



## Full length article

## E-cigarette use and respiratory disorder in an adult sample

Thomas A. Wills<sup>a,\*</sup>, Ian Pagano<sup>a</sup>, Rebecca J. Williams<sup>b</sup>, Elizabeth K. Tam<sup>c</sup><sup>a</sup> Cancer Prevention Program, University of Hawaii Cancer Center, 701 Ilalo Street, Honolulu, HI, 96813, USA<sup>b</sup> Office of Public Health Studies, University of Hawaii at Manoa, 1960 East-West Road, Honolulu, HI, 96822, USA<sup>c</sup> Department of Medicine, John A. Burns School of Medicine, 1356 Lusitana Street, 7th floor, Honolulu, HI 96813, USA

## ARTICLE INFO

## Keywords:

E-cigarettes  
Smoking  
Asthma  
COPD  
Adults

## ABSTRACT

**Objectives:** Little evidence is available on the association of e-cigarettes with health indices. We investigated the association of e-cigarette use with diagnosed respiratory disorder among adults in data from the Behavioral Risk Factor Surveillance Survey (BRFSS).

**Methods:** The 2016 Hawaii BRFSS, a cross-sectional random-dial telephone survey, had 8087 participants; mean age was 55 years. Items asked about e-cigarette use, cigarette smoking, and being diagnosed by a health professional with (a) asthma or (b) chronic obstructive pulmonary disease. Multivariable analyses tested associations of e-cigarette use with the respiratory variables controlling for smoking and for demographic, physical, and psychosocial variables.

**Results:** Controlling for the covariates and smoking there was a significant association of e-cigarette use with chronic pulmonary disorder in the total sample (AOR = 2.58, CI 1.36–4.89,  $p < 0.01$ ) and a significant association with asthma among nonsmokers (AOR = 1.33, CI 1.00–1.77,  $p < 0.05$ ). The associations were stronger among nonsmokers than among smokers. Results were similar for analyses based on relative risk and absolute risk. There was also a greater likelihood of respiratory disorder for smokers, females, and persons with overweight, financial stress, and secondhand smoke exposure.

**Conclusions:** This is the first study to show a significant independent association of e-cigarette use with chronic respiratory disorder. Several aspects of the data are inconsistent with the possibility that e-cigarettes were being used for smoking cessation by persons with existing respiratory disorder. Theoretical mechanisms that might link e-cigarettes use and respiratory symptoms are discussed.

## 1. Introduction

The use of electronic smoking devices (e-cigarettes) has increased in recent years and the prevalence of e-cigarette use is now substantial among both adolescents and adults (Jamal et al., 2017; Wilson and Wang, 2017; Zernike, 2018). Given this prevalence, it is desirable to have knowledge about the health consequences of e-cigarette use (Glantz and Bareham, 2018; Muthy, 2017). Laboratory research using animal models and cell cultures has indicated that e-cigarettes have biological effects that could lead to tissue injury (Chun et al., 2017; St. Helen and Eaton, 2018). For example, e-cigarette vapor has been shown to have cytotoxic effects on lung cells (Lee et al., 2018) and to produce physiological defects usually seen in Chronic Obstructive Pulmonary Disease (COPD; Garcia-Arcos et al., 2016). At present, however, the generalization of these findings from laboratory paradigms to epidemiological samples is unclear. There is limited knowledge on e-cigarette use with clinical or subclinical variables, and reviews have emphasized

the importance of research testing such questions (US Department of Health and Human Services, 2016; Stratton et al., 2018). Accordingly, we investigated whether there was an association of e-cigarette use with diagnosed respiratory disorder in a representative sample of adults.

Previous research has provided evidence of an association of asthma with e-cigarette use, primarily from studies of adolescents. For example, a study with high school students in Hawaii found an association of e-cigarette use with asthma that was independent of cigarette smoking and marijuana use as well as several demographic variables (Schweitzer et al., 2017). This concurs with findings from adolescents in Asian countries (Cho and Paik, 2016; Wang et al., 2016) and the US state of Florida (Choi and Bernat, 2018). These results are theoretically consistent with physiological effects observed in laboratory studies (Clapp and Jaspers, 2017). While asthma may begin at earlier ages (Akinbami et al., 2014), the suggestion that e-cigarettes could maintain or exacerbate asthma (Clapp and Jaspers, 2017) led us to predict that an

\* Corresponding author at: Cancer Prevention Program, University of Hawaii Cancer Center, 701 Ilalo Street, Room 528, Honolulu, HI, 96813, USA.

E-mail address: [twills@cc.hawaii.edu](mailto:twills@cc.hawaii.edu) (T.A. Wills).

<https://doi.org/10.1016/j.drugalcdep.2018.10.004>

Received 5 July 2018; Received in revised form 5 October 2018; Accepted 8 October 2018

Available online 07 November 2018

0376-8716/© 2018 Elsevier B.V. All rights reserved.

association of e-cigarette use with asthma would be observed among adults.

There is less evidence about chronic respiratory disorder but a study with high school students in California found an association of e-cigarette use with reports of bronchitis symptoms (McConnell et al., 2017). Yao et al. (2017) studied a US national sample of current cigarette smokers and found that e-cigarette use was associated with a higher likelihood of wheezing and having multiple colds in the past 30 days, suggesting that e-cigarette use could increase susceptibility to upper respiratory infection. A study with an adult sample in Sweden (Hedman et al., 2018) found an association of e-cigarette with respiratory symptoms (e.g., long-standing cough, recurrent wheezing) but did not assess diagnosed respiratory disorder. Hence there is still little epidemiological evidence on chronic respiratory disorder and this has been suggested as a priority for investigation (Stratton et al., 2018). The present research included a measure of chronic pulmonary disorder and based on a body of research from in vitro and animal studies (Chun et al., 2017), we hypothesized that e-cigarette use would be related to chronic respiratory disorder in adults.

### 1.1. Study aims and hypotheses

To summarize, several lines of research suggest that a relation of e-cigarette use to respiratory disorder might occur among adults. Hence, we investigated whether e-cigarette use is associated with items indexing asthma and pulmonary disorder in a representative sample aged 18 years and over and whether e-cigarette use and combustible cigarette smoking could have synergistic effects for respiratory symptomatology (Cho and Paik, 2016). Because respiratory disorder is a multifactorial condition, having several different risk factors that may be correlated, we included measures of known risk factors as controls. For example, e-cigarette use and cigarette smoking tend to be correlated (Dutra and Glantz, 2014; Wills et al., 2015) so it is crucial to control for this potential confound. In addition, asthma and pulmonary symptoms are related to psychosocial factors including financial adversity (Beck et al., 2014; Kopel et al., 2014) and second-hand smoke exposure (McConnell et al., 2017) which also could be related to e-cigarette use. Obesity is a physical risk factor for asthma (Gennuso et al., 1998; von Mutius et al., 2001) so its contribution also needs to be evaluated. Thus the goal of this research was to determine the association of e-cigarette use with asthma and chronic pulmonary disorder controlling for these other factors so as to obtain a more precise test for e-cigarettes. We predicted that in this diverse sample of adults there would be positive associations of e-cigarette use with asthma and with pulmonary disorder. Because of a possibility that effects of e-cigarettes for airway irritation observed in laboratory studies could augment effects of smoking, which is not currently known (Chun et al., 2017), we also tested for an interaction of e-cigarettes and cigarette smoking.

## 2. Methods

### 2.1. Participants and procedure

This research used data from the Behavioral Risk Factor Surveillance Survey (BRFSS), an annual cross-sectional, random-digit-dialed survey that includes adult participants aged 18 years or older (CDC, 2011). The BRFSS uses a multistage sampling design to select a representative sample of the noninstitutionalized adult population in each of the 50 US states. Since 2011 the methodology has included reaching and interviewing participants on cellular telephones as well as landlines and using a dual-frame survey methodology to improve reliability and representativeness of the data (Hu et al., 2011). The present research uses data from the 2016 BRFSS conducted in the state of Hawaii. This survey had an overall response rate of 43%, a figure that compares favorably with other states and national surveys (CDC, 2017). The final sample had a total of 8087 participants. Details on sample

representativeness for the BRFSS survey procedure and validity of the BRFSS measures for assessing chronic disease are reviewed elsewhere (Pierannunzi et al., 2013; Li et al., 2012). Demonstrations of the generalizability of results from Hawaii to other parts of the US have been shown in a number of studies (Soneji et al., 2017; Watkins et al., 2018; Wills et al., 2013) as has generalizability to other countries (Best et al., 2018; Lozano et al., 2017; Treuer et al., 2017).

### 2.2. Measures

#### 2.2.1. Demographics

The survey included items on gender (female/male) and age in years (write-in). The item on primary ethnicity asked: “Which one of these groups would you say best represents your race?” Response options included: Alaska Native/American Indian, Black or African-American, Asian (Chinese, Filipino, Japanese, Other Asian), Pacific Islander (Native Hawaiian, Other Pacific Islander), and Caucasian. Educational level (“What is the highest grade or year of school you have completed?”) had five response options (Grades 1–8, 9–11, 12 years, 1–3 years college, 4 years college or more).

#### 2.2.2. E-cigarette use

A clarifying instruction prior to asking the e-cigarette items stated: “Electronic cigarettes and other ‘vaping’ products include electronic hookahs (e-hookahs), vape pens, e-cigs, and others. These products are battery powered and usually contain nicotine and flavors such as fruit, mint, or candy.” The item on ever e-cigarette use asked, “Have you ever used an electronic cigarette or other electronic ‘vaping’ product in your entire life.” (Yes/No/Not Sure). The item on current use asked, “Do you now use electronic cigarettes or other electronic ‘vaping’ products every day, some days, or not at all.”

#### 2.2.3. Cigarette smoking

A clarifying instruction prior to the cigarette items stated: “For cigarettes do not include electronic cigarettes (e-cigarettes, NJOY, Bluetip), herbal cigarettes, cigars, cigarillos, little cigars, pipes, bidis, kreteks, water pipes (hookahs), or marijuana.” The basic item on cigarette smoking asked, “Have you smoked at least 100 cigarettes in your entire life?” (Yes/No/Not Sure). Persons who answered Yes to this question were then asked about current smoking: “Do you now smoke cigarettes every day, some days, or not at all.” Persons who indicated current smoking (some days or every day) were asked, “During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking” (Yes/No). Persons answering Yes to lifetime smoking but No to current smoking were asked, “How long has it been since you last smoked a cigarette?” (7 options, within past month to 10 years or more).

#### 2.2.4. Respiratory disorder

Items followed the lead-in: “Has a doctor, nurse, or other health professional ever told you that you had any of the following.” Items were: “Were you ever told you had asthma?” “Do you still have asthma?” and “Were you ever told you have chronic obstructive pulmonary disease (COPD), emphysema, or chronic bronchitis?” Response options were Yes/No/Not Sure.

#### 2.2.5. Covariates

Body mass index was assessed with the items, “About how much do you weigh without shoes?” and “About how tall are you without shoes?” (Write-in for both.) This was coded as a four-level variable for overweight status (Underweight, Normal Weight, Overweight, Obese). Exposure to second-hand smoke was assessed with the item: “On how many of the past 7 days did anyone smoke in your home while you were there?” Response options were None, Number of days (write-in, 1–7), or I was not at home past 7 days. Financial stress was assessed with two items: “How often in the past 12 months would you say you were

worried or stressed about: having enough money to pay your rent/mortgage” and “How often in the past 12 months would you say you were worried or stressed about having enough money to buy nutritious meals?” Response options Never, Rarely, Sometimes, Usually, Always.

### 2.3. Data analysis

Prevalence estimates for substance use and respiratory symptoms were computed with weighted analyses using SAS Proc Surveyfreq, accounting for stratum. For analysis we used binary indices for ever-occurrence of asthma and COPD; for asthma we also computed a three-level index for never had asthma, previous asthma (but not current), and current asthma. For tobacco product use the basic analysis used binary indices (ever used e-cigarettes, smoked cigarettes > 100x). A continuous measure for age was recoded to 8 levels (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and 90–99 years). Educational level was recoded to four levels (grade school/some high school, high school graduate, some college, college graduate). For analysis two small ethnic groups (Alaska Native and African American) were dropped as they caused convergence problems because of small cell sizes in stratified analyses. A categorical variable for overweight status was recoded to three levels (under- or normal weight, overweight, obese). For financial stress, raw scores for the two items were summed and the summary score was recoded to a five-level variable (Never, Rarely Stressed, Somewhat Stressed, Often Stressed, Always Stressed).

Preliminary analyses examined the relation of age to measures of respiratory disorder and tobacco use. Zero-order relations of the predictor variables with respiratory disorder, e-cigarette use and smoking, controlling for age, were analyzed in logistic regression with SAS Surveylogistic. Multivariable analyses for relative risk were performed in logistic regression with a binary index for respiratory disorder (asthma or COPD) as the criterion. E-cigarettes and smoking were the primary predictors. Entered as demographic covariates were age, gender, educational level, and ethnicity (six binary indices for Native Hawaiian, Filipino, Japanese, Chinese, Pacific Islander, and Other Asian, contrasted against Caucasian as the reference group). Also entered as covariates were overweight status, second-hand smoke exposure, and financial stress. A four-category variable was constructed for tobacco product usage (1 = Never used e-cigarettes, Nonsmoker; 2 = Smoker, Never used e-cigarettes; 3 = Ever used e-cigarettes, Nonsmoker; 4 = Used e-cigarettes and Smoker) and pairwise comparisons of relative risk for asthma or COPD were computed from the model. To test for interaction in prediction of the criterion variables we entered the cross-product of e-cigarette use and smoking after entry of their two main-effect terms and all the covariates. To complement the analyses of relative risk we also report measures of absolute risk for asthma and COPD using the same models (cf. Noordzij et al., 2017); these are presented stratified by age.

There was little missing data for the asthma or COPD items but there were appreciable rates of missing data for some of the covariates. Accordingly, we conducted a full-information analysis using multiple imputation for the predictors (Rubin, 1987) so as to maximize sample size and minimize potential bias. This was performed using the SAS 9.4 Proc MI procedure with 20 imputations based on the Markov Chain Monte Carlo method (Schafer et al., 2002). The multivariable analyses were based on unweighted sample sizes of 8069 for asthma and 8063 for COPD.

## 3. Results

### 3.1. Sample characteristics

Table 1 reports the sample’s characteristics. The weighted sample was 50% female and mean age was 55 years. Proportions for primary perceived race/ethnicity were 13% Native Hawaiian, 18% Filipino, 20% Japanese, 6% Chinese, 20% Japanese, 3% Other Asian, 3% Other

**Table 1**  
Frequencies and Percentages for Study Variables.

Variable	Levels	Unweighted frequency	Weighted Percent	Weighted frequency	percent	
Gender	Female	4,314	53	561,749	50	
	Male	3,772	47	570,279	50	
	missing	1	125			
Age (years)	18-29	880	11	221,319	20	
	30-39	973	12	217,418	19	
	40-49	933	12	156,532	14	
	50-59	1,496	19	180,961	16	
	60-69	1,947	24	174,450	16	
	70-79	1,165	15	103,098	9	
	80-89	497	6	51,365	5	
	90-99	113	1	14,983	1	
	missing	83	12,028			
Race/ethnicity	Nat. Hawaiian	1,096	14	137,735	13	
	Filipino	1,026	13	194,530	18	
	Japanese	1,518	19	221,102	20	
	Chinese	379	5	63,363	6	
	Pac. Islander	185	2	31,868	3	
	Other Asian	160	2	28,059	3	
	Caucasian	3,374	43	390,153	36	
	Black	104	1	31,019	3	
		missing	245	2	34,322	
	Education	Grade school	293	4	101,139	9
HS graduate		2,103	26	326,062	29	
Some college		2,241	28	382,107	34	
Coll. graduate		3,428	42	319,228	28	
		missing	22	3,617		
Ever diagnosed with asthma	No	6,727	83	934,626	83	
	Yes	1,342	17	195,278	17	
		missing	18	2,249		
Have asthma now	No	7,213	90	1,006,519	89	
	Yes	832	10	120,293	11	
		missing	42	5,342		
Ever diagnosed with COPD	No	7,615	94	1,083,315	96	
	Yes	448	6	45,098	4	
		missing	24	3,741		
Ever used e-cigarettes	No	6,427	83	837,973	78	
	Yes	1,346	17	239,079	22	
		missing	314	55,101		
Use e-cigarettes now	Not at all	7,536	97	1,030,695	96	
	Some days	144	2	27,143	2	
	Every day	91	1	18,997	2	
		missing	316	55,317		
Smoked > 100x	No	4,538	58	663,946	62	
	Yes	3,246	42	414,696	38	
		missing	303	53,511		
Smoke cigarettes now	Not at all	6,844	88	937,239	87	
	Some days	270	3	44,645	4	
	Every day	664	9	96,040	9	
		missing	309	54,229		
Weight status	Normal	3,271	43	448,025	42	
	Overweight	2,621	34	357,240	34	
	Obese	1,767	23	251,883	24	
		missing	428	75,005		
Secondhand smoke	None	6,438	92	855,432	91	

(continued on next page)

Table 1 (continued)

Variable	Levels	Unweighted frequency	Weighted Percent	Weighted frequency	percent
exposure	1-4 days	185	3	28,690	3
	5-7 days	393	6	56,630	6
	missing	1,071	191,402		
Worried about finances during past 12 months	Never	3,268	53	401,932	50
	Rarely	1,406	23	201,913	25
	Sometimes	839	14	121,017	15
	Usually	381	6	50,713	6
	Always	251	4	36,036	4
	missing	1,942	320,542		

Pacific Islander, and 36% Caucasian. Education level was 9% less than high school, 29% high school graduate, 34% some college, and 28% college graduate.

The estimated prevalence in the overall sample was 17% for ever had asthma and 4% for ever had COPD; the weighted N for these analyses was approximately 1,129,000 participants. (For this comparison we report lifetime rates because there was no item corresponding to current COPD.) The estimated prevalence of ever e-cigarette use in the overall sample was 22% and the prevalence of cigarette smoking (smoked > 100 cigarettes) was 38%. For current e-cigarette use, overall prevalence was 2% (some days) and 2% (every day). For current cigarette smoking, overall prevalence was 4% (some days) and 9% (every day).

Asthma and chronic pulmonary disorder were correlated (Supplemental Table 1). For example, the estimated prevalence of COPD was 3% among persons who never had asthma but was 17% among persons who had asthma. However, 48% of persons with COPD had not had asthma, and these data supported performing separate analyses for asthma and COPD.

The patterns of data for respiratory symptoms and tobacco use were strongly age-dependent but the direction of the relationship differed across variables (Supplemental Table 2). Reports of asthma tended to decrease with age while reports of COPD increased with age. Cigarette smoking increased in frequency across most of the age groups whereas e-cigarette use was more frequent among the younger age groups. Financial stress showed an almost linear decrease with age. The prevalence of overweight was not linearly age-dependent but there was indication of a quadratic trend. These data supported including age as a covariate for all of the analyses.

E-cigarette use and cigarette smoking were correlated, as is typical in other studies (Glantz and Bareham, 2018; Dutra and Glantz, 2014; Wills et al., 2015). Cross-tabulations for ever-use and current use of e-cigarettes and cigarettes showed significant associations (Supplemental Table 3). For example, 12% of nonsmokers had ever used e-cigarettes compared with 39% for smokers. The cross-tabulation of e-cigarette use and smoking was comparable across most age groups, excepting for 80–99 year groups, where the prevalence of e-cigarette use was low.

### 3.2. Bivariate relations for variables

Logistic regression analyses were used to compute bivariate relations of the study variables with asthma and chronic pulmonary disorder, including age as a covariate (Supplemental Table 4). E-cigarette use and cigarette smoking showed significant positive associations with both asthma and COPD (odds ratios > 1) whereas inverse relations were noted for educational level and male gender for asthma (odds ratios < 1). Asthma and COPD were positively associated with overweight status, financial stress, and exposure to secondhand smoke (for COPD). For these analyses the coding compared a given ethnic group with all other groups. Relative to other groups, Native Hawaiians had significantly higher prevalence for asthma and COPD and Caucasians

Table 2

Relative Risk (Odds Ratio and CI) in Multivariate Model for Asthma with Pairwise Comparisons.

Variable	AOR	CI	p
Age	0.93	0.89 - 0.97	.0002
Age**2	1.01	0.99 - 1.03	.37
E-cigarette use	1.27	0.96 - 1.67	.10
Cigarette smoking	1.27	1.10 - 1.47	.001
E-cig X smoking	0.78	0.56 - 1.09	.15
Pairwise comparisons			
Dual vs. none	1.26	1.04 - 1.53	.02
Smok vs. none	1.27	1.10 - 1.47	.001
E-cig vs. none	1.27	0.96 - 1.67	.10
Dual vs. e-cig	1.00	0.73 - 1.35	.98
Smok vs. e-cig	1.00	0.74 - 1.35	.98
Dual vs. smok	0.99	0.80 - 1.22	.94
Gender (male)	0.62	0.55 - 0.70	< .0001
Education	0.94	0.88 - 1.01	.10
Financial stress	1.13	1.06 - 1.20	.0003
Overweight status	1.28	1.17 - 1.39	< .0001
Secondhand smoke	1.00	0.87 - 1.13	.95
Native Hawaiian <sup>A</sup>	1.53	1.28 - 1.82	< .0001
Filipino	0.95	0.78 - 1.16	.63
Japanese	0.97	0.81 - 1.15	.71
Chinese	0.96	0.69 - 1.33	.82
Pacific Islander	0.56	0.36 - 0.89	.01
Other Asian	0.75	0.45 - 1.24	.27

Note: For usage groups: None = never used e-cigarettes, nonsmoker; E-cig = Only used e-cigarettes, nonsmoker; Smok = Only smoked cigarettes, nonsmoker; Dual = Used e-cigarettes and smoked cigarettes.

<sup>A</sup> Ethnicity contrasts are coded with Caucasians as the reference group.

were elevated for COPD, whereas Japanese and Chinese, and Other Asians tended to have lower prevalence for asthma and in two cases for COPD.

Bivariate correlations with e-cigarette use and cigarette smoking controlling for age (Supplemental Table 5) indicated male gender and financial stress were positively associated with smoking and e-cigarette use whereas educational level was inversely associated with these variables; also there were significant zero-order associations of secondhand smoke exposure and overweight status with smoking and e-cigarette use. Using the same coding, higher rates of smoking and e-cigarette use were noted for Native Hawaiians and Caucasians whereas lower rates were noted for Filipinos, Japanese, and Chinese.

### 3.3. Multivariable models

In multivariable analyses, measures of e-cigarette use and cigarette smoking were entered together in logistic regression with age and the other covariates, with asthma or chronic pulmonary disorder as the criterion. A quadratic term for age was included in the models. As noted in Analytic Methods, six dummy variables were entered to code ethnicity, with Caucasians as the reference group. As indicated in Table 2, cigarette smoking was positively associated with asthma in the overall sample, AOR = 1.27 (CI = 1.10–1.47),  $p = .001$ , but e-cigarette use was marginal, AOR = 1.27 (CI 0.96–1.67),  $p = .10$ . The interaction was inverse in direction, AOR = 0.78, but did not reach significance. Pairwise comparisons indicated the smoking-only group and the dual-user group had higher rates of asthma relative to the nonuser group ( $p = .001$  and  $p = .02$ , respectively) but the e-cigarette only group was marginal ( $p = .10$ ). The interaction was interpreted by conducting separate analyses for nonsmokers and smokers. These indicated there was a significant association of e-cigarette use with asthma among nonsmokers (AOR = 1.33, CI 1.00–1.77,  $p < .05$ ) but not among smokers (AOR = 0.92, CI 0.73–1.15, ns.). Results for the covariates indicated asthma was inversely associated with age and positively associated with overweight status, financial stress, Native Hawaiian ethnicity, and female gender. The model for asthma was repeated with age restricted to

**Table 3**  
Relative Risk (Odds Ratio and CI) in Multivariate Model for Chronic Pulmonary Disorder with Pairwise Comparisons.

Variable	AOR	CI	p
Age	1.49	1.37- 1.62	< .0001
Age**2	0.97	0.94 - 1.00	.05
E-cigarette use	2.58	1.36 - 4.89	.004
Cigarette smoking	2.98	2.34 - 3.78	< .0001
E-cig X smoking	0.51	0.26 - 1.00	.05
Pairwise comparisons			
Dual vs. none	3.92	2.82 - 5.44	< .0001
Smok vs. none	2.98	2.34 - 3.78	< .0001
E-cig vs. none	2.58	1.36 - 4.89	.004
Dual vs. e-cig	1.52	0.81 - 2.87	.20
Smok vs. e-cig	1.16	0.62 - 2.17	.65
Dual vs. smok	1.32	0.98 - 1.77	.07
Gender (male)	0.71	0.58 - 0.88	.001
Education	0.88	0.79 - 0.98	.03
Financial stress	1.19	1.08 - 1.31	.0006
Overweight status	1.11	0.96 - 1.27	.15
Secondhand smoke	1.37	1.15 - 1.63	.0003
Native Hawaiian <sup>A</sup>	1.11	0.84 - 1.48	.47
Filipino	0.82	0.58 - 1.17	.27
Japanese	0.62	0.46 - 0.83	.001
Chinese	0.58	0.30 - 1.12	.11
Pacific Islander	1.16	0.56 - 2.40	.69
Other Asian	0.56	0.21 - 1.51	.25

Note: For usage groups: None = never used e-cigarettes, nonsmoker; E-cig = Only used e-cigarettes, nonsmoker; Smok = Only smoked cigarettes, nonsmoker; Dual = Used e-cigarettes and smoked cigarettes.

<sup>A</sup> Ethnicity contrasts are coded with Caucasians as the reference group.

the lower six age categories (i.e., < 80 years) and with listwise deletion of missing data. The results from these analyses were not substantially different than the ones reported here.

In the multivariable analysis for chronic pulmonary disorder (Table 3), e-cigarette use and smoking showed significant independent associations with pulmonary disorder; the effect size was larger for smoking (AOR = 2.98, CI 2.34–3.78) than for e-cigarettes (AOR = 2.58, CI 1.36–4.89) but both were significant. Pairwise comparisons indicated that relative to the nonuser group there were higher rates of disorder for both the e-cigarette only group ( $p = .004$ ), the cigarette only group ( $p = .0001$ ), and the dual user group ( $p = .0001$ ). The interaction term was significant (AOR = 0.51, CI 0.26–1.00,  $p < .05$ ). Subgroup analyses indicated there was a significant association of e-cigarette use with COPD among nonsmokers (AOR = 2.98, CI 1.51–5.88,  $p < .01$ ), but the association was not significant among smokers (AOR = 1.29, CI 0.94–1.77, ns.). Covariate effects in the multivariate model indicated COPD was positively associated with second-hand smoke exposure, financial stress, and female gender; and was inversely associated with education and Japanese ethnicity. These analyses were repeated using variant models similar to those used for asthma; results from these analyses were not substantially different from those reported here.

Data on the absolute risk for asthma and for pulmonary disorder are presented for each of the usage groups in Tables 4 and 5, respectively. (For concise presentation, persons over 80 are not included.) For asthma, absolute risk was moderate and declined with age (Fig. 1A). Absolute risk was higher for both the e-cigarette only group and the smoking-only group and the dual user group did not differ significantly from these (Table 3); hence in the figure the lines for these three groups converge. For the COPD item the level of absolute risk was lower than for asthma and tended to increase with age (Fig. 1B). The e-cigarette only group and smoking only group had higher rates than the nonuser group, with the dual-user group having an even higher rate, consistent with the independent contributions noted in the regression analyses (Table 3). Thus the data for absolute risk were consistent with the analyses for relative risk, showing both e-cigarette use and cigarette

**Table 4**  
Absolute Risk from Multivariate Model for Asthma, by Age Group and Usage Group.

Age (years)	Usage group			
	Nonuser	Smok only	E-cig only	Dual user
20.0	19.0%	22.9%	22.8%	22.8%
22.5	18.5%	22.3%	22.3%	22.2%
25.0	18.0%	21.8%	21.7%	21.6%
27.5	17.5%	21.3%	21.2%	21.1%
30.0	17.1%	20.8%	20.7%	20.6%
32.5	16.7%	20.3%	20.2%	20.2%
35.0	16.3%	19.9%	19.8%	19.7%
37.5	16.0%	19.4%	19.4%	19.3%
40.0	15.6%	19.0%	19.0%	18.9%
42.5	15.3%	18.7%	18.6%	18.5%
45.0	15.0%	18.3%	18.3%	18.2%
47.5	14.7%	18.0%	17.9%	17.9%
50.0	14.5%	17.7%	17.6%	17.5%
52.5	14.2%	17.4%	17.3%	17.3%
55.0	14.0%	17.1%	17.0%	17.0%
57.5	13.7%	16.8%	16.8%	16.7%
60.0	13.5%	16.6%	16.5%	16.5%
62.5	13.4%	16.4%	16.3%	16.3%
65.0	13.2%	16.2%	16.1%	16.1%
67.5	13.0%	16.0%	15.9%	15.9%
70.0	12.9%	15.8%	15.8%	15.7%
72.5	12.7%	15.6%	15.6%	15.5%
75.0	12.6%	15.5%	15.4%	15.4%
77.5	12.5%	15.4%	15.3%	15.3%
80.0	12.4%	15.3%	15.2%	15.1%

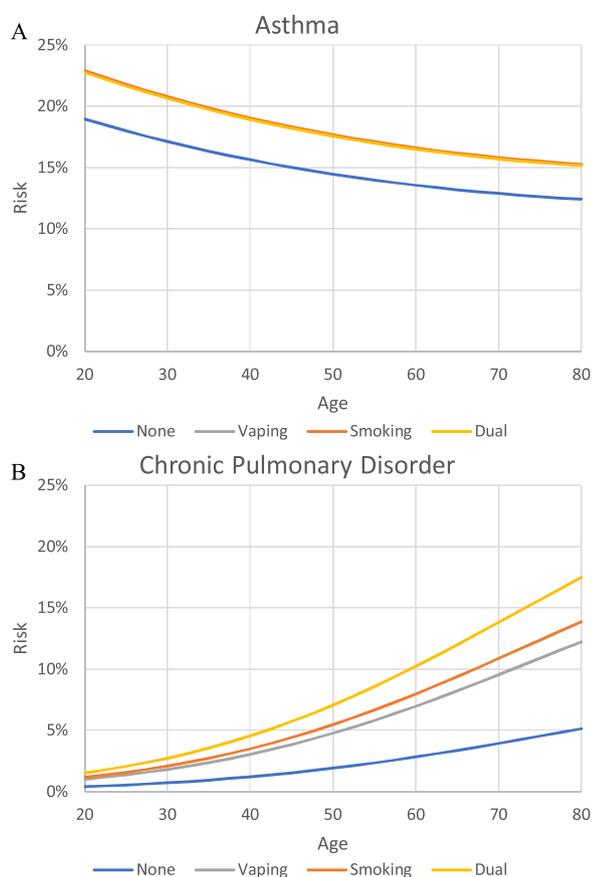
**Table 5**  
Absolute Risk from Multivariate Model for Chronic Pulmonary Disorder, by Age Group and Usage Group.

Age (years)	Usage group			
	Nonuser	Smok only	E-cig only	Dual user
20.0	0.4%	1.2%	1.0%	1.5%
22.5	0.5%	1.4%	1.2%	1.8%
25.0	0.5%	1.6%	1.4%	2.1%
27.5	0.6%	1.8%	1.6%	2.4%
30.0	0.7%	2.1%	1.8%	2.7%
32.5	0.8%	2.4%	2.1%	3.1%
35.0	0.9%	2.7%	2.4%	3.5%
37.5	1.1%	3.1%	2.7%	4.0%
40.0	1.2%	3.5%	3.0%	4.5%
42.5	1.4%	3.9%	3.4%	5.1%
45.0	1.5%	4.4%	3.8%	5.7%
47.5	1.7%	4.9%	4.3%	6.4%
50.0	1.9%	5.5%	4.8%	7.1%
52.5	2.1%	6.0%	5.3%	7.8%
55.0	2.3%	6.6%	5.8%	8.6%
57.5	2.6%	7.3%	6.4%	9.4%
60.0	2.8%	8.0%	7.0%	10.2%
62.5	3.1%	8.7%	7.6%	11.1%
65.0	3.4%	9.4%	8.2%	12.0%
67.5	3.6%	10.1%	8.9%	12.9%
70.0	3.9%	10.8%	9.5%	13.8%
72.5	4.2%	11.6%	10.2%	14.7%
75.0	4.5%	12.4%	10.9%	15.6%
77.5	4.8%	13.1%	11.5%	16.6%
80.0	5.1%	13.9%	12.2%	17.5%

smoking associated with higher rates of respiratory disorder and the independent contributions being particularly notable for chronic pulmonary disorder.

#### 4. Discussion

The purpose of this research was to study the association of e-cigarette use with two indices of diagnosed respiratory disorder among



**Fig. 1.** Absolute risk of respiratory disorder, by age, for four tobacco usage groups.

1A. Absolute risk for asthma. 1B. Absolute risk for chronic pulmonary disorder.

adults. Findings indicated that e-cigarette use was associated with respiratory disorder independent of cigarette smoking, age, and a range of physical and psychosocial covariates. Results were similar for analyses based on relative risk and absolute risk of asthma and COPD. These results are consistent with several studies showing e-cigarette use related to respiratory symptoms (Cho and Paik, 2016; Hedman et al., 2018; McConnell et al., 2017; Schweitzer et al., 2017); to our knowledge the finding for COPD is novel. The fact that the findings were independent of the covariates means that the results cannot be attributed to a correlation of e-cigarette use with third variables measured here such as gender, education, and financial stress. In addition, the present research delineated racial/ethnic differences in e-cigarette use and respiratory disorder, knowledge which can be utilized to understand and ultimately reduce health disparities.

The primary finding of this research is that e-cigarette use showed a significant association with respiratory disorder among adults. This was true for both asthma and chronic pulmonary disorder. Because the items did not determine exactly when symptoms of asthma or pulmonary disorder originated, there are two possible interpretations of the data. One possible interpretation is that participants began using e-cigarettes when they developed asthma or pulmonary disorder; but it is difficult to think of a reason for why people would do this because e-cigarette vapor has lung irritant properties (e.g., Anderson et al., 2016; Larcombe et al., 2017; Reidel et al., 2018; Wu et al., 2014). As a variant explanation, it could be posited that persons who used e-cigarettes did so to reduce or quit smoking when they developed a respiratory disorder. However, this interpretation would be inconsistent with the data, which showed that the significant associations of e-cigarettes with respiratory disorder occurred primarily among nonsmokers, not among smokers. Moreover, the smoking cessation items indicated that most of

the quitters had stopped smoking many years ago and that current e-cigarette use was not related to stopping smoking (data not shown). Thus reverse-causation arguments do not seem very tenable on logical or empirical grounds.

An alternative interpretation is that e-cigarette use contributed to the development or maintenance of respiratory symptoms or the transition from initial symptomatology to chronic disorder. Data from other studies give plausibility to this interpretation because they show e-cigarette use is associated with asthma and bronchitis in high school samples (Choi and Bernat, 2018; McConnell et al., 2017; Schweitzer et al., 2017), ages that precede the development of chronic pulmonary disorder. While this interpretation has plausibility on the grounds of consistency with other epidemiological studies and coherence with existing biological knowledge (Chun et al., 2017; Clapp and Jaspers, 2017), longitudinal research is needed for studying the extent to which e-cigarettes are related to onset of symptomatology or maintenance of existing symptoms.

Biological plausibility is relevant because recent reviews based on controlled laboratory and clinical research have suggested possible mechanisms for a relation of e-cigarettes to respiratory symptoms (Chun et al., 2017; Clapp and Jaspers, 2017). For example, cell studies have implicated e-cigarette aerosol in generation of reactive oxygen species, contributing to oxidative stress that could affect airway cells (Ji et al., 2016; Lerner et al., 2015; Zhao et al., 2018). Other studies have shown cytotoxic and inflammatory effects of e-cigarette vapor for airway cells, effects that could contribute to respiratory symptoms (Larcombe et al., 2017; Lee et al., 2018; Rowell et al., 2017; Wu et al., 2014). Additionally, studies focusing on immune system parameters have provided evidence that exposure to e-cigarette aerosol impairs immune system function, increasing susceptibility to infection (Hwang et al., 2016; Martin et al., 2016; Reidel et al., 2018; Sussan et al., 2015). Whether such mechanisms are involved in observed associations for respiratory disorder needs to be considered in further epidemiological research.

#### 4.1. Study limitations

While this research used a large representative sample, was based on items that asked about diagnosed disease, and included a number of relevant covariates, some aspects could be noted as limitations. First, the study was cross-sectional and temporal relations between variables cannot be definitively established. Second, the study lacked a detailed measure of smoking history and the survey did not include items on marijuana, which is relevant for asthma (Strong et al., 2018). Though prior studies have shown effects for e-cigarettes independent of marijuana (e.g., Schweitzer et al., 2017), this is a possible limitation and needs to be considered in further research. Third, the respiratory variables were based on self-report, and while validity of BRFSS variables for indexing chronic disease conditions has been previously demonstrated (Li et al., 2012; Pierannunzi et al., 2013), the findings could be confirmed in further research using direct physical examination or biochemical indices. Finally, the sample was from one US state and generalization to other areas needs to be studied.

#### 4.2. Conclusions

In summary, this research found an association of e-cigarette use with respiratory disorder in a diverse sample of adults with analyses including demographic and psychosocial controls. Though temporal aspects of the findings need to be clarified, the results are consistent with other studies suggesting a linkage of e-cigarette use with respiratory symptoms at other ages. The fact that findings for respiratory symptoms occurred primarily for nonsmokers argues against several alternative interpretations of the results. Further research is needed to obtain more evidence on whether e-cigarette use may be adding to respiratory disorder in the population among nonsmokers (Glantz and

Bareham, 2018; US Department of Health and Human Services, 2016).

### Role of funding source

Dr. Wills and Dr. Pagano were supported by grant P30 CA071789 from the National Cancer Institute. The funding agency played no role in analysis and interpretation of the data, preparation of the manuscript, and decision to submit the report for publication. The content is solely the responsibility of the authors and does not necessarily reflect official policy of the U.S. Department of Health and Human Services.

### Contributors

TAW, RJW, and EKT formulated the research questions; RJW helped obtain the data; TAW and IP developed the analytic plan and performed the statistical analyses; TAW drafted and revised the manuscript; all authors reviewed and edited drafts of the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

### Conflict of interest

All authors state that they do not have any financial relationships with any organizations that might have an interest in the submitted work or any other relationships or activities that could appear to have influenced the submitted work.

### Acknowledgments

We thank the staff of the Hawaii State Department of Health for assisting with access to the data and providing information for the analysis.

### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2018.10.004>.

### References

- Akinbami, L.J., Moorman, J.E., Simon, A.E., Schoendorf, K.C., 2014. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. *J. Allergy Clin. Immunol.* 134, 547–553.
- Anderson, C., Majeste, A., Hanus, J., Wang, S., 2016. E-cigarette aerosol exposure induces reactive oxygen species, DNA damage, and cell death in vascular endothelial cells. *Toxicol. Sci.* 152, 334–340.
- Beck, A.F., Huang, B., Simmons, J.M., Moncrief, T., Sauers, H.S., Chen, C., et al., 2014. Role of financial and social hardships in asthma racial disparities. *Pediatrics* 133, 431–439.
- Best, C., Haseen, F., Currie, D., Ozakino, G., MacKintosh, A.M., et al., 2018. Relationships between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tob. Control* 27, 373–378.
- CDC, 2011. At A Glance: Conducting the Behavioral Risk Factor Surveillance System (BRFSS). US Department of Health and Human Services, Centers for Disease Control.
- CDC, 2017. BRFSS 2016 Summary Data Quality Report. US Department of Health and Human Services, Centers for Disease Control.
- Cho, J.H., Paik, S.Y., 2016. Association between electronic cigarette use and asthma among high school students in South Korea. *PLoS One* 11, e0151022.
- Choi, K., Bernat, D., 2018. E-cigarette use among Florida youth with and without asthma. *Am. J. Prev. Med.* 51, 446–453.
- Chun, L.F., Moazed, F., Calfee, C.S., Matthay, M.A., Gotts, J.E., 2017. Pulmonary toxicity of e-cigarettes. *Am. J. Physiol. Lung Cell Mol. Physiol.* 313, L193–L206.
- Clapp, P.W., Jaspers, I., 2017. Electronic cigarettes: their constituents and potential links to asthma. *Curr. Allergy Asthma Rep.* 17 (17), 79.
- Dutra, L.M., Glantz, S.A., 2014. Electronic cigarettes and conventional cigarette use among US adolescents. *JAMA Pediatr.* 168, 610–617.
- Garcia-Arcos, I., Geraghty, P., Baumlin, N., et al., 2016. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax* 71, 1119–1129.
- Gennuso, J., Epstein, L.H., Paluch, R.A., Cerny, F., 1998. The relationship between asthma and obesity in urban minority children and adolescents. *Arch. Pediatr. Adolesc. Med.* 152, 1197–2000.
- Glantz, S.A., Bareham, D.W., 2018. E-cigarettes: use, effects on health, risks, and policy implications. *Ann. Rev. Public Health* 39, 28.1–28.21.
- Hedman, L., Backman, H., Stridsman, C., Bosson, J.A., Lundback, M., Lindberg, A., et al., 2018. Association of electronic cigarette use with smoking habits, demographic factors, and respiratory symptoms. *JAMA Netw. Open* 1 (3), e180789.
- Hu, S.S., Pierannunzi, C., Balluz, L., 2011. Integrating a multimode design into a national random-digit-dialed telephone survey. *Prev. Chron. Dis.* 8, A145.
- Hwang, J.H., Lyles, M., Sladewski, K., Enany, S., McEachern, E., Mathew, D.P., et al., 2016. Electronic cigarette inhalation alters innate immunity and airway cytokines while increasing the virulence of colonizing bacteria. *J. Mol. Med.* 94, 667–679.
- Jamal, A., Gentzke, A., Hu, S.S., Cullen, K.A., Apelberg, B.J., Homa, D.M., King, B.A., 2017. Tobacco use among middle and high school students: United States, 2011–2016. *MMWR Morb. Mortal. Wkly. Rep.* 66, 597–603.
- Ji, E.H., Sun, B., Zhao, T., Shu, S., Chang, C.H., Messadi, D., Xia, T., Zhu, Y., Hu, S., 2016. Characterization of electronic cigarette aerosol and its induction of oxidative stress response in oral keratinocytes. *PLoS One* 11, e0169380.
- Kopel, L.S., Phipatanakul, W., Gaffin, J.M., 2014. Social disadvantage and asthma control in children. *Pediatr. Respir. Rev.* 15, 256–262.
- Larcombe, A.N., Janka, M.A., Mullins, B.J., Berry, L.J., Bredin, A., Franklin, P.J., 2017. The effects of electronic cigarette aerosol exposure on inflammation and lung function in mice. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 313, L67–L79.
- Lee, H.-W., Park, S.-H., Weng, M.-W., et al., 2018. E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *PNAS* 29 (January). <https://doi.org/10.1073/pnas.1718185115>. 2018.
- Lerner, C.A., Sundar, I.K., Yao, H., Gerloff, J., Ossip, D.J., McIntosh, S., et al., 2015. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PLoS One* 10, e0116732.
- Li, C., Balluz, L.S., Ford, E.S., Okoroa, C.A., Zhao, G., Pierannunzi, C., 2012. A comparison of prevalence estimates for selected health indicators of chronic diseases or conditions from the Behavioral Risk Factor Survey Surveillance System, the National Health Interview Survey, and the National Health and Nutrition Examination Survey, 2007-2008. *Prev. Med.* 54, 381–387.
- Lozano, P., Barrientos-Gutierrez, I., Arollo-Santillan, E., Morello, P., Mejia, R., Sargent, J.D., Thrasher, J.F., 2017. A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents. *Drug Alcohol Depend.* 180, 427–430.
- Martin, E.M., Clapp, P.W., Rebuli, M.E., Pawlak, E.A., Glista-Baker, E., Benowitz, N.L., Fry, R.C., Jaspers, I., 2016. E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke. *Am. J. Physiol. Lung Cell Mol. Physiol.* 311, L135–L144.
- McConnell, R., Barrington-Trimis, J.L., Wang, K., Urman, R., Hong, H., Unger, J., Samet, J., Leventhal, A., Berhane, K., 2017. Electronic cigarette use and respiratory symptoms in adolescents. *Am. J. Respir. Crit. Care Med.* 195, 1043–1049.
- Muthy, V.H., 2017. E-cigarette use among youth and young adults: a major public health concern. *JAMA Pediatr.* 171, 209–210.
- Noordzij, M., van Diepen, M., Caskey, F.C., Jager, K.J., 2017. Relative risk versus absolute risk: one cannot be interpreted without the other. *Nephrol. Dial. Transplant.* 32, ii13–ii18.
- Pierannunzi, C., Hu, S.S., Balluz, L., 2013. A systematic review of publications assessing reliability and validity of the Behavioral Risk Factor Surveillance System (BRFSS), 2004–2011. *BMC Med. Res. Methodol.* 13, 49.
- Reidel, B., Radicioni, G., Clapp, P., Ford, A.A., Abdelwahab, S., Rebuli, M.E., et al., 2018. E-cigarette use causes a unique innate immune response in the lung involving increased neutrophilic activation and altered mucin secretion. *Am. J. Resp. Crit. Care Med.* 197, 492–501.
- Rowell, T.R., Reeber, S.L., Lee, S.L., Harris, R.A., Nethery, R.C., Herring, A.H., Glish, G.L., Tarraan, R., 2017. Flavored e-cigarette liquids reduce proliferation and viability in the CALU3 airway epithelial cell line. *Am. J. Physiol. Lung Cell Mol. Physiol.* 313, L52–L66.
- Rubin, D.B., 1987. *Multiple Imputation for Nonresponse in Surveys*. Wiley, New York, NY.
- Schafer, J.L., Graham, J.W., 2002. Missing data: our view of the state of the art. *Psychol. Methods* 7, 147–177.
- Schweitzer, R.J., Wills, T.A., Tam, E., Pagano, I., Choi, K., 2017. E-cigarette use and asthma in a multiethnic sample of adolescents. *Prev. Med.* 105, 226–231.
- Soneji, S., Barrington-Trimis, J., Wills, T.A., et al., 2017. E-cigarette use and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. *JAMA Pediatr.* 171, 788–797.
- St. Helen, G., Eaton, D.L., 2018. Public health consequences of e-cigarettes. *JAMA Intern. Med.* 7 (May). <https://doi.org/10.1001/jamainternmed.2018.1600>. 2018.
- Stratton, K., Kwan, L.Y., Eaton, D.L. (Eds.), 2018. *Public Health Consequences of E-Cigarettes: A Consensus Study Report of the National Academies of Science, Engineering, and Medicine*. National Academies Press, Washington, DC.
- Strong, D.R., Myers, M.G., Pulvers, K., Noble, M., Brikmanis, K., Doran, N., 2018. Marijuana use among US tobacco users: findings from wave 1 of the population assessment of tobacco health (PATH) study. *Drug Alcohol Depend.* 186, 16–22.
- Sussan, T.E., Gaghate, S., Thimmulappa, R.K., Ma, J., Kim, J.H., Sudini, K., et al., 2015. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PLoS One* 10, e0116861.
- Treuer, J.L., Rozema, A.D., Mathijssen, J.J.P., Oers, H., Vink, J.M., 2017. E-cigarette and waterpipe use in two Dutch adolescent cohorts: cross-sectional and longitudinal associations with conventional cigarette smoking. *Eur. J. Epidemiol.* 19 (December). <https://doi.org/10.1007/s10654017-0345-9>. 2017.
- U.S. Department of Health and Human Services, 2016. *E-Cigarette Use Among Youth and Young Adults: a Report of the Surgeon General*. U.S. Department of Health and

- Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA.
- von Mutius, E., Schwartz, J., Neas, L.M., Dockery, D., Weiss, S.T., 2001. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 56, 835–838.
- Wang, M.P., Ho, S.Y., Leung, L.T., Lam, T.H., 2016. Electronic cigarette use and respiratory symptoms in Chinese adolescents in Hong Kong. *JAMA Pediatr.* 170, 89–91.
- Watkins, S.L., Glantz, S.A., Chaffee, B.W., 2018. Association of noncigarette tobacco product use with future cigarette smoking among youth in the population assessment of tobacco and health (PATH) study, 2013–2015. *JAMA Pediatr.* 172, 181–187.
- Wills, T.A., Bantum, E.O., Pokhrel, P.A., et al., 2013. Dual-process model of substance use: tests in two diverse populations. *Health Psychol.* 32, 533–542.
- Wills, T.A., Knight, R., Williams, R., et al., 2015. Risk factors for exclusive e-cigarette use and dual e-cigarette and tobacco use in adolescents. *Pediatrics* 135, e43–e51.
- Wilson, F.A., Wang, Y., 2017. Recent findings on the prevalence of e-cigarette use among adults in the U.S. *Am. J. Prev. Med.* 52, 385–390.
- Wu, Q., Jiang, D., Minor, M., Chu, H.W., 2014. E-cigarette liquid increases inflammation and virus infection in primary human airway epithelial cells. *PLoS One* 9, e108342.
- Yao, T., Max, W., Sung, H., Glantz, S.A., Goldberg, R.L., Wang, J.B., et al., 2017. Relationship between spending on electronic cigarettes, 30-day use, and disease symptoms among current adult cigarette smokers in the U.S. *PLoS One* 12, e0187399.
- Zernike, K., 2018. Schools Struggle With Vaping Explosion. *New York Times* April 2, 2018.
- Zhao, S., Zhang, Y., Sisler, J.D., Shaffer, J., Leonard, S.S., Morris, A.M., Qian, Y., Bello, D., Demokritou, P., 2018. Assessment of reactive oxygen species generated by electronic cigarettes using acellular and cellular approaches. *J. Hazard. Mater.* 344, 549–557.