.2 (17.25)	79.9 (19.05)	0.13
Mean FVC in liters (SD)	3.23 (.93)	3.42 (.99)	0.15
Mean FEV1/FVC% (SD)	77.2 (9.85)	77.9 (10.65)	0.72
Mean FEF25–75 in liters/second (SD)	2.3 (0.97)	2.56 (1.22)	0.33
Mean FET in seconds (SD)	5.09 (1.85)	4.59 (1.68)	0.05
Mean systolic BP in mmHg (SD)	125.5 (14.4)	125.3 (13.0)	0.13
Mean diastolic BP in mmHg (SD)	77.8 (10.7)	80.0 (9.4)	0.13
Mean pulse in beats/minute (SD)	79.6 (13.2)	82.1 (12.3)	0.16
Mean weight in pounds (SD)	192.8 (53.1)	187.5 (49.8)	0.46

Abbreviations: SD=Standard deviation, PSCDI=Penn State Cigarette Dependence Index, CO=Exhaled carbon monoxide, FEV1=Forced expiratory volume in 1 second, FVC=Forced vital capacity, FEV1/FVC%=FEV1/FVC ratio, FEF25–75= Forced expiratory flow at 25–75% of FVC, FET=Forced expiratory time, BP=Blood pressure.

Table 2:

Results from the linear mixed effects models by group demonstrating the association of e-cig or cig-sub times used on changes in health outcomes from baseline to 1 month and baseline to 3 months.

	1-month follow up		3-month follow up	
	E-cig* (n=191)	Cig-sub* (n=72)	E-cig (n=191)	Cig-sub (n=72)
Health outcome	β (p-value)	β (p-value)	β (p-value)	β (p-value)
CO	-0.0576 (0.64)	-0.171 (0.57)	-0.1078 (0.38)	-0.1332 (0.68)
FEV1	0.0048 (0.21)	0.0004 (0.96)	0.0009 (0.84)	-0.0151 (0.13)
FVC	0.0037 (0.31)	-0.0036 (0.71)	0.0028 (0.51)	-0.0262 (0.02)
FEV1/FVC%	0.0839 (0.15)	0.2457 (0.09)	0.0875 (0.31)	0.1358 (0.55)
FEF25–75	0.0006 (0.94)	-0.0028 (0.87)	0.0026 (0.72)	-0.0336 (0.08)
FET	-0.0057 (0.76)	-0.0394 (0.49)	0.0257 (0.17)	-0.0071 (0.91)
Systolic BP*	-0.1858 (0.23)	-0.6523 (0.11)	-0.1419 (0.40)	-0.4533 (0.31)
Diastolic BP	-0.0191 (0.82)	0.0291 (0.92)	-0.0149 (0.87)	0.3884 (0.27)
Pulse	-0.1252 (0.37)	0.6408 (0.11)	0.0639 (0.74)	-0.1351 (0.82)
Weight	-0.0152 (0.72)	0.0153 (0.87)	0.0632 (0.37)	0.1965 (0.36)

Covariates included in each of the 10 models: age, race, education level, gender, follow up visit (1 month or 3 months), group (e-cig or cig-sub), e-cig or cig-sub times used, days used the study product, and cigarettes per day.

Abbreviations: E-cig=Electronic cigarette, Cig-sub=Cigarette substitute, CO=Exhaled carbon monoxide, FEV1=Forced expiratory volume in 1 second; FVC=Forced vital capacity, FEV1/FVC%=FEV1/FVC ratio, FEF25–75=Forced expiratory flow at 25–75% of FVC, FET=Forced expiratory time, BP=Blood pressure.