RESEARCH ARTICLE

Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study

Julie B. Wang[1,2,3], Jeffrey E. Olgin[2], Gregory Nah[2], Eric Vittinghoff[4], Janine K. Cataldo[3], Mark J. Pletcher[4], Gregory M. Marcus[2]*

1 24K Data, Washington, DC, United States of America, 2 Division of Cardiology, School of Medicine, University of California, San Francisco, United States of America, 3 Physiological Nursing, School of Nursing, University of California, San Francisco, United States of America, 4 Department of Epidemiology and Biostatistics, University of California, San Francisco, United States of America

* greg.marcus@ucsf.edu

Abstract

E-cigarettes are promoted as healthier alternatives to conventional cigarettes. Many cigarette smokers use both products. It is unknown whether the additional use of e-cigarettes among cigarette smokers (dual users) is associated with reduced exposure to tobacco-related health risks. Cross-sectional analysis was performed using baseline data from the Health eHeart Study, among English-speaking adults, mostly from the United States. Cigarette use (# cigarettes/day) and/or e-cigarette use (# days, # cartridges, and # puffs) were compared between cigarette only users vs. dual users. Additionally, we examined cardiopulmonary symptoms/ conditions across product use: no product (neither), e-cigarettes only, cigarettes only, and dual use. Among 39,747 participants, 573 (1.4%) reported e-cigarette only use, 1,693 (4.3%) reported cigarette only use, and 514 (1.3%) dual use. Dual users, compared to cigarette only users, reported a greater median (IQR) number of cigarettes per day, 10.0 (4.0–20.0) vs. 9.0 (3.0–15.0) ($p < .0001$), a lower (worse) median (IQR) SF-12 general health score, 3.3 (2.8–3.8) vs. 3.5 (2.8–3.9) ($p = .0014$), and a higher (worse) median (IQR) breathing difficulty score in the past month, 2.0 (1.0–2.0) vs. 1.0 (1.0–2.0) ($p = .001$). Of the 19 cardiopulmonary symptoms/ conditions, having a history of arrhythmia was significantly different between cigarette only users (14.2%) and dual users (17.8%) ($p = .02$). In this sample, dual use was not associated with reduced exposure to either (i) cigarettes, compared to cigarette only users or (ii) e-cigarettes, compared to e-cigarette only users. E-cigarette only use, compared to no product use, was associated with lower general health scores, higher breathing difficulty scores (typically and past month), and greater proportions of those who responded 'yes' to having chest pain, palpitations, coronary heart disease, arrhythmia, COPD, and asthma. These data suggest the added use of e-cigarettes alone may have contributed to cardiopulmonary health risks particularly respiratory health risks.

Data Availability Statement: The data underlying this study were collected in the Health eHeart Study. All three Co-PI's of the Health eHeart Study contributed to the current manuscript and are listed as co-authors. Data access and ethical and legal restrictions about sharing the Health eHeart Study are under the purview of Health eHeart Study administrators (not the authors). The authors confirm that they did not have any special access privileges that others would not have. The first and senior authors conceived of the idea and sent a formal request, along with a detailed proposal of

Introduction

The harmful health effects of tobacco use are well-established, including an array of cardiovascular and pulmonary diseases and cancers [1]. Nearly 15% of the U.S. adult population smoke cigarettes [2]. Although most smokers want to quit, and repeatedly make quit attempts, they frequently relapse even with the assistance of evidence-based cessation therapeutics [3]. Since the emergence of e-cigarettes (and vapes), cigarette smokers have initiated e-cigarette use with the intention to reduce or quit smoking conventional cigarettes [4–11]. E-cigarette companies have promoted e-cigarettes as less harmful than cigarettes, and as a cessation aid, although without formal approval by the US Food and Drug Administration to make such therapeutic claims [12]. As of 2014, nearly 4% of adults reported e-cigarette use every day or on some days [13] and 59% of e-cigarette user also reported cigarette use [14]. It is unclear whether dual users are smoking fewer cigarettes, given the additional source of nicotine via e-cigarettes, compared to those who only smoke cigarettes. The present study examines exposure to tobacco- and e-cigarette-related toxicants and health risks by product use, particularly, whether the additional use of e-cigarettes among cigarette smokers, or dual use, was associated with benefits such as reduced risk exposure.

A major barrier to quitting smoking is the addictiveness of nicotine, which is compounded by cigarette engineering that maximizes the addictive potential of delivered nicotine [15–17]. A longitudinal study among the US population reported smokers who made a quit attempt were more likely to use e-cigarettes over current FDA-approved pharmacotherapies [18]. Smokers' preferences for e-cigarettes over approved cessation methods might be explained by the novelty of e-cigarettes, although it has also been shown that products such as nicotine patches, gum, and inhalers were less efficient than e-cigarettes in delivering nicotine [19]. Epidemiologic data indicate that approximately 22% of e-cigarette users were recent former cigarette smokers (< 1 year) and 16% were current cigarette smokers [13]. These data suggest that some smokers may have quit with the aid of e-cigarettes. A substantial subset of the population however are dual users, and, unless they quit smoking cigarettes, are exposed to harmful substances associated with cigarettes and potentially e-cigarettes.

Hypothetically, among dual users, the addition of nicotine from e-cigarettes should supplant nicotine levels otherwise met by smoking cigarettes and thereby reduce their cigarette intake. However, e-cigarettes deliver lower levels of plasma nicotine compared to conventional cigarettes [19–21], which could leave dual users unsatisfied and likely to titrate their nicotine intake to reach satiety. Therefore, it is unclear whether dual users are smoking fewer cigarettes per day and reducing their exposure to tobacco smoke and nicotine, or if they are smoking the same amount and merely introducing more toxicants and nicotine from the added use of e-cigarettes. Experimental studies have found a link between e-cigarette use and effects on pulmonary function, including irritation and restriction of airways, from the effects of propylene glycol, which is a main ingredient of e-liquids [22]. The synergistic effect of dual use is largely unknown with respect to nicotine dependence and both short-term and long-term health effects. Epidemiologic data on dual use and health is scarce and warrants further investigation.

The Health eHeart Study is an ongoing internet-based study aims to collect and analyze mobile and digital health data, with an enrollment goal of one million participants worldwide, to discover novel approaches to preventing and treating heart disease [23]. It includes assessment of cigarette and e-cigarette use *and* health symptoms and conditions. The primary purpose of the present study was to assess whether dual users smoke fewer/more cigarettes per day, and therefore might have lower/higher risk exposure from conventional cigarettes, compared to those who smoke only cigarettes. A secondary aim was to compare differences in the prevalence of pulmonary and cardiovascular health symptoms and conditions across product

use groups particularly between cigarette only users and dual users. These findings can inform whether dual users might be at greater exposure to toxicants and health risks, and therefore, might require more tailored guidance for quitting cigarettes and e-cigarettes.

Methods

Study design

We conducted cross-sectional analyses using data from the Health eHeart Study, which includes English-speaking adults aged 18 years and over. Health eHeart is an on-going longitudinal cardiovascular cohort study. For the present analysis, we analyzed available baseline data from March 8, 2013 (beginning of recruitment) to March 1, 2017. Participants are recruited worldwide via the lay press, promotional events, word-of-mouth, social media, e-mail, and clinic visits and invited to complete a set of web-based surveys at baseline and every 6 months for 2 years. Majority of participants were from the United States. Survey topics include basic and social demographics, family history, medical history, activity level and other lifestyle habits, including cigarette and e-cigarette use, and technology use. In the present study, we examined participants' product use: (i) no product use (neither), (ii) cigarettes only, (iii) e-cigarettes only, or (iv) both (dual use), including e-cigarette and cigarette dose. Additionally, we examined relationships between product use and health outcomes including cardiopulmonary symptoms and conditions. The Health eHeart Study was approved by the University of California, San Francisco Committee on Human Research. All participants provided informed consent through the internet.

Measures

Demographics, lifestyle, and well-being. Basic and social demographics included age, sex, race/ethnicity, education, income, familial relationships, and technology use. Lifestyle and well-being were measured using validated survey instruments, which included the 7-item International Physical Activity Questionnaire [24], 9-item Patient Health Questionnaire (mood) [25], and 7-item General Anxiety Disorder Scale [26].

Product categories: Neither, e-cigarettes, cigarettes, and dual use. Participants who responded (1) "yes" to "Have you ever smoked cigarettes regularly (at least 1 cigarette per day and a total of 100 cigarettes in your lifetime)?" and (2) "every day" or "some days" to "Do you smoke now?" were defined as (current) *cigarette users*. Number of cigarettes was assessed with the question "On average, how many cigarettes per day do you smoke?" Those who responded, "every day" or "some days" to "Do you now use e-cigarettes" were defined as (current) *e-cigarette users*. E-cigarette dose was asked in several ways: (1) "On how many of the past 30 days did you use an e-cigarette?"; (2) "On average, [on those days you used e-cigarettes], about how many cartridges or refills did you usually use each day?" Those who qualified as both a cigarette user and e-cigarette user were defined as *dual users*. No product use was categorized as *neither*.

Medical symptoms & conditions. Medical symptoms and conditions that might be associated with either cigarette or e-cigarette dual use were included for analysis. The SF-12 General Health Questionnaire was used to calculate an overall health score [27]. Two separate items assessed breathing difficulty: (1) "This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 (nothing at all) where your breathing is causing you no difficulty at all and progresses through to number 10 (maximal) where your breathing difficulty is maximal. How much difficulty does your breathing cause you *typically*?" and (2) "In thinking about your breathing, and any difficulties you may have with your breathing, what level of difficulty best describes your breathing normally over the *past month*?" Response

options were: (i) I only get breathless with strenuous exercise; (ii) I get short of breath when hurrying on level ground or walking up a slight hill; (iii) On level ground, I walk slower than people of the same age because of the breathlessness or have to stop for breath when walking at my own pace; (iv) I stop for breath after walking about 100 yards or after a few minutes on level ground; and (v) I am too breathless to leave the house or I am breathless when dressing.

Other medical symptoms and conditions included chest pain, "Have you had any pain, discomfort or pressure in your chest anytime over the past year." "Have you ever been told by a doctor or nurse that you have, or have been treated for, any of the following conditions (in the past or currently)?": palpitations, loss of consciousness or syncope, high blood pressure or hypertension, high cholesterol, diabetes, coronary artery disease/ angina, heart attack, blocked arteries (legs), blood clots (veins or lungs), congestive heart failure, stroke or TIA (transient ischemic attack), enlarged heart, atrial fibrillation, arrhythmia, sleep apnea, COPD, asthma, or cardiac arrest.

Statistical analysis. Descriptive analysis was performed for all variables. Means (SD) were calculated for parametric continuous variables and compared using *t* tests, linear regression, ANOVA, or ANCOVA; and percentages for categorical variables using Chi-square tests. The distributions of continuous variables that were not normally described are summarized as medians with interquartile ranges (IQR), and those described were compared using the Wilcoxon-Mann-Whitney test. Basic demographic variables and lifestyle and well-being factors were compared across e-cigarette, cigarette, and dual users. In separate models, we compared (i) number of cigarettes smoked per day between cigarette only users and dual users and (ii) e-cigarette dose variables between e-cigarette only users and dual users (i.e., number of days in the past 30 days, number of cartridges/refills per day, and number of puffs per day). Multivariate models adjusted for age, sex, race, education, physical activity, PQH score, and GAD score.

In the health symptoms/conditions analysis, we compared general health scores and two separate breathing difficulty scores (*typically* and *in the past month*), and frequency of "yes" responses to ever or currently having a symptom or condition, between cigarette only users and dual users. Additional analysis compared the same set of health symptoms/ conditions across mutually exclusive product groups: neither (reference), e-cigarettes only, cigarettes only, and both. Separate ANCOVA were fitted for general health, difficulty breathing (typically), difficulty breathing (past month), chest pain, palpitations, lost consciousness or syncope, high blood pressure, high cholesterol, diabetes, coronary artery disease, heart attack, blocked arteries in the legs, blood clots, congestive heart failure, stroke, enlarged heart, atrial fibrillation, arrhythmia, sleep apnea, COPD, asthma, and cardiac arrest. Multivariate models were adjusted for age, sex, race, education, cigarettes per day, coronary artery disease, congestive heart failure, and COPD. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary NC).

Results

Sample characteristics

In the ongoing Health eHeart Study, the 39,747 participants who had complete baseline data at the time of analysis were included in our study. In this sample, participants were mostly non-Hispanic White, female, and with particularly high levels of education. A total of 573 (1.4%) reported using e-cigarettes only, 1,693 (4.3%) cigarettes only, and 514 (1.3%) reported dual use (Table 1). Among e-cigarette only users, 118 (21%) reported that they had never smoked even one cigarette in their lifetime. E-cigarette only users were younger, more likely to be male, Asian, and have a high school level of education. Cigarette only users were more likely to be male, in the "other" race/ethnicity, and have less than a high school level of education. Dual

Table 1. Prevalence of e-cigarette only, cigarette only, and dual use in the past 30 days by demographic characteristics and lifestyle and well-being factors in the health eheart study, N = 39,747*.

	N	E-cigarette use only (N = 573) % or median (IQR)	Cigarette use only (N = 1,693) % or median (IQR)	Dual use (N = 514) % or median (IQR)	p-value
Overall	39,747	1.4	4.3	1.3	
Demographics					
Age, years	39,645	41.4 (18)	45 (21)	46 (18)	< .0001*
Sex					
Female	27,600	1.1	3.9	1.3	< .0001*
Male	12,047	2.3	5.0	1.4	
Race/ ethnicity					
Non-Hispanic White	32,302	1.4	3.9	1.3	.99
Hispanic	2,761	2.3	5.4	1.1	
Black/African-American	2,014	0.7	5.3	1.3	
Asian	1,723	3.8	4.7	3.5	
Other	445	2.7	12.8	2.3	
Education					
< High school	171	1.8	21.1	4.1	.0007*
High school graduate	2,166	2.9	7.9	3.1	
Some college	8,169	2.1	6.2	2.0	
College graduate	11,466	1.4	2.9	0.8	
≥ Post graduate	12,419	0.6	2.1	0.4	
Lifestyle and Well-being					
Physical activity (MET-min/week)	20,094	2,538.5 (2,973)	2,493.0 (3,661)	2,377.5 (3,222)	.0007*
Mood (PHQ-9 score, past 2 weeks)	39,543	6.0 (8.0)	7.0 (8.0)	8.0 (9.0)	< .0001*
Anxiety (GAD-7 score, past 2 weeks)	39,539	5.0 (8.0)	6.0 (9.0)	7.0 (9.0)	.0008*

* Available responses were included in the analysis; physical activity was collected in a subset of the Health eHeart Study population

https://doi.org/10.1371/journal.pone.0198681.t001

users were most likely to be Asian and have less than a high school level of education. Dual users reported the lowest physical activity levels, followed by cigarette only users, then e-cigarette only users. Dual users also exhibited higher depression and higher anxiety scores compared to cigarette only users.

E-cigarette and cigarette use

Among e-cigarette users, 53% reported using e-cigarettes only, and 47% were dual users. There were no significant differences in e-cigarette dose measures in those who reported e-cigarette only use and dual use for number of: (i) days of e-cigarette use in the past month, (ii) cartridges/refills per day, or (iii) puffs per day (Fig 1). For those who reported cigarette use, 77% reported using cigarettes only and 23% were dual users. Dual use was associated with a slightly higher median number of cigarettes smoked per day (10.0 cigarettes per day, IQR = 3.0–15.0) compared to those who reported smoking only cigarettes (9.0 cigarettes per day, IQR = 4.0–20.0), and this difference was statistically significant after adjusting for covariates ($p < .0001$) (Fig 2).

Medical symptoms and conditions

Compared to those who only smoked cigarettes, dual users exhibited worse median general health scores and breathing scores. Dual use, as compared to smoking cigarettes only, was
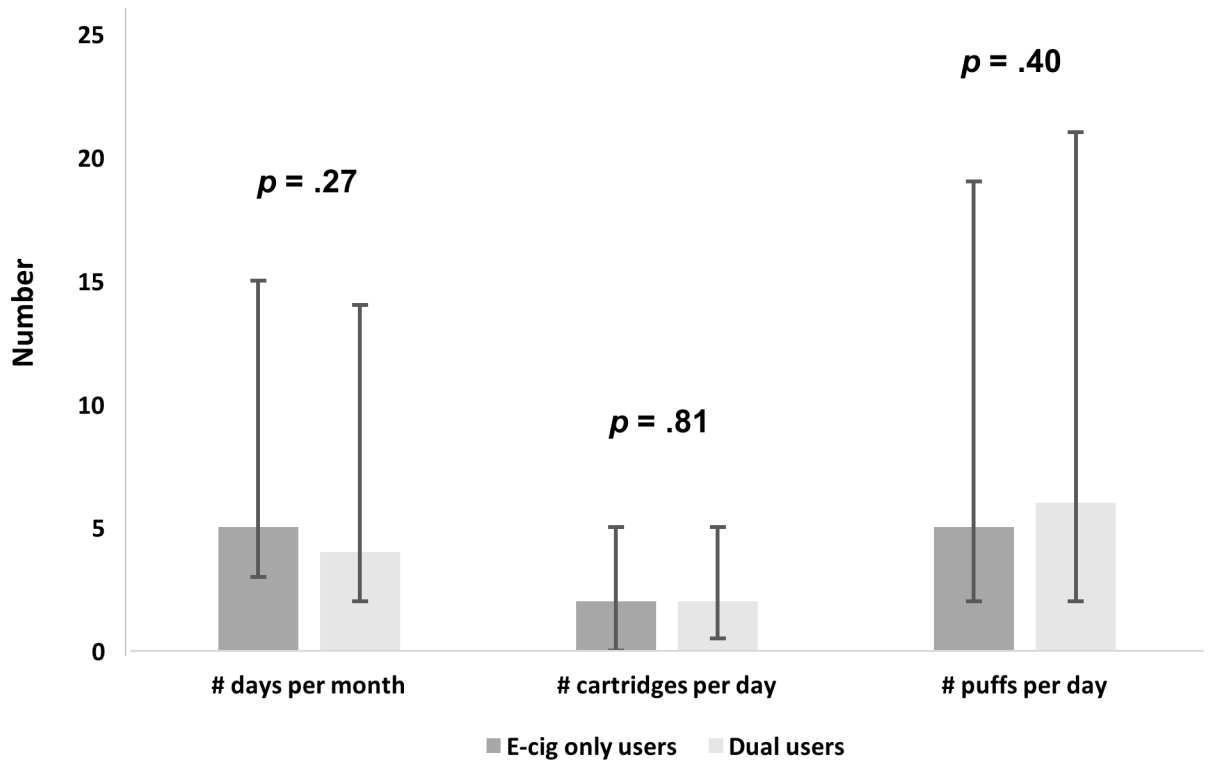
Fig 1. E-cigarette use dose measures among e-cigarette only users and dual users. (a) # days per month was defined as "number of days of e-cigarette use in the past 30 days" (b) # cartridges per day: "number of e-liquid cartridges/refills used per day" (c) # puffs per day: "number of puffs off an e-cigarette per day." Error bars denote the interquartile range.

Fig 2. Median number of cigarettes smoked per day among cigarette only users and dual users. Dual use was associated with a slightly higher median number of cigarettes smoked per day ($p < .0001$). Error bars denote the interquartile range.

Fig 3. Median SF-36 general health scores, breathing difficulty "typically" scores, and breathing difficulty in the "past month" scores, among cigarette only users and dual users. Du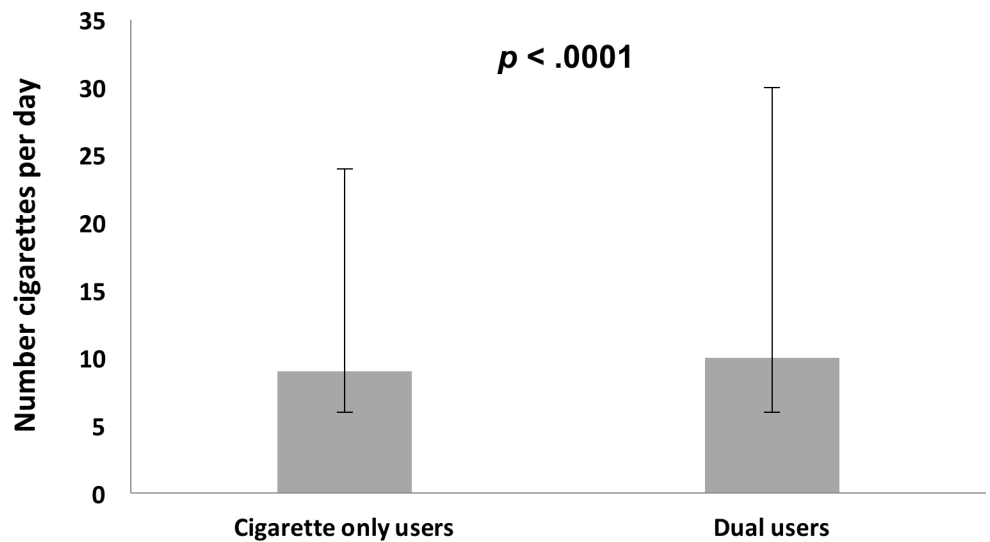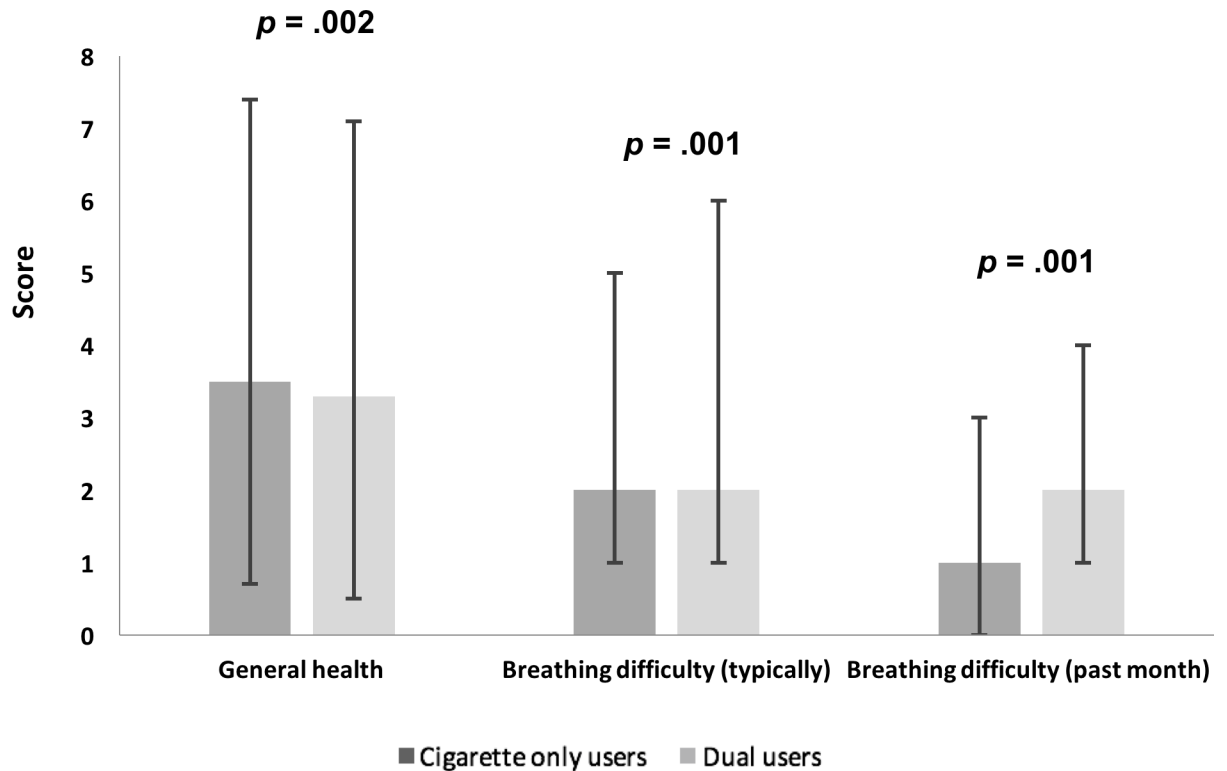al use was associated with lower (poorer) general health scores (ADJ p = .002) and higher (poorer) past month breathing difficulty scores (ADJ p = .001). Models adjusted for age, sex, race, education, cigarettes per day, coronary artery disease, congestive heart failure, and COPD. Error bars denote the interquartile range.

associated with lower general health scores (worse) (UADJ: ß = -.04, 95% CI: -.06 to -.01, p = .003; ADJ: ß = -.02, 95% CI: -.05 to .01, p = .002), comparable breathing difficulty scores *typically* (UADJ: ß = .003, 95% CI: .-007 to .01, p = .53; ADJ: ß = -.0009, 95% CI: -.01 to .01, p = .001), and higher (worse) breathing difficulty scores in the *past month* (UADJ: ß = .02, 95% CI: -.009 to .04, p = .21; ADJ: ß = .01, 95% CI: -.02 to .04, p = .001), after adjusting for age, sex, race, education, cigarettes smoked per day, coronary artery disease, congestive heart failure, and COPD (Fig 3). In examining the 19 cardiopulmonary conditions and risk factors between the two groups, only having a history of an arrhythmia was found to be significantly different between cigarette only users (14.2%) and dual users (17.8%) after adjusting for covariates (p = .02) (Fig 4).

E-cigarette use alone was associated with risk of health symptoms and conditions. Compared to those who reported no product use (reference group), those who reported e-cigarette only use, had lower (worse) general health scores, higher (worse) breathing difficulty scores, both *typically* and in the *past month*, and were more likely to report chest pain, palpitations, coronary artery disease, arrhythmia, COPD, and asthma (Table 2).

Discussion

In the Health eHeart Study, there was no evidence of reduced exposure to cigarettes, e-cigarettes, or health risks among dual users. These data suggest that, in this sample, the added use of e-cigarettes did not appear to supplant nicotine levels that might have otherwise been delivered via combustible cigarettes. An alternative explanation is that those with higher baseline
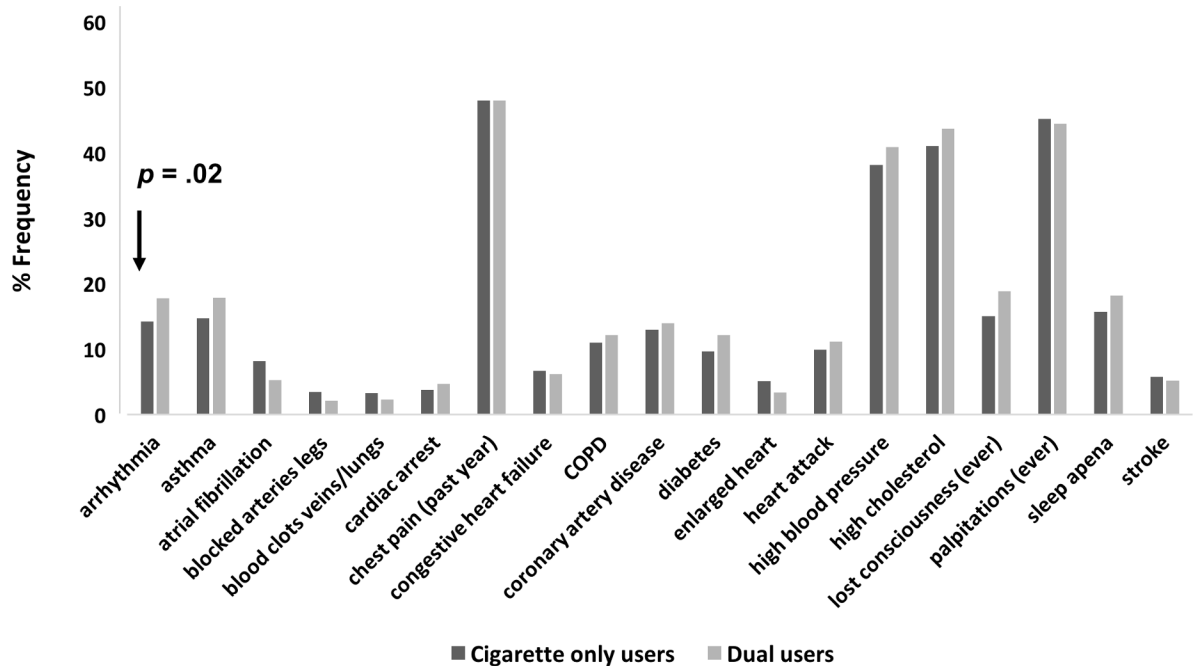
Fig 4. Percent of "yes" responses to past or current medical symptoms or conditions among cigarette only users and dual users. The only statistically significant difference between cigarette only users and dual users was arrhythmia (ADJ $p = .02$). Models adjusted for age, sex, race, education, cigarettes per day, and as needed, coronary artery disease, congestive heart failure, and COPD.

https://doi.org/10.1371/journal.pone.0198681.g004

nicotine dependence, who typically smoke more cigarettes per day, were more likely to be dual users. Greater nicotine dependence among dual users might explain why some studies have shown that e-cigarettes were not associated with reduced smoking or quitting smoking [28–33]. In this study, dual use was associated with smoking a median of one more cigarette per day compared to those who smoked only cigarettes. This was a small and statistically significant difference. Dual use was also associated with poorer general health and greater breathing difficulty in the past month compared to those who smoked only cigarettes. Given the rather small differential in the median number of cigarettes smoked per day between dual users and cigarette only users, the role specifically that of e-cigarettes in dual users warrants further investigation. These data provide epidemiologic evidence that dual use and e-cigarette use alone were associated with greater cardiopulmonary health risks. More studies are needed to examine both short-term and long-term health effects of e-cigarette use and potential synergistic effects of dual use.

Dual use and cigarette/e-cigarette exposure

In the present study, even with the use of e-cigarettes, dual users did not smoke fewer cigarettes than those who smoked only cigarettes. It may be possible that the added nicotine from e-cigarettes did not satisfy dual users' nicotine levels enough to reduce their usual cigarette intake. Studies have shown that e-cigarettes deliver lower levels of plasma nicotine than conventional cigarettes [20, 21], although more experienced e-cigarette users can also adjust their devices and e-liquid nicotine concentrations to achieve their desired nicotine levels [19, 22]. In the Health eHeart Study sample, there were no detectable differences in e-cigarette use dose, as measured by number of days, cartridges/ refills, and puffs per day, between those who reported using e-cigarettes only and dual users. Overall, dual users had greater exposure to toxicants

Table 2. Medical symptoms and conditions by product use, N = 34,279.

	Neither	E-cigarette Use Only	Cigarette Use Only	Dual Use	*p*-value unadjusted	*p*-value adjusted*
	N (mean or %)	N (mean or %)	N (mean or %)	N (mean or %)		
General health score	36,506 (3.8)	588 (3.5)	1626 (3.4)	480 (3.3)	< .0001	< .0001
Breathing difficulty, typically	31,924 (1.8)	483 (2.3)	1274 (2.5)	365 (2.5)	< .0001	< .0001
Breathing difficulty, past month	31,909 (1.3)	483 (1.4)	1273 (1.6)	365 (1.6)	< .0001	< .0001
Chest pain	10,730 (32.9%)	232 (47.3%)	685 (52.0%)	197 (51.7%)	< .0001	< .0001
Palpitations	14,477 (44.5%)	266 (55.3%)	721 (54.8%)	211 (55.5%)	< .0001	.002
Lost consciousness/ syncope	4,582 (14.1%)	413 (15.7%)	1119 (15.0%)	309 (18.7%)	.01	.06
High blood pressure	11,931 (36.5%)	167 (34.0%)	507 (38.2%)	157 (40.9%)	.07	.02
High cholesterol	13,812 (42.3%)	158 (32.1%)	544 (41.1%)	167 (43.7%)	.21	.29
Diabetes	2,578 (7.9%)	33 (6.7%)	129 (9.7%)	47 (12.2%)	.0005	.02
Coronary artery disease	3,248 (9.9%)	54 (10.9%)	174 (13.0%)	54 (14.0%)	< .0001	< .0001
Heart attack	1,931 (5.9%)	28 (5.7%)	132 (9.9%)	43 (11.2%)	< .0001	.67
Blocked arteries in the legs	550 (1.7%)	9 (1.8%)	46 (3.5%)	8 (2.1%)	< .0001	.34
Blood clots	1,104 (3.4%)	19 (3.9%)	43 (3.3%)	9 (2.3%)	.47	.58
Congestive heart failure	1,303 (4.0%)	16 (3.2%)	89 (6.7%)	24 (6.2%)	< .0001	.09
Stroke	1,218 (3.7%)	13 (2.6%)	77 (5.8%)	20 (5.2%)	.0004	.53
Enlarged heart	1,330 (4.1%)	20 (4.1%)	68 (5.1%)	13 (3.4%)	.32	.23
Atrial fibrillation	2,732 (8.4%)	20(4.1%)	108 (8.2%)	20 (5.3%)	.03	.91
Arrhythmia	4,444 (13.8%)	74 (15.1%)	183 (14.2%)	66 (17.8%)	.08	.03
Sleep apnea	4,260 (13.3%)	75 (15.8%)	195 (15.4%)	63 (17.2%)	.002	.58
COPD	1,209 (3.7%)	33 (6.7%)	146 (11.0%)	47 (12.2%)	< .0001	.001
Asthma	3,356 (10.3%)	81 (16.5%)	195 (14.7%)	69 (17.9%)	< .0001	.003
Cardiac arrest	697 (2.1%)	7 (1.4%)	50 (3.8%)	18 (4.7%)	< .0001	.39

* Adjusted models included age, sex, race, education, cigarettes per day, coronary artery disease, congestive heart failure, and COPD

from using both cigarettes and e-cigarettes. This finding is consistent with a study by Shahab et al. (2017), where exposure to carcinogens and toxins was not substantially reduced in dual users compared to those who smoked only cigarettes [34].

In the Health eHeart Study sample, one fifth of e-cigarette users reported never smoking cigarettes, whereas the remaining majority of e-cigarette users were former cigarette smokers. This is consistent with a study by Zhu et al. (2017), which reported a significant association between a substantial increase in e-cigarette use among cigarette smokers and smoking cessation rates at the US population level [35]. These data suggest that some cigarette users, perhaps those with lower nicotine dependence, might have successfully quit smoking cigarettes with the aid of e-cigarettes. However, dual use was not associated with reduced risk of tobacco exposure compared to smoking cigarettes alone. Further, the added exposure to e-cigarette toxicants, including more nicotine, might have adverse health outcomes.

Dual use, nicotine dependence, and health

Dual users are exposed to toxicants from cigarette smoke, e-cigarette vapor, and nicotine from both products. In the Health eHeart study, dual users were more likely to report lower general health scores and greater breathing difficulty. The health risks of first- and secondhand cigarette smoke exposure are well-established [1], and the evidence for e-cigarettes on pulmonary and cardiovascular health risks is growing. In the present study, compared to those who did

not use either e-cigarettes or cigarettes, participants who reported e-cigarette use alone were more likely to report both short-term and long-term pulmonary symptoms and conditions, including breathing difficulty, asthma, and COPD. Compared to those who used e-cigarettes alone, participants who reported dual use had even greater risk of breathing difficulty, asthma, and COPD. These findings support other studies to suggest that e-cigarettes may have adverse health effects on the respiratory system. Previous studies have reported e-cigarette vapor contain aerosols and other particles, including propylene glycol, that are associated with increased risk of airway irritation and resistance [36–39]. Studies from animal and basic science models have consistently shown specific e-cigarette liquid flavorings contain respiratory toxins [40–43]. Compared to those who reported neither e-cigarette or cigarette use, those who reported e-cigarette only use were more likely to report chest pain, palpitations, coronary artery disease, and an arrhythmia, which supports findings from other studies where e-cigarette use was associated with cardiac conditions such as arrhythmias and hypertension [44]. These conditions may be attributed to the increased exposure to nicotine (from e-cigarettes), which itself is associated with acute cardiovascular events and accelerated atherogenesis [45, 46].

These study findings provide early epidemiologic evidence to suggest that dual users are at higher risk of breathing difficulty and arrhythmias, and that this increased risk is likely attributable to e-cigarette use or the potential combined effect of cigarette and e-cigarette use. More studies are needed to elucidate the relationship between dual use and both short- and long-term health outcomes. In the meantime, we recommend dual users treat e-cigarettes (at the very least) like other nicotine replacement pharmacotherapies and recognize the potential for increased nicotine exposure. There is also the added risk of exposure to e-cigarette toxicants and the potential synergistic effect of dual use on health. Therefore, dual users are encouraged to stop smoking cigarettes and e-cigarettes to minimize tobacco and e-cigarette-related health risks.

Limitations

The cross-sectional nature of the present analysis limits causal inferences that can be made from these results. The timing of e-cigarette initiation was not available. The Health eHeart Study sample was not representative of the general US population, which could induce selection bias, and therefore limits the generalizability of our findings. For example, prevalence rates for cigarettes and e-cigarettes were lower in Health eHeart Study participants compared to the general US population. This discrepancy is likely due to higher proportions of Health eHeart Study participants, who were female, older age, and those with particularly high levels of education, which are factors associated with lower smoking prevalence rates in the general US population [47].

A validated measure of e-cigarette dose was not available, nor does one exist for comparison, which limits our ability to accurately assess frequency, quantity, and type of e-cigarette/ e-liquid use. The wide variation in e-cigarette/ vape devices, e-liquids, settings, and individual uptake that influence nicotine delivery and absorption add to the complexity in measuring e-cigarette dose [48]. In addition, it is important to mention that self-reported outcomes might result in recall bias, although the participants in this study did not necessarily know which predictors (such as e-cigarette use or smoking as opposed to all of the covariates collected in many surveys in the Health eHeart Study) would be used to assess relationships with which symptoms. The Health eHeart Study does not include assessment of baseline nicotine dependence levels. It is uncertain whether smokers with greater nicotine dependence, which is positively associated with the total number of cigarettes smoked per day and greater difficulty quitting smoking [49], were more likely to use e-cigarettes, which might explain why dual use was not

associated with smoking fewer cigarettes or reduced health risks. For example, smokers who have had greater difficulty quitting smoking, prolonged exposure to tobacco smoke, and prevalence of respiratory issues, could have been more inclined to initiate e-cigarette use with the intention to reduce or quit smoking conventional cigarettes. More epidemiologic studies, including longitudinal studies, are needed to further examine dual use, exposure to cigarette and e-cigarette toxicants, and health outcomes, while accounting for baseline nicotine dependence levels.

Conclusions

These data demonstrate that, among dual users, the use of e-cigarettes was not associated with less exposure to tobacco smoke or health risks. It provides epidemiologic evidence specifically linking e-cigarettes, and possibly a synergistic relationship between cigarettes and e-cigarettes, to having adverse pulmonary and cardiovascular health symptoms/conditions. Many smokers are adopting e-cigarettes for smoking cessation, which warrants effective strategies to help dual users wean off both cigarettes and e-cigarettes.

Acknowledgments

Author Contributions

Conceptualization: Julie B. Wang, Gregory M. Marcus.

Formal analysis: Julie B. Wang, Gregory Nah, Eric Vittinghoff, Mark J. Pletcher, Gregory M. Marcus.

Funding acquisition: Julie B. Wang, Jeffrey E. Olgin, Mark J. Pletcher, Gregory M. Marcus.

Investigation: Julie B. Wang, Gregory M. Marcus.

Methodology: Julie B. Wang, Eric Vittinghoff, Mark J. Pletcher, Gregory M. Marcus.

Resources: Julie B. Wang, Jeffrey E. Olgin, Mark J. Pletcher, Gregory M. Marcus.

Supervision: Gregory M. Marcus.

Writing – original draft: Julie B. Wang, Gregory M. Marcus.

Writing – review & editing: Julie B. Wang, Jeffrey E. Olgin, Eric Vittinghoff, Janine K. Cataldo, Mark J. Pletcher, Gregory M. Marcus.

References

1. Warren GW, Alberg AJ, Kraft AS, Cummings KM. The 2014 Surgeon General's report: "The Health Consequences of Smoking–50 Years of Progress": a paradigm shift in cancer care. Cancer. 2014 Jul 1; 120(13):1914–6. https://doi.org/10.1002/cncr.28695 PMID: 24687615

2. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current Cigarette Smoking Among Adults—United States, 2005–2015. MMWR Morb Mortal Wkly Rep. 2016; 65(44):1205–1211. https://doi.org/10.15585/mmwr.mm6544a2 PMID: 27832052

3. Rigotti NA. Treatment of Tobacco Use and Dependence. N Engl J Med. 2002; 346(7):506–512. https://doi.org/10.1056/NEJMcp012279 PMID: 11844853

4. Etter J-F. Electronic cigarettes: a survey of users. BMC Public Health. 2010; 10(1):231. https://doi.org/10.1186/1471-2458-10-231 PMID: 20441579

5. Etter J-F, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction. 2011; 106(11):2017–2028. https://doi.org/10.1111/j.1360-0443.2011.03505.x PMID: 21592253

6. Etter J-F, Bullen C. A longitudinal study of electronic cigarette users. Addict Behav. 2014; 39(2):491–494. https://doi.org/10.1016/j.addbeh.2013.10.028 PMID: 24229843

7. Foulds J, Veldheer S, Berg A. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. Int J Clin Pract. 2011; 65(10):1037–1042. https://doi.org/10.1111/j.1742-1241.2011.02751.x PMID: 21801287

8. Siegel MB, Tanwar KL, Wood KS. Electronic Cigarettes As a Smoking-Cessation Tool. Am J Prev Med. 2011; 40(4):472–475. https://doi.org/10.1016/j.amepre.2010.12.006 PMID: 21406283

9. Dawkins L, Turner J, Roberts A, Soar K. "Vaping" profiles and preferences: an online survey of electronic cigarette users. Addiction. 2013; 108(6):1115–1125. https://doi.org/10.1111/add.12150 PMID: 23551515

10. Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: An Internet survey. Drug Alcohol Rev. 2013; 32(2):133–140. https://doi.org/10.1111/j.1465-3362.2012.00512.x PMID: 22994631

11. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in the European Union: analysis of a representative sample of 27460 Europeans from 28 countries. Addiction. 2016; 111 (11):2032–2040. https://doi.org/10.1111/add.13506 PMID: 27338716

12. Ayers JW, Leas EC, Allem J-P, Benton A, Dredze M, Althouse BM, et al. Why do people use electronic nicotine delivery systems (electronic cigarettes)? A content analysis of Twitter, 2012–2015. Olson DR, ed. PLoS One. 2017; 12(3):e0170702. https://doi.org/10.1371/journal.pone.0170702 PMID: 28248987

13. Schoenborn CA, Gindi RM. Electronic Cigarette Use Among Adults: United States, 2014 Key findings. 2014. https://www.cdc.gov/nchs/data/databriefs/db217.pdf. Accessed March 21, 2017.

14. Centers for Disease Control and Prevention. QuickStats: Cigarette Smoking Status* Among Current Adult E-cigarette Users,† by Age Group—National Health Interview Survey,§ United States, 2015. MMWR Morb Mortal Wkly Rep. 2016; 65(42):1177. https://doi.org/10.15585/mmwr.mm6542a7 PMID: 27787495

15. Douglas CE. Taking aim at the bull's-eye: the nicotine in tobacco products. Tob Control. 1998; 7 (3):215–218. https://doi.org/10.1136/tc.7.3.215 PMID: 9825406

16. Benowitz NL, Henningfield JE, Connolly G. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. N Engl J Med. 1994; 331(2):123–125. https://doi.org/10.1056/NEJM199407143310212 PMID: 7818638

17. Food and Drug Administration, HHS. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents. Final rule. Fed Regist. 2010; 75(53):13225–13232. http://www.ncbi.nlm.nih.gov/pubmed/20383919. Accessed April 19, 2017. PMID: 20383919

18. Zhuang Y-L, Cummins SE, Y Sun J, Zhu S-H. Long-term e-cigarette use and smoking cessation: a longitudinal study with US population. Tob Control. 2016; 25(Suppl 1):i90–i95. https://doi.org/10.1136/tobaccocontrol-2016-053096 PMID: 27697953

19. Benowitz NL, Donny EC, Hatsukami DK. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game. Addiction. 2017; 112(1):6–7. https://doi.org/10.1111/add.13534 PMID: 27555354

20. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev. 2010; 19(8):1945–1953. https://doi.org/10.1158/1055-9965.EPI-10-0288 PMID: 20647410

21. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tob Control. 2010; 19(2):98–103. https://doi.org/10.1136/tc.2009.031567 PMID: 20378585

22. Grana R, Benowitz N, Glantz SA. E-Cigarettes: A Scientific Review. Circulation. 2014; 129(19):1972–1986. https://doi.org/10.1161/CIRCULATIONAHA.114.007667 PMID: 24821826

23. Guo X, Vittinghoff E, Olgin JE, Marcus GM, Pletcher MJ. Volunteer Participation in the Health eHeart Study: A Comparison with the US Population. Sci Rep. 2017; 7(1):1956. https://doi.org/10.1038/s41598-017-02232-y PMID: 28512303

24. Hagströmer M, Oja P, Sjöström M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. 2017. https://doi.org/10.1079/PHN2005898

25. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. J Gen Intern Med. 2001; 16(9):606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x PMID: 11556941

26. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder. Arch Intern Med. 2006; 166(10):1092. https://doi.org/10.1001/archinte.166.10.1092 PMID: 16717171

27. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996; 34(3):220–233. http://www.ncbi.nlm.nih.gov/pubmed/8628042. Accessed March 28, 2017. PMID: 8628042

28. Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong HH, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. Am J Prev Med. 2013; 44(3):207–215. https://doi.org/10.1016/j.amepre.2012.10.018 PMID: 23415116

29. Grana RA, Popova L, Ling PM, CM N, SM Z. A Longitudinal Analysis of Electronic Cigarette Use and Smoking Cessation. JAMA Intern Med. 2014; 174(5):812. https://doi.org/10.1001/jamainternmed.2014.187 PMID: 24664434

30. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. Nicotine Tob Res. 2013; 15(10):1787–1791. https://doi.org/10.1093/ntr/ntt061 PMID: 23658395

31. Popova L, Ling PM. Alternative Tobacco Product Use and Smoking Cessation: A National Study. Am J Public Health. 2013; 103(5):923–930. https://doi.org/10.2105/AJPH.2012.301070 PMID: 23488521

32. Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. Le Foll B, ed. PLoS One. 2013; 8(6):e66317. https://doi.org/10.1371/journal.pone.0066317 PMID: 23826093

33. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet. 2013; 382(9905):1629–1637. https://doi.org/10.1016/S0140-6736(13)61842-5 PMID: 24029165

34. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Udeni Alwis K, et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users. Ann Intern Med. 2017; 166(6):390. https://doi.org/10.7326/M16-1107 PMID: 28166548

35. Zhu S-H, Zhuang Y-L, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ. 2017; 358. http://www.bmj.com/content/358/bmj.j3262. Accessed July 27, 2017.

36. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. Chest. 2012; 141(6):1400–1406. https://doi.org/10.1378/chest.11-2443 PMID: 22194587

37. Heydari G, Ahmady A, Chamyani F, Masjedi M, Fadaizadeh L. Electronic cigarette, effective or harmful for quitting smoking and respiratory health: A quantitative review papers. Lung India. 2017; 34(1):25. https://doi.org/10.4103/0970-2113.197119 PMID: 28144056

38. Moazed F, Calfee CS. The Canary in the Coal Mine Is Coughing: Electronic Cigarettes and Respiratory Symptoms in Adolescents. Am J Respir Crit Care Med. 2017; 195(8):974–976. https://doi.org/10.1164/rccm.201611-2259ED PMID: 28409686

39. Flower M, Nandakumar L, Singh M, Wyld D, Windsor M, Fielding D. Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy. Respirol Case Reports. 2017; 5(3):e00230. https://doi.org/10.1002/rcr2.230 PMID: 28392919

40. Barrington-Trimis JL, Samet JM and McConnell R. Flavorings in electronic cigarettes: an unrecognized respiratory health hazard? JAMA. 2014; 312(23):2493–2494. https://doi.org/10.1001/jama.2014.14830 PMID: 25383564

41. Sherwood CL and Boitano S. Airway epithelial cell exposure to distinct e-cigarette liquid flavorings reveals toxicity thresholds and activation of CFTR by the chocolate flavoring 2, 5-dimethypyrazine. Respir Res. 2016; 17(1):57. https://doi.org/10.1186/s12931-016-0369-9 PMID: 27184162

42. Gerloff J, Sundar IK, Freter R, Sekera ER, Friedman AE, Robinson R, et al. Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography–mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. Appl In Vitro Toxicol. 2017; 3(1):28–40. https://doi.org/10.1089/aivt.2016.0030 PMID: 28337465

43. Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL, Glish GL, et al. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. Am J Physiol Lung Cell Mol Physiol. 2017; 313(2):L278–L292. https://doi.org/10.1152/ajplung.00452.2016 PMID: 28495856

44. Lippi G, Favaloro E, Meschi T, Mattiuzzi C, Borghi L, Cervellin G. E-cigarettes and cardiovascular risk: beyond science and mysticism. Semin Thromb Hemost. 2013; 40(1):060–065. https://doi.org/10.1055/s-0033-1363468 PMID: 24343348

45. Benowitz NL, Fraiman JB. Cardiovascular effects of electronic cigarettes. Nat Rev Cardiol. 2017; 14(8):447–456. https://doi.org/10.1038/nrcardio.2017.36 PMID: 28332500

46. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol. 1997; 29(7):1422–1431. http://www.ncbi.nlm.nih.gov/pubmed/9180099. Accessed March 23, 2017. PMID: 9180099

47. Jamal A, Homa DM, O'Connor E, Babb SD, Caraballo RS, Singh T, et al. Current cigarette smoking among adults—United States, 2005–2014. MMWR Morb Mortal Wkly Rep. 2015; 64(44):1233–1240. https://doi.org/10.15585/mmwr.mm6444a2 PMID: 26562061

48. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. Sci Rep. 2014; 4:4133. https://doi.org/10.1038/srep04133 PMID: 24569565

49. Borland R, Yong H-H, O'Connor RJ, Hyland A, Thompson ME. The reliability and predictive validity of the Heaviness of Smoking Index and its two components: findings from the International Tobacco Control Four Country study. Nicotine Tob Res. 2010; 12 Suppl(Suppl 1):S45–50. https://doi.org/10.1093/ntr/ntq038 PMID: 20889480