American Journal of
Preventive Medicine

RESEARCH ARTICLE

Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis

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Introduction: E-cigarettes deliver an aerosol of nicotine by heating a liquid and are promoted as an alternative to combustible tobacco. This study determines the longitudinal associations between e-cigarette use and respiratory disease controlling for combustible tobacco use.

Methods: This was a longitudinal analysis of the adult Population Assessment of Tobacco and Health Waves 1, 2, and 3. Multivariable logistic regression was performed to determine the associations between e-cigarette use and respiratory disease, controlling for combustible tobacco smoking, demographic, and clinical variables. Data were collected in 2013−2016 and analyzed in 2018−2019.

Results: Among people who did not report respiratory disease (chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or asthma) at Wave 1, the longitudinal analysis revealed statistically significant associations between former e-cigarette use (AOR=1.31, 95% CI=1.07, 1.60) and current e-cigarette use (AOR=1.29, 95% CI=1.03, 1.61) at Wave 1 and having incident respiratory disease at Waves 2 or 3, controlling for combustible tobacco smoking, demographic, and clinical variables. Current combustible tobacco smoking (AOR=2.56, 95% CI=1.92, 3.41) was also significantly associated with having respiratory disease at Waves 2 or 3. Odds of developing respiratory disease for a current dual user (e-cigarette and all combustible tobacco) were 3.30 compared with a never smoker who never used e-cigarettes. Analysis controlling for cigarette smoking alone yielded similar results.

Conclusions: Use of e-cigarettes is an independent risk factor for respiratory disease in addition to combustible tobacco smoking. Dual use, the most common use pattern, is riskier than using either product alone.

Am J Prev Med 2019;000(000):1−9.

INTRODUCTION

Respiratory diseases are leading causes of morbidity and mortality in the U.S.[1,2] Smoking is a major cause[3] and, like combustible tobacco products, e-cigarettes expose users to nicotine, ultrafine particles, and other toxicants.[4] Some pulmonary toxicants are in e-cigarette aerosol at higher levels than combusted cigarettes, including propylene glycol,[5] diacetyl[6,7] (butter flavor), cinnamaldehyde[8] (cinnamon), benzaldehyde (cherry), and metals.[9,10]

Animal studies found that e-cigarettes increase pulmonary inflammation and oxidative stress while inhibiting the immune response.[11] Repeated exposure to acrolein produced by heating propylene glycol and glycerin in e-liquids causes chronic pulmonary inflammation, reduction of host defense, neutrophil recruitment and activation, mucus hypersecretion, and protease-mediated lung tissue damage, which are linked to development of chronic obstructive pulmonary disease[12] (COPD). Mice exposed to nicotine e-cigarette aerosol exhibit increased

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0749-3797/$36.00
https://doi.org/10.1016/j.amepre.2019.07.028

airway and alveolar cell death and airspace enlargement similar to COPD,[13] and rats suffer emphysematous airspace enlargement and loss of lung vascular elements.[14] E-cigarette exposure depresses pulmonary immune defenses against viral and bacterial infection in mice.[15] Inhalation of nicotine e-cigarette aerosol disrupts airway barrier function and induces systemic inflammation in mice.[16] Consistent with these experimental results, people who use e-cigarettes experience decreased expression of immune-related genes in their nasal cavities, with more genes suppressed than among cigarette smokers, indicating immune suppression in the nasal mucosa.[17] E-cigarette use upregulates expression of platelet-activating factor receptor in users' nasal epithelial cells,[18] an important molecule involved in the ability of *Streptococcus pneumoniae*, the leading cause of bacterial pneumonia, to attach to cells that it infects. E-cigarette users exhibit significant increases in aldehyde detoxification− and oxidative stress−related proteins associated with cigarette smoke, providing additional evidence that e-cigarettes may adversely affect the profile of innate defense proteins in airway secretions similar to that observed among cigarette smokers.[19] Epithelial cells from human lung biopsy samples reveal that about 300 proteins are differentially expressed in smoker and e-cigarette user airways, with only 78 proteins commonly altered in both groups, suggesting that the propylene glycol/vegetable glycerin carrier used in e-cigarettes might explain the differences.[20]

Consistent with the biology, cross-sectional studies found associations between e-cigarettes and respiratory disease among children[21−23] and adults (Perez et al., 2018. E-cigarette use is associated with emphysema, chronic bronchitis and COPD. *In: American Thoracic Society 2018 International Conference*).[24] A longitudinal study of individuals with COPD found that e-cigarette use was associated with chronic bronchitis and COPD exacerbations and more rapid decline in lung function, adjusting for tobacco smoking.[25]

This paper uses the first 3 waves of the public use data files for the Population Assessment of Tobacco and Health (PATH) to determine the longitudinal association between e-cigarette use and respiratory diseases, controlling for combustible tobacco use and other risk factors in a large representative sample of U.S. adults.

METHODS

Data were collected in 2013−2016 and analyzed in 2018−2019.

Study Population

This study used the adult (aged ≥18 years) sample in PATH Waves 1 (September 2013 to December 2014), 2 (October 2014 to October 2015), and 3 (October 2015 to October 2016), a nationally representative, population-based, longitudinal study (Appendix Figure 1, available online). The weighted response rate at Wave 1 household screener was 54.0%; among screened households, the overall weighted response rate at Wave 1 adult interview was 74.0%. The weighted adult retention rates at Waves 2 and 3 were 83.2% and 78.4%, respectively. The University of California San Francisco Committee on Human Research ruled this study exempt.

Measures

Lung or respiratory disease at Wave 1 was assessed with the question: *Has a doctor or other health professional ever told you that you had any of the following lung or respiratory conditions? (yes or no): COPD, chronic bronchitis, emphysema, and asthma.* Respondents who answered *yes* to any of these questions were coded as having lung or respiratory disease at Wave 1.

Lung or respiratory disease at Waves 2 and 3 was assessed with the question: *In the past 12 months, has a doctor, nurse, or other health professional told you that you had any of the following lung or respiratory conditions? (yes or no): COPD, chronic bronchitis, emphysema, and asthma*. Respondents who answered *yes* to any of these questions were coded as having lung or respiratory disease at Wave 2 or 3.

Respondents who ever used an e-cigarette, ever used fairly regularly, and currently used every day or some days were considered current users. Respondents who reported that they ever used e-cigarettes but do not currently use e-cigarettes were considered former users. Respondents who reported that they have never used e-cigarettes, even once or twice, were considered never users.

Respondents who currently smoked cigarettes, traditional cigars, filtered cigars, cigarillos, pipe tobacco, or hookah every day or some days (regardless of whether they have smoked 100 cigarettes in their lifetime) were considered current combustible tobacco smokers. Respondents who ever smoked and currently do not smoke at all were classified as former smokers. Respondents who reported that they have never smoked, even 1 or 2 puffs, were classified as never smokers.

The same definitions were used to define conventional cigarette smoking status.

Demographic variables assessed at Wave 1 were age, BMI, sex (male or female), race/ethnicity (white, black, and other), and poverty level (below or above 100% of the poverty line).

In Wave 1, respondents who answered *yes* to *Has a doctor, nurse, or other health professional ever told you that you had high blood pressure?* were coded as having high blood pressure. Respondents who answered *yes* to *Has a doctor, nurse, or other health professional ever told you that you had high cholesterol?* were coded as having high cholesterol. Respondents who answered *yes* to *Has a doctor, nurse, or other health professional ever told you that you had diabetes, sugar diabetes, high blood sugar, or borderline diabetes?* were coded as having diabetes mellitus.

Statistical Analysis

Logistic regression was used to quantify cross-sectional association between e-cigarette use (former and current) and respiratory disease at Wave 1, controlling for combustible tobacco smoking (former and current), age, BMI, sex, poverty level, race/ethnicity, and clinical variables. The reference condition was people who had never used e-cigarettes or smoked combusted tobacco products (cigarettes in the subsidiary analysis).

Among respondents who did not report any respiratory disease at Wave 1, logistic regression was used to quantify the longitudinal association between e-cigarette use at Wave 1 and incident respiratory disease at either Wave 2 or Wave 3 combined, controlling for combustible tobacco smoking (former and current), age, BMI, sex, poverty level, race/ethnicity, and clinical variables at Wave 1. Waves 2 and 3 were combined to increase the number of events and the power of the study, essentially treating the study as a 2-year longitudinal follow up from baseline when e-cigarette use was assessed.

A separate analysis was performed on the effect of e-cigarette use on respiratory disease after controlling for cigarette smoking only, demographic, and clinical variables.

The PATH-provided different weights for the cross-sectional and follow up data sets were used as specified in the PATH Study user guide.[26] Survey package, version 3.33-2 in R was used for statistical analyses accounting for the complex survey design.

There are very little missing data in PATH. The number of dropped cases was only 1,028 (respiratory disease, *n*=127; e-cigarette users, *n*=42; any combustible tobacco smokers, *n*=774; conventional cigarette smokers, *n*=85), 5.3% of the sample. Given the very low level of missing data, list-wise deletion was used.

RESULTS

Table 1 shows baseline descriptive statistics and Appendix Table 1, available online, shows the relationships between e-cigarette use and combusted tobacco and cigarette smoking. A total of 5,466 (15.1%) adults reported that they had respiratory disease at baseline. Table 2 shows the descriptive statistics stratified by respiratory disease at Wave 1 and combined Waves 2 and 3. Appendix Table 2, available online, reports detailed information by specific diagnosis.

Among people who did not report respiratory disease at Wave 1, tobacco users who reported new respiratory disease at Waves 2 or 3 tended to be more addicted, as measured by shorter time to first tobacco product use and frequency of tobacco product use (Appendix Table 3, available online). There were no differences in use of flavored tobacco products (Appendix Table 4, available online).

Table 3 (left columns) shows the cross-sectional associations between e-cigarette use and having had respiratory disease at Wave 1 adjusting for combustible tobacco smoking, demographic, and clinical variables. The risk of having had respiratory disease was significantly associated with former e-cigarette use (AOR=1.34, 95% CI=1.23, 1.46) and current e-cigarette use (AOR=1.32, 95% CI=1.17, 1.49). The risk of having had respiratory disease was also significantly associated with former combustible tobacco smoking (AOR=1.29, 95% CI=1.14, 1.47) and current combustible tobacco smoking (AOR=1.61, 95% CI=1.42, 1.82). Effects of e-cigarette and all combustible tobacco use were independent risk factors for respiratory disease (variance inflation factors <1.2).

Table 1. Demographic, Clinical, and Tobacco Use Variables at Wave 1 Baseline (*n*=32,320)

Variables	Weighted %
Respiratory disease	
Yes	15.1
No	84.9
Tobacco use	
E-cigarette user	
Never	82.3
Former	12.2
Current	5.5
Combustible tobacco smoker	
Never	28.6
Former	45.4
Current	26.0
Cigarette smoker	
Never	33.2
Former	45.4
Current	21.4
Demographic	
Age in years	
18–24	13.1
25–34	17.7
35–44	16.5
45–54	17.9
55–64	16.6
65–74	11.1
75 and above	7.1
BMI (±SD), kg/m^2	28.00 (±6.8)
Sex	
Male	48.1
Female	51.9
Poverty level/income	
Below poverty (<100% of poverty guideline)	25.2
At or above poverty (≥100% of poverty guideline)	74.8
Race/ethnicity	
White	77.9
Black	12.3
Other	9.8
High blood pressure	
Yes	27.8
No	72.2
High cholesterol	
Yes	23.0
No	77.0
Diabetes mellitus	
Yes	14.0
No	86.0

Among people who did not report respiratory disease at Wave 1, the longitudinal analysis revealed statistically

Table 2. Respiratory Disease, Tobacco Use, Clinical and Demographic Variables

Variables	Respiratory disease		*p*-value
Wave 1 (*n*=32,320)			
E-cigarette user	Yes (*n*=5,457)	No (*n*=26,646)	
Never	3,123 (76.5)	17,511 (83.3)	<0.001
Former	1,590 (16.1)	6,248 (11.5)	
Current	744 (7.4)	2,887 (5.2)	
Combustible tobacco smoker	Yes (*n*=5,212)	No (*n*=25,467)	
Never	597 (22.0)	4,220 (29.7)	<0.001
Former	1,684 (46.1)	8,689 (45.4)	
Current	2,931 (31.9)	12,558 (24.9)	
Cigarette smoker	Yes (*n*=5,449)	No (*n*=26,581)	
Never	914 (25.9)	6,172 (34.5)	<0.001
Former	1,848 (46.3)	9,689 (45.3)	
Current	2,687 (27.9)	10,720 (20.2)	
Wave 2 or 3[a]			
E-cigarette user	Yes (*n*=1,116)	No (*n*=18,194)	
Never	635 (74.1)	12,114 (83.7)	<0.001
Former	314 (17.2)	4,188 (11.2)	
Current	167 (8.7)	1,892 (5.1)	
Combustible tobacco smoker	Yes (*n*=1,069)	No (*n*=17,464)	
Never	110 (21.9)	2,995 (30.1)	<0.001
Former	259 (36.8)	6,229 (46.1)	
Current	700 (41.3)	8,240 (23.8)	
Cigarette smoker	Yes (*n*=1,114)	No (*n*=18,152)	
Never	170 (25.9)	4,313 (34.8)	<0.001
Former	284 (37.0)	6,893 (46.1)	
Current	660 (37.1)	6,946 (19.1)	
Covariates at Wave 1			
Demographic			
Age in years			<0.001
18–24	1,461 (13.3)	7,622 (12.9)	
25–34	873 (14.4)	5,438 (18.3)	
35–44	752 (14.0)	4,168 (17.0)	
45–54	832 (16.2)	3,982 (18.2)	
55–64	843 (18.5)	3,114 (16.3)	
65–74	503 (14.8)	1,599 (10.4)	
75 and above	202 (8.8)	781 (6.8)	
BMI (±SD), kg/m^2	29.4 (±8.1)	27.8 (±7.2)	<0.001
Sex			
Male	2,344 (40.9)	13,898 (49.4)	<0.001
Female	3,122 (59.1)	12,811 (50.6)	
Poverty level/income			
Below poverty	1,954 (29.9)	7,950 (24.3)	<0.001
At or above poverty	2,990 (70.1)	16,207 (75.7)	
Race/ethnicity			
White	3,991 (78.5)	19,795 (77.8)	0.326
Black	843 (12.6)	4,178 (12.3)	
Other	632 (8.9)	2,736 (9.9)	
Clinical status			
High blood pressure			
Yes	1,765 (39.1)	5,334 (25.8)	<0.001
No	3,686 (60.9)	21,321 (74.2)	

(*continued on next page*)

Table 2. Respiratory Disease, Tobacco Use, Clinical and Demographic Variables (*continued*)

Variables	Respiratory disease		*p*-value
High cholesterol			
Yes	1,350 (31.2)	4,119 (21.5)	<0.001
No	4,101 (68.8)	22,536 (78.5)	
Diabetes mellitus			
Yes	971 (21.9)	2,601 (12.6)	<0.001
No	4,490 (78.1)	24,079 (87.4)	

Note: Numbers in parentheses are weighted percentages or SDs. Chi-square analysis was used for counts and *t*-test for continuous variables.
[a]Excluding respondents who had respiratory disease at Wave 1, *n*=19,475.

significant associations between former e-cigarette use (AOR=1.31, 95% CI=1.07, 1.60) and current e-cigarette use (AOR=1.29, 95% CI=1.03, 1.61) at Wave 1 and having incident respiratory disease at Waves 2 or 3 adjusting for combustible tobacco smoking, demographic, and clinical variables. Current combustible tobacco smoking (AOR=2.56, 95% CI=1.92, 3.41) was also significantly associated with having respiratory disease at Waves 2 or 3 (Table 3, right columns). Effects of e-cigarette and all combustible tobacco use were independent risk factors for respiratory disease (all variance inflation factors <1.2).

A supplemental analysis using cigarette smoking instead of any combustible tobacco product smoking also yielded statistically significant associations between former e-cigarette use (AOR=1.24, 95% CI=1.03, 1.50) and current e-cigarette use (AOR=1.23, 95% CI=1.00, 1.51) at Wave 1 and having incident respiratory disease at Waves 2 or 3 adjusting for demographic and clinical variables (Appendix Table 5, available online). Among the former cigarette smokers, 79.2% quit >1 year ago, 17.1% reported quitting in the past year, and the remaining 3.2% reported quitting in the last 30 days. Current cigarette smoking (AOR=2.70, 95% CI=2.12, 3.45) was also significantly associated with having respiratory disease at Waves 2 or 3. Effects of e-cigarette and conventional cigarette use were independent risk factors for respiratory disease (all variance inflation factors <1.2).

Consistent with existing literature, this study found increased risk of respiratory disease associated with hypertension[27,28] and diabetes[29] (Appendix Table 5, available online).

E-cigarette use at Wave 1 was associated with elevated point estimates of incidence of specific respiratory conditions (COPD, chronic bronchitis, emphysema, and asthma) at Waves 2 or 3. However, because of the small number of incidents at Wave 2 and 3, some of these point estimates did not reach statistical significance (Appendix Table 6, available online), which is why the primary analysis combined all the respiratory conditions (i.e., to increase statistical power). Pooling conditions also avoids the problem of double counting, as some of these respiratory diseases tend to occur together.

This study assessed the possibility of reverse causality by estimating the odds of initiating e-cigarette use by Wave 2 or 3 combined as a function of having respiratory disease at Wave 1 among people who had never used e-cigarettes at Wave 1 (Table 4). Having respiratory disease at Wave 1 significantly predicted future e-cigarette use ($p<0.001$).

DISCUSSION

This study is the first population-based longitudinal analysis of the association between e-cigarette use and incident respiratory disease, with current e-cigarette use elevating the odds of developing incident respiratory disease by a factor of 1.29 (95% CI=1.03, 1.61) in the longitudinal sample. The risk of respiratory disease is independent of, and in addition to, the risks associated with current combustible tobacco smoking (AOR=2.56, 95% CI=1.92, 3.41), as well as cigarettes alone. This finding is consistent with what would be expected based on animal[11–16] and human studies[17–20] of the biological effects of e-cigarettes as well as cross-sectional studies of e-cigarette use and respiratory illness[21–24] and a longitudinal study of people with COPD.[25] The risks that were identified in this longitudinal analysis were similar to the risks found in the cross-sectional analysis of PATH Wave 1 for e-cigarettes (AOR=1.29 for current users in the longitudinal analysis vs AOR=1.32 in the cross-sectional analysis; Table 3). The point estimate of risk was lower than the AOR (1.86; 95% CI=1.22, 2.83) Perez et al. (E-cigarette use is associated with emphysema, chronic bronchitis and COPD. *In: American Thoracic Society 2018 International Conference*) reported for the cross-sectional risk of COPD (including chronic bronchitis and emphysema), although the CIs overlap with

Table 3. Associations Between E-Cigarette Use and Respiratory Disease

	Cross-sectional associations between e-cigarette user and respiratory disease at Wave 1 (baseline)		Longitudinal association between incident respiratory disease (at Wave 2 or 3) and e-cigarette user at Wave 1 excluding people who reported respiratory disease at Wave 1	
Variables	**AOR (95% CI)**	***p*-value**	**AOR (95% CI)**	***p*-value**
E-cigarette user				
Never	ref		ref	
Former	**1.34 (1.23, 1.46)**	**<0.001**	**1.31 (1.07, 1.60)**	**0.009**
Current	**1.32 (1.17, 1.49)**	**<0.001**	**1.29 (1.03, 1.61)**	**0.026**
Combustible tobacco smoker				
Never	ref		ref	
Former	**1.29 (1.14, 1.47)**	**<0.001**	1.16 (0.87, 1.57)	0.315
Current	**1.61 (1.42, 1.82)**	**<0.001**	**2.56 (1.92, 3.41)**	**<0.001**
High blood pressure				
Yes	**1.40 (1.21, 1.61)**	**<0.001**	**1.27 (1.02, 1.58)**	**0.033**
High cholesterol				
Yes	**1.25 (1.11, 1.41)**	**<0.001**	1.04 (0.79, 1.38)	0.741
Diabetes mellitus				
Yes	**1.38 (1.20, 1.60)**	**<0.001**	1.30 (0.98, 1.72)	0.073
Age in years				
18–24	ref		ref	
25–34	**0.75 (0.67, 0.83)**	**<0.001**	**0.65 (0.49, 0.87)**	**0.004**
35–44	**0.74 (0.65, 0.85)**	**<0.001**	1.05 (0.80, 1.38)	0.741
45–54	**0.76 (0.66, 0.87)**	**<0.001**	**1.37 (1.08, 1.74)**	**0.012**
55–64	0.90 (0.76, 1.07)	0.242	1.33 (0.99, 1.78)	0.060
65–74	1.00 (0.84, 1.19)	0.993	1.22 (0.79, 1.88)	0.378
75 and above	1.05 (0.81, 1.36)	0.726	1.82 (1.02, 3.22)	0.044
BMI	**1.02 (1.02, 1.03)**	**<0.001**	**1.03 (1.02, 1.04)**	**<0.001**
Sex				
Female	**1.50 (1.37, 1.63)**	**<0.001**	**1.72 (1.41, 2.09)**	**<0.001**
Poverty level				
At or above poverty	**0.80 (0.72, 0.89)**	**<0.001**	**0.66 (0.54, 0.81)**	**<0.001**
Race/ethnicity				
White	ref		ref	
Black	0.89 (0.80, 1.01)	0.067	**1.39 (1.13, 1.72)**	**0.003**
Other	1.02 (0.85, 1.22)	0.837	1.15 (0.82, 2.11)	0.418
Sample size	32,320		19,475	
VIF	<1.2		<1.2	

Note: Boldface indicates statistical significance ($p<0.05$).
VIF, variance inflation factors.

this study estimates. Rather than doing a multivariate analysis, Perez and colleagues used propensity score matching to control for smoking, secondhand smoke exposure, and other covariates.

The finding that the effects of e-cigarettes and cigarette smoking were independent risks is consistent with the evidence of substantial differences in the proteins expressed in human lung epithelial cells derived from smoker and e-cigarette user airways.[20] Biomarker data from Wave 1 of PATH revealed higher levels of biomarkers of nicotine and toxicant exposure among dual users (e-cigarettes plus cigarettes) than smokers.[30] Levels among e-cigarette–only users were higher than for people who smoked but below levels of cigarette smokers.

Because the different products are independently associated with risk of developing pulmonary disease, it is possible to use the results in Table 3 to estimate the risks of other behaviors, including dual use and switching from combustible tobacco to e-cigarettes. For

Table 4. Reverse Causality Analysis: Longitudinal Predictors of Current E-Cigarette Use at Waves 2 or 3 as a Function of Reporting Respiratory Disease at Wave 1 Among Current Combustible Tobacco Smokers at Wave 1

Variables at Wave 1	AOR (95% CI)	*p*-value
Respiratory disease		
No	ref	
Yes	**1.44 (1.22, 1.70)**	**<0.001**
High blood pressure		
Yes	1.18 (0.95, 1.46)	0.130
High cholesterol		
Yes	0.88 (0.74, 1.06)	0.174
Diabetes mellitus		
Yes	1.16 (0.94, 1.44)	0.178
Age in years		
18–24	ref	
25–34	**0.59 (0.47, 0.73)**	**<0.001**
35–44	**0.43 (0.35, 0.53)**	**<0.001**
45–54	**0.24 (0.19, 0.30)**	**<0.001**
55–64	**0.18 (0.14, 0.23)**	**<0.001**
65–74	**0.11 (0.07, 0.15)**	**<0.001**
75 and above	**0.04 (0.01, 0.13)**	**<0.001**
BMI	0.99 (0.98, 1.00)	0.056
Sex		
Female	**1.46 (1.27, 1.68)**	**<0.001**
Poverty level/income		
At or above poverty	0.92 (0.80, 1.05)	0.232
Race/ethnicity		
White	ref	
Black	**0.51 (0.42, 0.62)**	**<0.001**
Other	0.90 (0.68, 1.17)	0.427
VIF	<1.2	
Total sample size	11,192	

Note: Boldface indicates statistical significance ($p<0.05$). Every day, some day, and current experimental users included.
VIF, variance inflation factors.

example, the total odds of developing respiratory disease among a former combustible tobacco smoker who currently uses e-cigarettes is (odds of respiratory disease among former combustible tobacco smoker) × (odds of respiratory disease among current e-cigarette user) = 1.16 × 1.29 = 1.50, compared with a never combustible tobacco smoker who has never used e-cigarettes. Thus, odds of developing respiratory disease for an individual who switched from combustible tobacco smoking to e-cigarette use would change by a factor of ([odds of respiratory disease among former combustible tobacco smoker] × [odds of respiratory disease among current e-cigarette user])/(odds of respiratory disease among current combustible tobacco smoker) = (1.16 × 1.29)/2.56 = 0.58. This result suggests that switching from combustible tobacco to e-cigarettes would lower risk of developing respiratory disease, but among combustible tobacco users who were not using e-cigarettes at Wave 1, only 0.9% of current e-cigarette users at Wave 2 and 0.8% at Wave 3 had switched exclusively to e-cigarettes. The numbers for cigarette smokers were 8.6% and 9.3%.

The much more common pattern is dual use, in which an e-cigarette user continues to smoke combusted tobacco products at the same time (93.7% of e-cigarette users at Wave 2 and 91.2% at Wave 3 also used combustible tobacco; 73.3% of e-cigarette users at Wave 2 and 64.9% at Wave 3 also smoked cigarettes). The total odds of developing respiratory disease for a current dual user is (odds of respiratory disease among current combustible tobacco smoker) × (odds of respiratory disease among current e-cigarette user) = 2.56 × 1.29 = 3.30 compared with a never smoker who never used e-cigarettes (which is similar to the direct estimate, AOR=3.04; Appendix Table 7, available online). The same situation applies to e-cigarettes and cigarettes (AOR=3.32). In other words, dual use of e-cigarettes and combustible tobacco (including cigarettes) is more dangerous than using either product alone.

The major strength of this study is that it is based on a large, nationally representative, randomly selected sample of the population, with longitudinal follow-up. The longitudinal design allows much stronger conclusions about causality than in earlier cross-sectional studies (although this study found similar risks for e-cigarettes in longitudinal and cross-sectional analyses). Another strength of the longitudinal component of the study is that the incident cases of respiratory disease occurred many years after e-cigarettes entered the market and information on new diagnoses was collected within a year of respondents being informed of their diagnoses.

Limitations

Several respiratory conditions were combined to obtain enough events to achieve adequate power. For the same reason, this study did not distinguish between daily and nondaily product use and included both established (smoked >100 cigarettes) and experimenters in the former smoker group.

There is a possibility of recall bias because use of e-cigarettes, conventional cigarettes, and other combustible tobacco products were self-reported as were clinical conditions. Participants with respiratory diseases might over-report e-cigarette, conventional cigarette, and other combustible tobacco use. There is also possibility of recall bias because doctor diagnoses of lung or respiratory diseases is reported by respondents rather than being based on actual hospital records but the questions. However, the question *Has a doctor or other health professional ever told you that you had any of the following lung or respiratory conditions: COPD, chronic bronchitis,*

emphysema, and asthma? is used widely in epidemiologic studies, including other federal surveys such as the National Health Interview Survey. This question has been validated against direct clinical observation in at least 2 studies; one reported that 98% of patients had clinically or spirometrically validated among self-reported diagnosis of COPD[31] and another found clinical validation in 83%, 84%, and 90% of nurses self-reporting diagnoses of COPD.[32] Research to validate analogous questions about myocardial infarction also found high agreement (81%−98%) with medical records.[33,34] The longitudinal follow-up was only 2 years, but COPD has been detected in people after 1−9 years of smoking.[35] In addition, this study examined incident cases, which may have been developing for some time before symptoms were manifest. The similarity of the cross-sectional and longitudinal estimates supports this idea.

As noted above, this study found $p<0.001$ for reverse causality, which could be consistent with a hypothesis that some individuals with respiratory disease try e-cigarettes believing they might be therapeutic. This study limited to control for intensity and type of e-cigarette use, which could affect the respiratory outcome. There is also always the possibility that other important confounders were not measured in the PATH study.

CONCLUSIONS

Current use of e-cigarettes appears to be an independent risk factor for respiratory disease in addition to all combustible tobacco smoking. Although switching from combustible tobacco, including cigarettes, to e-cigarettes theoretically could reduce the risk of developing respiratory disease, current evidence indicates a high prevalence of dual use, which is associated with increased risk beyond combustible tobacco use. In addition, for most smokers, using an e-cigarette is associated with lower odds of successfully quitting smoking.[4,36] E-cigarettes should not be recommended.

ACKNOWLEDGMENTS

This work was supported by grants R01DA043950 from the National Institute on Drug Abuse; P50CA180890 from the National Cancer Institute and the U.S. Food and Drug Administration Center for Tobacco Products; U54HL147127 from the National Heart, Lung, and Blood Institute and the Food and Drug Administration Center for Tobacco Products; and the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center Global Cancer Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH or the Food and Drug Administration. The funding agencies played no role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit for publication.

Author contributions: Concept and design, analysis or interpretation of data: DNB, SAG. Drafting of the manuscript: DNB. Critical revision of the manuscript: SAG.

No financial disclosures were reported by the authors of this paper.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2019.07.028.

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