ORIGINAL RESEARCH

Electronic Cigarette Use and Myocardial Infarction Among Adults in the US Population Assessment of Tobacco and Health

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Background—E-cigarettes are popular for smoking cessation and as an alternative to combustible cigarettes. We assess the association between e-cigarette use and having had a myocardial infarction (MI) and whether reverse causality can explain the observed cross-sectional association between e-cigarette use and MI.

Methods and Results—Cross-sectional analysis of the Population Assessment of Tobacco and Health Wave 1 for association between e-cigarette use and having had and MI. Longitudinal analysis of Population Assessment of Tobacco and Health Waves 1 and 2 for reverse causality analysis. Logistic regression was performed to determine the associations between e-cigarette initiation and MI, adjusting for cigarette smoking, demographic and clinical variables. Every-day (adjusted odds ratio, 2.25, 95% CI: 1.23–4.11) and some-day (1.99, 95% CI: 1.11–3.58) e-cigarette use were independently associated with increased odds of having had an MI with a significant dose-response ($P<0.0005$). Odds ratio for daily dual use of both products was 6.64 compared with a never cigarette smoker who never used e-cigarettes. Having had a myocardial infarction at Wave 1 did not predict e-cigarette use at Wave 2 ($P>0.62$), suggesting that reverse causality cannot explain the cross-sectional association between e-cigarette use and MI observed at Wave 1.

Conclusions—Some-day and every-day e-cigarette use are associated with increased risk of having had a myocardial infarction, adjusted for combustible cigarette smoking. Effect of e-cigarettes are similar as conventional cigarette and dual use of e-cigarettes and conventional cigarettes at the same time is risker than using either product alone. **(*J Am Heart Assoc.* 2019;8:e012317. DOI: 10.1161/JAHA.119.012317.)**

Key Words: e-cigarettes • epidemiology • myocardial infarction • smoking

Cardiovascular disease is the leading cause of death in the United States[1] and tobacco smoking is a major modifiable risk factor for cardiovascular disease, including myocardial infarction.[2] The risk of myocardial infarction is 2- to 5-fold higher among young smokers compared with never smokers,[2,3] with a non-linear dose-response curve with even the low levels of exposure associated with smoking a single cigarette a day[4] or breathing secondhand smoke conferring substantial risk.[5]

E-cigarettes are promoted as a smoking cessation device and less dangerous way to self-administer nicotine than conventional cigarettes[6,7] and people with cardiovascular disease are using e-cigarettes as a smoking cessation aid.[8] Like conventional cigarettes, e-cigarettes deliver nicotine as an inhaled aerosol of nicotine and ultrafine particles.[9] Fine particles increase cardiovascular risk.[10] E-cigarettes and combustible cigarettes have similar effects on endothelial function which increases the risk of cardiovascular disease.[11–15] E-cigarettes increase oxidative stress and the release of inflammatory mediators,[11,16] induce platelet activation, aggregation, and adhesion[17] and alters cardiovascular function in mice.[18–20] Acute exposure to electronic cigarettes with nicotine increases aortic stiffness[21] and cardiac sympathetic tone (reflected in heart rate variability) in a way associated with increased cardiac risk.[13] Nevertheless, the 2018 National Academies of Science, Engineering, and Medicine report *Public Health Consequences of E-Cigarettes*[22] observed that "there are no epidemiological studies evaluating clinical outcomes such as coronary heart disease . . .. This lack of data on e-cigarettes and clinical and subclinical

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Accompanying Tables S1 through S6 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012317

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Clinical Perspective

What Is New?

- Both e-cigarettes and combustible cigarettes are independently associated with increased risk of myocardial infarction.
- Dual use of e-cigarettes and combustible cigarettes is riskier than using either product alone and switching from combustible cigarettes to e-cigarettes is not associated with lower risk of myocardial infarction than continuing to smoke; complete cessation is the only way to reduce risk of myocardial infarction.
- These results are unlikely becauseof reverse causality, where smokers who had myocardial infarctions started using e-cigarettes in an effort to quit smoking.

What Are the Clinical Implications?

- E-cigarettes should not be promoted or prescribed as a less risky alternative to combustible cigarettes and should not be recommended for smoking cessation among people with or at risk of myocardial infarction.

atherosclerotic outcomes represents a major research need." Since then, 2 studies, 1 using data from the National Health Interview Survey[23] and another using data from the Behavioral Risk Factors Surveillance Survey,[24] found cross-sectional associations between e-cigarette use and having had a myocardial infarction among daily e-cigarette users controlling for cigarette smoking and other risk factors. Nevertheless, this finding remains controversial, because of concerns about reverse causality based on the possibility that after having a myocardial infarction smokers switched to e-cigarettes, which would induce a spurious association between e-cigarette use and myocardial infarction.[25,26] We use the Population Assessment of Tobacco and Health[27] (PATH) data set to test for the relationship between e-cigarette use and myocardial infarction, controlling for cigarette use, demographic and clinical variables and use the longitudinal data from PATH to test the reverse causality hypothesis.

Methods

Study Population and Design

We used PATH Waves 1 and 2 (Figure S1), a nationally representative population-based longitudinal cohort study to collect data on uses of tobacco products, health outcomes, risk perception, and attitudes.[27] The restricted use PATH data set is available at the University of Michigan National Addiction & HIV Data Archive Program.[28] The Wave 1 data set contained 32 320 adults aged ≥18 years and 28 362 adults in Wave 2, of whom 26 447 completed a Wave 1 interview. Wave 1 data were collected from September 2013 to December 2014 and Wave 2 data were collected 1 year later (from October 2014 to October 2015). PATH uses a 4-stage stratified probability sample technique. The weighted response rate at Wave 1 household screener was 54.0%; among screened households, overall weighted response rate at Wave 1 adult interview was 74.0%. The weighted retention rate for continuing adult at Wave 2 was 83.1%, and the weighted recruitment rate including youth aged <18 years at Wave 1 and ≥18 years (and so counted as adults at Wave 2) was 85.7%.[28] Informed consent was obtained by PATH. The University of California San Francisco (UCSF) Committee on Human Research approved this study.

Outcome Variables

Wave 1: Participants who responded "Yes" to the question "Has a doctor, nurse, or other health professional ever told you that you had a heart attack (myocardial infarction)?" were considered as having had a myocardial infarction.

Wave 2: Participants who responded "Yes" to the question "In the past 12 months, has a doctor, nurse, or other health professional told you that you had a heart attack (myocardial infarction)?" were considered as having had a myocardial infarction.

Independent Variables

Electronic cigarette use

Respondents who reported that they have ever used e-cigarettes, have used fairly regularly, and currently use every day were classified as "Every-day users." Respondents who reported that they have ever used e-cigarettes, have used fairly regularly, and currently use some days were considered as "Some-day users." Respondents who reported that they have ever used e-cigarettes and currently do not use them were considered "Former users." Respondents who reported that they have never used e-cigarettes, even once or twice were considered "Never users." Current experimental e-cigarette users (current e-cigarette users but never used e-cigarettes fairly regularly) were not included in the main analysis but were considered some-day users in a sensitivity analysis.

Cigarette smoking

Respondents who reported that they smoked at least 100 cigarettes in their lifetime and currently smoke every day were classified as "Every-day smokers." Respondents who reported that they smoked at least 100 cigarettes in their lifetime and currently smoke some days were classified as "Some-day smokers." Respondents who ever smoked cigarettes and have not smoked in the past 12 months or currently do not smoke at all were classified as "Former smokers." Respondents who reported that they have never smoked a cigarette, even 1 or 2 puffs were classified as "Never smokers." Respondents who were current smokers but who had not smoked 100 cigarettes (experimental smokers) were excluded from the main analysis, but included in a sensitivity analysis as some-day smokers.

Demographic variables

Demographic variables were assessed at Wave 1: age, body mass index (BMI), sex (men or women), race/ethnicity (white, black, Asian, and others), poverty level/income (below poverty: <100% of poverty line, at or above poverty: ≥100% of poverty line [poverty was calculated using this formula: [effective family income]/[poverty guideline]×100=family income as a percentage of the household size poverty guideline.]) and education.

Clinical variables

Wave 1: Respondents who answered "Yes" to the question "Has a doctor, nurse, or other health professional ever told you that you had a high blood pressure?" were considered as having "high blood pressure." Respondents who answered "Yes" to the question "Has a doctor, nurse or other health professional ever told you that you had a high cholesterol?" were considered as having "high cholesterol." Respondents who answered "Yes" to the question "Has a doctor, nurse, or other health professional ever told you that you had a diabetes, sugar diabetes, high blood sugar, or borderline diabetes?" were considered as having "diabetes mellitus."

Wave 2: Respondents who answered "Yes" to the question "In the past 12 months, has a doctor, nurse or other health professional told you that you had a high blood pressure?" were considered as having "high blood pressure." Respondents who answered "Yes" to the question "In the past 12 months, has a doctor, nurse, or other health professional told you that you had a high cholesterol?" were considered as having "high cholesterol". Respondents who answered "Yes" to the question "In the past 12 months, has a doctor, nurse, or other health professional told you that you had a diabetes, sugar diabetes, high blood sugar, or borderline diabetes?" were considered as having "diabetes mellitus."

Analysis

We calculated weighted estimates of e-cigarette and cigarette use and clinical and demographic variables at Wave 1 for the overall sample. We used Wave 1 sampling weights for analysis of Wave 1 and Wave 2 sampling weights for analysis of Wave 2[28] accounting for the complex survey design for all the outcomes.[29]

Multivariable logistic regressions were performed to examine the associations between e-cigarette use (former, some day and every day) and myocardial infarction at Wave 1 controlling for cigarette smoking (former, some day and every day), age, BMI, sex, poverty level, race/ethnicity, education, and clinical variables.

We tested for interaction between e-cigarette use and cigarette smoking in a logistic regression by combining some-day and every-day users into "current e-cigarette use" and "current smoking," then ran the logistic regression with these variables, their interaction, and the demographic and clinical variables. The *P* value for the interaction was 0.671. Likewise, we analyzed interaction for "former e-cigarette use" and "former smoking", and *P* value for this model was 0.192. As a result, interaction terms were omitted from the remaining analysis.

We tested for dose-response by replacing the categorical use variables with continuous variables (0=never, 1=former, 2=some day, 3=every day) in logistic regressions including the demographic and clinical variables.

We assessed the possibility of reverse causality accounting for the observed association between having had a myocardial infarction at Wave 1 being due to people who had a myocardial infarction preferentially trying to quit smoking with e-cigarettes. Specifically, we used logistic regression to predict every day e-cigarette use at Wave 2 as a function of having had a myocardial infarction at Wave 1 adjusting for age, BMI, sex, poverty level, and race/ethnicity among only every day, and only current (every day and some day) cigarette smoker at Wave 1 (excluding all e-cigarette users) as well as in the entire longitudinal sample.

We used "survey package" in R software for statistical analyses.

Results

Table 1 shows the descriptive statistics at Wave 1 baseline; 643 (2.4%) adults reported that they had a myocardial infarction. Table 2 shows the descriptive statistics stratified by myocardial infarction status at Wave 1 and first myocardial infarctions between Waves 1, 2, and 3 and Table S1 shows the descriptive statistics stratified by e-cigarette use at Wave 1. Among the adults who had myocardial infarctions as of Wave 1, 10.2% reported that they were former e-cigarette users, 1.6% were some-day e-cigarette users and 1.5% were every-day e-cigarette users, 58.8% adults reported that they were former cigarette smokers, 3.4% were some-day cigarette smokers and 20.4% were every-day cigarette smokers. The number of e-cigarette users who had first

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

Variables	Weighted Percentage
Myocardial infarction	
Yes	2.4
Tobacco use	
E-cigarette user	
Never	85.0
Former	12.6
Some day	1.4
Every day	1.0
Cigarette smoker	
Never	34.3
Former	46.9
Some day	3.8
Every day	15.0
Dual users*	69.0%
Demographic	
Age in y, mean (±SD)	46.7 (17.9±SD)
Body mass index (±SD) kg/m^2	28.0 (7.5±SD)
Sex	
Men	48.1
Women	51.9
Poverty level/income	
Below poverty (<100% of poverty guideline)	25.2
Race/ethnicity	
White alone	77.8
Black alone	12.4
Asian alone	5.5
Other, including multiracial	4.3
Education	
Less than high school	4.5
High school or equivalent	36.6
Some college and associate	31.0
Bachelor and advanced degree	27.9
High blood pressure	
Yes	27.8
High cholesterol	
Yes	23.0
Diabetes mellitus	
Yes	14.0

*Current (every day+some day) dual users=current cigarette smoker used e-cigarette at Wave 1/current e-cigarette user at Wave 1.

myocardial infarctions between Waves 1 and 2 (only 6 some-day and 2 every-day e-cigarette users) and Waves 2 and 3 (only 1 some-day and 3 every-day e-cigarette users) was small, so, as required by PATH reporting rules, we combined some-day and every-day e-cigarette users in Table 2 for the first myocardial infarction between Waves 1 and 2, and Waves 2 and 3.

The cross-sectional multivariable analysis of the relationship between e-cigarette use and having had a myocardial infarction at Wave 1 (Table 3) adjusting for cigarette smoking, demographic, and clinical variables yielded significant increases in the odds of having had a myocardial infarction for some-day e-cigarette users (adjusted odds ratio, 1.99, 95% CI: 1.11–3.58) and every-day e-cigarette users (adjusted odds ratio, 2.25, 95% CI: 1.23–4.11) The risk of having had a myocardial infarction was not significantly elevated in former e-cigarette users (adjusted odds ratio, 1.25, 95% CI: 0.93–1.69). All variance inflation factors were <1.1, indicating that the effects of e-cigarette and conventional cigarette use were independent risk factors for myocardial infarction.

As expected, any cigarette smoking, age, BMI, sex, poverty level, education, and high blood pressure, high cholesterol, and diabetes mellitus were significantly associated with increased risk of myocardial infarction.

There was a significant dose-response for both e-cigarette use (P<0.0005) and smoking (P=0.019) and myocardial infarction controlling for demographic and clinical variables (detailed results not shown).

The longitudinal analysis did not reveal any statistically significant associations between e-cigarette use at Wave 1 and having had a first myocardial infarction by Wave 2, perhaps because of the small numbers of first myocardial infarctions in e-cigarette users between Waves 1 and 2 (Table S2). Daily cigarette smoking was also not significantly associated with having had a first myocardial infarction at Wave 2.

The sensitivity analysis including current experimental e-cigarette user with some-day e-cigarette user and current experimental cigarette smokers with some-day cigarette smokers yielded similar results as the main analysis (Table S3).

Reverse Causality

There were 1990 respondents who started using e-cigarettes between Waves 1 and 2 (Table 4). Having had a myocardial infarction at Wave 1 did not predict every-day e-cigarette use at Wave 2 among overall follow-up sample (P=0.687), every-day cigarette smokers at Wave 1 (P=0.675), or current cigarette smokers at Wave 1 (P=0.634), adjusting for demographic and clinical variables. Similar results were

Table 2. Myocardial Infarctions, Tobacco Use, Clinical, and Demographic Variables

Variables (at Wave 1)	Myocardial Infarction at Wave 1 (All Respondents)		
Tobacco Use	Yes (n=643)	No (n=31 531)	*P* Value*
E-cigarette user	Weighted percent		
Never	86.7	85.0	0.073
Former	10.2	12.6	
Some day	1.6	1.4	
Every day	1.5	1.0	
Cigarette smoker			
Never	17.4	34.7	<0.001
Former	58.8	46.6	
Some day	3.4	3.9	
Every day	20.4	14.8	
	Myocardial infarction at Wave 1 (excluding dual users)		
E-cigarette use only (n=18 294)	Yes	No	
Never	96.0	93.4	0.017
Former	2.7	5.7	
Some day	0.3	0.3	
Every day	1.0	0.6	
Cigarette smoker only (n=26 652)			
Never	18.5	36.4	<0.001
Former	61.2	48.1	
Some day	2.5	3.2	
Every day	17.8	12.3	
	First Myocardial Infarction Between Waves 1 and 2 (Excluding Respondents Who Had MI at Wave 1)		
Tobacco Use	Yes (n=117)	No (n=25 609)	*P* Value*
E-cigarette user			
Never	86.5	84.9	0.645
Former	10.4	12.6	
Some day+every day[†]	3.1	2.5	
Cigarette smoker			
Never	7.8	34.0	<0.001
Former	68.8	47.6	
Some day	5.5	3.8	
Every day	18.3	14.6	
	First Myocardial Infarction Between Waves 2 and 3 (Excluding Respondents Who Had MI at Wave 1)		
Tobacco Use	Yes (n=89)	No (n=22 967)	*P* Value*
E-cigarette user			
Never	89.1	84.9	0.410
Former	9.2	12.6	
Some day+every day[†]	1.7	2.5	

Continued

Table 2. Continued

Variables (at Wave 1)	Myocardial Infarction at Wave 1 (All Respondents)		
Tobacco Use	Yes (n=643)	No (n=31 531)	*P* Value*
Cigarette smoker			
Never	20.3	34.6	0.107
Former	61.1	47.0	
Some day	2.1	3.8	
Every day	16.5	14.7	
Demographics (at Wave 1)			
Age in y, mean (±SD)	66.5 (±13.17)	46.1 (±17.7)	<0.001
Body mass index (±SD) kg/m^2	29.7 (±10.2)	28.0 (±7.4)	<0.001
Sex			
Men	71.1	47.5	<0.001
Women	28.9	52.5	
Poverty level/income			
Below poverty	24.8	25.2	0.885
At or above poverty	75.2	74.8	
Race/ethnicity			
White	84.3	77.7	<0.001
Black	10.5	12.4	
Asian	0.9	5.6	
Other	4.3	4.3	
Education			<0.001
Less than high school	11.7	4.3	
High school or equivalent	461	36.3	
Some college and associate	28.1	31.2	
Bachelor and advanced degree	14.1	28.2	
Clinical status			
High blood pressure			
Yes	72.5	26.8	<0.001
High cholesterol			
Yes	67.7	21.9	<0.001
Diabetes mellitus			
Yes	39.6	13.4	<0.001

*Chi-square for counts, *t* test for continuous variables.
†Some-day and every-day e-cigarette users combined because PATH does not allow reporting results for cell sizes <3, and there were only 2 everyday e-cigarette users who had first myocardial infarctions between Waves 1 and 2 and only 3 every-day e-cigarette users who had first myocardial infarctions between Waves 2 and 3. Wave 1 data were collected from September 2013 to December 2014, Wave 2 from October 2014 to October 2015, and Wave 3 from October 2015 to October 2016.

obtained for any e-cigarette use (every day or some day) at Wave 2 (Table S4).

Discussion

This study confirms earlier[23,24] findings that e-cigarette use is an independent risk factor for having had a myocardial infarction controlling for cigarette smoking, demographic and clinical risk factors. The magnitudes of the effects in this study are similar to the updated analysis by Alzahrani and Glantz[30] using the 2014, 2015, and 2016 from the National Health Interview Survey (some-day e-cigarette user [odds ratio: 1.99, 95% CI: 1.11–3.58 in this study versus 1.49: 1.08–2.09 in Alzahrani et al] and every-day e-cigarette user

Table 3. Adjusted Odds Ratios for Myocardial Infarction at Wave 1

Variables	AOR (95% CI)	*P* Value
E-cigarette use		
Never	Reference	
Former	1.25 (0.93–1.69)	0.147
Some day	1.99 (1.11–3.58)	0.024
Every day	2.25 (1.23–4.11)	0.010
Cigarette use		
Never	Reference	
Former	1.48 (1.01–2.15)	0.047
Some day	2.38 (1.40–4.06)	0.002
Every day	2.95 (1.91–4.56)	<0.001
High blood pressure		
Yes	2.08 (1.56–2.77)	<0.001
High cholesterol		
Yes	3.01 (2.31–3.92)	<0.001
Diabetes mellitus		
Yes	1.49 (1.09–2.03)	0.013
Age in y	1.07 (1.06–1.08)	<0.001
Body mass index, kg/m^2	1.02 (1.00–1.03)	0.016
Sex		
Women	0.27 (0.18–0.39)	<0.001
Poverty level/income		
At or above poverty	0.72 (0.49–1.04)	0.086
Race/ethnicity		
White	Reference	
Black	0.86 (0.63–1.16)	0.324
Asian	0.31 (0.07–1.38)	0.127
Other	1.37 (0.83–2.25)	0.226
Education		
Less than high school	1.49 (1.05–2.13)	0.030
High school or equivalent	Reference	
Some college and associate	0.97 (0.72–1.29)	0.814
Bachelor and advanced degree	0.62 (0.44–0.87)	0.007
Sample size	32 320	
VIF	<1.1	

Adjusted odds ratio adjusts for cigarette smoking (former, some day and every day), age, body mass index, sex, poverty level, race/ethnicity, education, and clinical variables. VIF indicates variance inflation factor.

[2.25: 1.23–4.11 versus 2.14: 1.41–3.25]). Odds of myocardial infarction among former e-cigarette users are not significantly elevated in either study. The increased odds of myocardial infarction are similarly and significantly associated with smoking in both studies, with higher estimates in the present study (former [1.48: 1.01–2.15 versus 1.70: 1.51–1.91], some day [2.38: 1.40–4.06 versus 2.36; 1.80–3.09] and every day [2.95: 1.91–4.56 versus 2.72: 2.29–3.24]). Vindhyal et al[31] reported that e-cigarette use is significantly associated with MI (odds ratio [OR] 1.56 [1.45–1.68]), stroke (OR 1.30 [1.20–1.40]), and circulatory problems (OR 1.44 [1.25–1.65]) using the 2014, 2016, and 2017 National Health Interview Survey. Ndunda and Muutu[24] found that compared with non-users, e-cigarette users (without specifying frequency of use, but controlling for smoking and other risk factors) the odds of having had a myocardial infarction (OR 1.59 [1.53–1.66]) that was lower than in this study, although the CIs overlapped. They also found higher risks for angina or coronary heart disease (OR 1.4 [1.35–1.46]) and stroke (OR 1.71 [1.64–1.8]) using 2016 Behavioral Risk Factor Surveillance System.

Both the present and earlier[23,24] results are based on cross-sectional analysis, which raises the possibility of reverse causality,[25,26] specifically that after having had a myocardial infarction people might preferentially attempt to quit smoking using e-cigarettes. In a cross-sectional analysis of the National Health Interview Survey, Stokes et al[8] reported that individuals with cardiovascular disease who recently quit smoking or recently attempt to quit were more likely to use e-cigarettes than those who did not report a recent quit attempt, which may indicate that e-cigarettes were being used for smoking cessation. We used the longitudinal data in PATH to test directly for reverse causality by testing whether having had a myocardial infarction at Wave 1 predicted e-cigarette use at Wave 2 among people who were cigarette smokers at Wave 1 (Table 4). The results did not approach statistical significance (P>0.62 for all outcomes), strongly suggesting that reverse causality is not an issue. In addition, the presence of a statistically significant dose-response is consistent with a causal effect.

Our results on the lack of reverse causality are consistent with Gaalema et al[32] who concluded based on longitudinal analysis of the first 2 waves of PATH, that having a myocardial infarction was not a significant predictor of initiating non-combusted tobacco (mostly e-cigarettes) use (P=0.20). Furthermore, they found, "cardiac status was significantly negatively associated with switching completely from combusted to non-combusted products. While 9.2% of those with no change in health status switched (from combusted tobacco, mostly cigarettes) to non-combusted use, none of those experiencing a new MI switched (P=0.0015)." Thus, any differential misclassification is in the direction opposite to what would be required for reverse causality to explain our results, which strengthens our conclusion that e-cigarette use is associated with the risk of having had an MI. Our finding is also consistent with Alzahrani et al's[26] cross-sectional analysis of reverse causality using the National Health Interview Survey, which found a non-significant

Table 4. Reverse Causality Analysis: Adjusted Odds Ratios for Every Day e-Cigarette Use at Wave 2*

Variables at Wave 1	Among Overall Follow-Up Sample		Among Every-Day Cigarette Smoker at Wave 1†		Among Current Cigarette Smoker at Wave 1†	
	AOR (95% CI)	*P* Value	AOR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
MI						
No	Reference		Reference		Reference	
Yes	0.85 (0.38–1.90)	0.687	0.80 (0.28–2.26)	0.675	0.79 (0.30–2.07)	0.634
High blood pressure						
Yes	1.08 (0.83–1.41)	0.550	0.89 (0.63–1.26)	0.526	0.88 (0.64–1.21)	0.422
High cholesterol						
Yes	1.08 (0.79–1.47)	0.618	1.38 (0.94–2.03)	0.106	1.54 (1.08–2.18)	0.019
Diabetes mellitus						
Yes	0.92 (0.61–1.38)	0.684	0.96 (0.66–1.40)	0.820	0.95 (0.65–1.38)	0.775
Age	0.97 (0.96–0.98)	<0.001	0.97 (0.96–0.98)	<0.001	0.98 (0.97–0.99)	<0.001
Body mass index, kg/m^2	0.99 (0.98–1.00)	0.147	1.00 (0.99–1.02)	0.735	1.00 (0.98–1.01)	0.847
Sex						
Women	0.72 (0.59–0.89)	0.002	0.81 (0.60–1.10)	0.183	0.83 (0.64–1.09)	0.195
Poverty level/income						
At or above poverty	1.01 (0.80–1.28)	0.918	1.36 (1.04–1.78)	0.028	1.26 (0.98–1.62)	0.077
Race/ethnicity						
White	Reference		Reference		Reference	
Black	0.28 (0.18–0.43)	<0.001	0.24 (0.12–0.51)	<0.001	0.26 (0.14–0.50)	<0.001
Asian	0.31 (0.13–0.73)	0.009	0.18 (0.02–2.07)	0.171	0.24 (0.04–1.51)	0.133
Other	0.92 (0.63–1.35)	0.683	0.97 (0.53–1.76)	0.916	0.93 (0.53–1.63)	0.804
Education						
Less than high school	0.62 (0.38–1.00)	0.056	0.95 (0.48–1.89)	0.884	0.83 (0.44–1.56)	0.565
High school or equivalent	Reference		Reference		Reference	
Some college and associate	1.03 (0.82–1.28)	0.814	1.26 (0.96–1.66)	0.099	1.15 (0.90–1.48)	0.257
Bachelor and advanced degree	0.40 (0.28–0.56)	<0.001	1.38 (0.84–2.29)	<0.001	1.01 (0.67–1.52)	0.973
VIF	<1.1		<1.1		<1.1	
Number of new e-cigarette users between Waves 1 and 2	1990		776		946	
Sample size	26 447		7378		9284	
Minimum detectable effect (OR)‡	1.51		1.39		1.35	

Adjusted odds ratio (AOR) adjusts for age, BMI, sex, poverty level, race/ethnicity, education, and clinical variables. BMI indicates bone mass index; OR, odds ratio; VIF, variance inflation factor.
*Some-day and former e-cigarette users excluded from the analysis.
†Excluding e-cigarette users.
‡To achieve 0.80 power with α=0.005 (2-tail) with observed sample size calculated using GPower 3.1.92.

association between MI and e-cigarette use when controlling for covariates.

Like Alzahrani et al,[23,30] we found that the increased odds of having had a myocardial infarction associated with e-cigarette use were independent of the increased odds associated with smoking. This result means that dual use of e-cigarettes and conventional cigarettes, the most common use pattern for e-cigarette users, is more dangerous than use of either product alone (69% of current e-cigarette users were also smoking cigarettes in our sample at Wave 1, which is similar to the 70% Stokes et al[8] reported among people with cardiovascular disease in the National Health Interview Survey). For example, the total odds of having had a myocardial infarction among every-day cigarette smokers who also use e-cigarettes every day (dual users)—the most common use pattern (Table 1)—is (odds of myocardial infarction among every-day smokers)× (odds of myocardial infarction among every-day e-cigarette user)=2.95×2.25=6.64 compared with a never cigarette smoker who has never used e-cigarettes (which is similar from additional regression analysis estimating the effect directly, Adjusted Odds Ratio (AOR): 5.06, 95% CI: 1.99–12.83, Table S5). Odds of having had a myocardial infarction for individuals who switched from every-day combustible cigarette smoking to every-day e-cigarette use would change by a factor of ([odds of myocardial infarction among former combustible cigarette smokers]×[odds of myocardial infarction among every-day e-cigarette user])/(odds of myocardial infarction among every-day combustible cigarette smoker) =3.33/2.95=1.13, which is virtually no benefit in terms of myocardial infarction risk. More importantly, the total odds of having had a myocardial infarction for an individual who switched from every-day combustible cigarette smoking to every-day e-cigarette use compared with quitting smoking would be ([odds of myocardial infarction among former smokers]×[odds of myocardial infarction among every-day e-cigarette user])/(odds of myocardial infarction among former cigarette smokers)=(1.48×2.25)/1.48=2.25.

As discussed above, we cannot infer temporality from the cross-sectional finding that e-cigarette use is associated with having had an MI and it is possible that first MIs occurred before e-cigarette use. PATH Wave 1 was conducted in 2013 to 2014, only a few years after e-cigarettes started gaining popularity on the US market around 2007. To address this problem we used the PATH questions "How old were you when you were first told you had a heart attack (also called a myocardial infarction) or needed bypass surgery?" and the age when respondents started using e-cigarettes and cigarettes (1) for the very first time, (2) fairly regularly, and (3) every day. We used current age and age of first MI to select only those people who had their first MIs at or after 2007 (Table S6). While the point estimates for the e-cigarette effects (as well as other variables) remained about the same as for the entire sample, these estimates were no longer statistically significant because of a small number of MIs among e-cigarette users after 2007. Note that this analysis does not capture reinfarctions occurring after 2007, whose risk could be increased by e-cigarette use as it is for continued smoking conventional cigarettes.[33,34]

One could argue that the cleanest study would have been one that only examined the association of sole e-cigarette use with myocardial infarction. In contrast, most e-cigarette users are dual users with cigarettes so it is important to study the effects of e-cigarette use simultaneously with cigarette use. Our analysis quantified the additional risk of MI associated with e-cigarette use in addition to cigarette smoking among dual users. Limiting the analysis to sole e-cigarette users would not only be less clinically relevant, but would substantially reduce the sample size and the power of the analysis to detect an effect.

Limitations

While PATH is a longitudinal study, there were only 8 people who used e-cigarettes and had first myocardial infarctions during this follow-up, so there was not enough power to detect an effect. Confirming this problem, every-day and former-conventional cigarette smoking were not significant either. While longitudinal studies are more desirable than cross-sectional studies, the reality is that it will be years before enough myocardial infarctions have occurred to do a meaningful analysis. In the meantime, millions of people are using e-cigarettes and clinicians are being asked about them and this cross-sectional analysis can be used to inform decision making about these products.

Response for both e-cigarette and combustible cigarette use were self-reported, which could lead to recall bias. Participants with myocardial infarction might over-report e-cigarette and cigarette use, but previous work found that compared with biochemical monitoring with cotinine levels, self-reporting in myocardial infarction survivors tended to understate the prevalence of smoking.[35] Myocardial infarction was self-reported which also could lead recall bias, but the questions "Has a doctor, nurse, or other health professional ever told you that you had a heart attack (myocardial infarction)?" and "In the past 12 months, has a doctor, nurse, or other health professional told you that you had a heart attack (myocardial infarction)?" have been found to have high agreement (81%–98%) with medical records.[36,37]

Other possible risk factors including family history of myocardial infarction, angina, and heavy alcohol use are not available in the PATH data set. There is no information on the duration since smoking or e-cigarette cessation. In the main analysis, it also is unknown whether the reported myocardial infarction occurred before or after the respondents' initiated e-cigarettes and cigarettes use.

Conclusions

As one would expect based on what is known about the biological effects of e-cigarette use, in the cross-sectional analysis some-day and every-day e-cigarette use is associated with increased risk for having myocardial infarction, adjusted for combustible cigarette smoking, demographic and clinical variables. This result is unlikely because of reverse causality. Former, some-day, and every-day combustible cigarette smoking is also independently associated with myocardial infarction among adults in the United States. Dual use of the e-cigarette and combustible cigarettes results in higher risk of myocardial infarction than using either product alone and switching from cigarettes to e-cigarettes was not associated with any benefits in terms of reduced myocardial infarction risk. E-cigarettes should not be promoted or prescribed as a less risky alternative to combustible cigarettes and should not be recommended for smoking cessation among people with or at risk of myocardial infarction.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Myocardial Infarctions, tobacco use, clinical, and demographic variables.

Variables (at Wave 1)	E-cigarette Use at Wave 1 (Weighted percent)				
	Never	**Former**	**Some Day**	**Every Day**	**P-value***
Myocardial Infarction					
Yes	2.4	1.9	2.6	3.4	0.073
No	97.6	98.1	97.4	96.6	
Cigarette smoker					
Never	40.7	3.6	1.9	0.5	<0.001
Former	50.3	34.7	16.2	51.2	
Some day	2.0	11.4	14.2	19.9	
Every day	7.0	50.3	67.7	28.4	
Demographics					
Age in years, mean (±SD)	48.6 (±17.9)	36.8 (±14.4)	35.7 (±13.5)	41.0 (±15.2)	<0.001
Body Mass Index (±SD) kg/m^2	28.1 (±7.5)	27.7 (±7.0)	27.7 (±7.0)	27.9 (±6.6)	<0.001
Sex					
Male	46.8	54.3	54.2	54.4	<0.001
Female	53.2	45.7	45.8	45.6	
Poverty level/income					
Below poverty	22.9	33.1	27.4	35.1	<0.001
At or above poverty	77.1	66.9	72.6	64.9	
Race/ethnicity					
White	77.6	78.6	79.1	84.8	<0.001
Black	12.5	12.0	10.3	6.6	
Asian	5.9	3.6	3.1	2.7	
Other	3.9	5.7	7.5	5.9	
Education					
Less than high school	35.1	13.2	39.6	39.9	<0.001
High school or equivalent	4.7	3.5	3.9	3.4	
Some college and associate	29.5	37.8	41.8	42.9	
Bachelor and advanced degree	30.8	15.5	14.7	13.7	
Clinical status					
High blood pressure					
Yes	29.2	21.1	22.6	23.1	<0.001
No	70.8	78.9	77.4	76.9	
High cholesterol					
Yes	24.5	15.5	14.4	18.6	<0.001
No	75.5	84.5	85.6	81.4	
Diabetes mellitus					
Yes	14.8	9.9	11.8	11.3	<0.001
No	85.2	90.1	88.2	88.7	

*Chi-square for counts, t-test for continuous variables.
Wave 1 data were collected from September 2013 to December 2014

Table S2. Adjusted odds ratios for myocardial infarction (MI) at Wave 2, excluding respondents who had a MI at Wave 1.

Variables	AOR (95% CI)	P-value
E-cigarette user at wave 1		
Never	Reference	
Former	1.10 (0.56, 2.18)	0.775
Some day	2.12 (0.64, 7.08)	0.225
Every day	-	-
Cigarette smoker at wave 1		
Never	Reference	
Former	3.40 (0.66, 17.50)	0.147
Some day	6.66 (1.30, 34.00)	0.025
Every day	3.05 (0.57, 16.49)	0.198
High blood pressure		
Yes	1.74 (0.80, 3.79)	0.165
High cholesterol		
Yes	0.82 (0.37, 1.85)	0.642
Diabetes mellitus		
Yes	1.64 (0.56, 4.82)	0.372
Age	1.06 (1.03, 1.08)	<0.001
Body Mass Index	1.01 (0.99, 1.04)	0.289
Sex		
Female	0.47 (0.22, 1.03)	0.062
Poverty level/income		
At or above poverty	1.23 (0.54, 2.81)	0.616
Race/ethnicity		
White	Reference	
Black	1.07 (0.50, 2.26)	0.870
Asian	-	-
Other	1.46 (0.40, 5.37)	0.568
Education		
Less than high school	2.20 (0.51, 9.53)	0.299
High school or equivalent	Reference	
Some college and associate	0.93 (0.43, 2.01)	0.864
Bachelor and advanced degree	0.10 (0.02, 0.59)	0.012
Sample size	25,820	
VIF	<1.2	

Adjusted Odds Ratio adjusts for cigarette smoking (former, some day and every day), age, BMI, sex, poverty level, race/ethnicity, education, and clinical variables.
VIF: Variance Inflation Factor

Table S3. Adjusted odds ratio for myocardial infarction at Wave 1 baseline including experimental e-cigarette users and smokers as some day users.

Variables	**AOR (95% CI)**	**P-value**
E-cigarette user		
Never	Reference	
Former	1.27 (0.95, 1.69)	0.113
Some day	1.62 (1.04, 2.54)	0.037
Every day	2.20 (1.20, 4.05)	0.013
Cigarette smoker		
Never	Reference	
Former	1.47 (1.01, 2.14)	0.047
Some day	2.22 (1.37, 3.60)	0.002
Every day	2.94 (1.91, 4.51)	<0.001
High blood pressure		
Yes	2.09 (1.60, 2.72)	<0.001
High cholesterol		
Yes	3.10 (2.40, 3.99)	<0.001
Diabetes mellitus		
Yes	1.46 (1.09, 1.97)	0.013
Age in years	1.07 (1.06, 1.08)	<0.001
Body Mass IndexI	1.02 (1.00, 1.03)	0.026
Sex		
Female	0.28 (0.20, 0.40)	<0.001
Poverty level/income		
At or above poverty	0.73 (0.52, 1.02)	0.069
Race/ethnicity		
White	Reference	
Black	0.83 (0.63, 1.09)	0.186
Asian	0.32 (0.08, 1.23)	0.101
Other	1.34 (0.84, 2.12)	0.217
Education		
Less than high school	1.52 (1.08, 2.14)	0.020
High school or equivalent	Reference	
Some college and associate	1.01 (0.77, 1.33)	0.923
Bachelor and advanced degree	0.64 (0.45, 0.89)	0.011
Sample size	32,320	
VIF	<1.1	

Adjusted Odds Ratio adjusts for cigarette smoking (former, some day and every day), age, BMI, sex, poverty level, race/ethnicity, education, and clinical variables.
VIF: Variance Inflation Factor

Table S4. Adjusted odds ratios for current (every day or some day) e-cigarette use at Wave 2.*

	Among overall follow up sample		**Among every day cigarette smoker at wave 1¥**		**Among current cigarette smoker at wave 1¥**	
Variables at Wave 1	**AOR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**
MI						
No	Reference		Reference		Reference	
Yes	1.45 (0.94, 2.25)	0.099	1.52 (0.90, 2.56)	0.121	1.40 (0.86, 2.28)	0.173
High blood pressure						
Yes	1.32 (1.12, 1.55)	0.001	1.16 (0.96, 1.41)	0.125	1.16 (0.97, 1.38)	0.114
High cholesterol						
Yes	0.91 (0.74, 1.12)	0.384	1.08 (0.83, 1.42)	0.567	1.13 (0.89, 1.44)	0.303
Diabetes mellitus						
Yes	0.93 (0.72, 1.18)	0.543	1.03 (0.81, 1.32)	0.789	1.05 (0.83, 1.31)	0.697
Age	0.97 (0.96, 0.98)	<0.001	0.97 (0.96, 0.97)	<0.001	0.97 (0.96, 0.98)	<0.001
Body Mass Index	1.00 (0.99, 1.00)	0.359	1.00 (0.99, 1.01)	0.806	1.00 (0.99, 1.01)	0.981
Sex						
Female	0.83 (0.73, 0.94)	0.006	1.10 (0.91, 1.33)	0.317	1.06 (0.90, 1.25)	0.482
Poverty level/income						
At or above poverty	0.91 (0.78, 1.05)	0.202	1.29 (1.09, 1.53)	0.004	1.19 (1.02, 1.39)	0.032
Race/ethnicity						
White	Reference		Reference		Reference	
Black	0.38 (0.30, 0.48)	<0.001	0.35 (0.24, 0.51)	<0.001	0.39 (0.27, 0.55)	<0.001
Asian	0.55 (0.39, 0.78)	0.001	0.69 (0.51, 1.52)	0.363	0.69 (0.36, 1.33)	0.279
Other	1.05 (0.84, 1.31)	0.659	1.07 (0.75, 1.51)	0.721	1.12 (0.84, 1.49)	0.451
Education						
Less than high school	0.89 (0.65, 1.21)	0.449	1.13 (0.77, 1.67)	0.532	1.07 (0.75, 1.53)	0.705
High school or equivalent	Reference		Reference		Reference	
Some college and associate	1.06 (0.90, 1.24)	0.475	1.42 (1.18, 1.69)	<0.001	1.31 (1.09, 1.56)	0.004
Bachelor and advanced degree	0.38 (0.31, 0.47)	<0.001	1.52 (1.08, 2.13)	0.018	1.18 (0.90, 1.54)	0.234
Number of new e-cigarette users between Waves 1 and 2	1,990		776		946	
Sample size	26,447		7,378		9,284	
VIF	<1.2		<1.1		<1.1	

*Former e-cigarette users excluded from the analysis.

¥ Excluding e-cigarette users
Adjusted Odds Ratio adjusts for age, BMI, sex, poverty level, race/ethnicity, education, and clinical variables.
VIF: Variance Inflation Factor

Table S5. Cross-sectional associations between conventional cigarette smoker and myocardial infarction at Wave 1 baseline among daily cigarette only users and daily dual users.

Variables	AOR (95% CI)	P-value
Cigarette smoker		
Never cigarette and e-cigarette user	Reference	
Every day cigarette smoker and never e-cigarette user	2.86 (1.70, 4.79)	<0.001
Every day cigarette and every day e-cigarette user	5.06 (1.99, 12.83)	<0.001
High blood pressure		
Yes	1.80 (0.95, 3.42)	0.073
High cholesterol		
Yes	3.11 (2.03, 4.77)	<0.001
Diabetes mellitus		
Yes	1.54 (0.93, 2.55)	0.095
Age in years	1.06 (1.04, 1.08)	<0.001
Body Mass Index	1.02 (0.99, 1.04)	0.260
Sex		
Female	0.24 (0.12, 0.50)	<0.001
Poverty level/income		
At or above poverty	0.80 (0.45, 1.43)	0.457
Race/ethnicity		
White	Reference	
Black	0.81 (0.47, 1.41)	0.456
Asian	0.16 (0.02, 1.14)	0.071
Other	0.64 (0.24, 1.74)	0.387
Education		
Less than high school	0.83 (0.44, 1.55)	0.557
High school or equivalent	Reference	
Some college and associate	0.90 (0.51, 1.61)	0.734
Bachelor and advanced degree	0.45 (0.18, 1.09)	0.082
Sample size	10,230	
VIF	<1.6	

VIF: Variance Inflation Factor

Table S6. Adjusted odds ratios for myocardial infarction at Wave 1.

	MI 2007 or later		Entire sample	
Variables	**AOR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**
E-cigarette use				
Never	Reference		Reference	
Former	1.27 (0.85, 1.88)	0.250	1.25 (0.93, 1.69)	0.147
Some day	1.52 (0.43, 5.30)	0.515	1.99 (1.11, 3.58)	0.024
Every day	1.90 (0.69, 5.22)	0.216	2.25 (1.23, 4.11)	0.010
Cigarette use				
Never	Reference		Reference	
Former	1.62 (0.97, 2.68)	0.066	1.48 (1.01, 2.15)	0.047
Some day	2.34 (1.16, 4.75)	0.020	2.38 (1.40, 4.06)	0.002
Every day	3.22 (1.91, 5.42)	<0.001	2.95 (1.91, 4.56)	<0.001
High blood pressure				
Yes	2.24 (1.35, 3.72)	0.002	2.08 (1.56, 2.77)	<0.001
High cholesterol				
Yes	2.32 (1.54, 3.51)	<0.001	3.01 (2.31, 3.92)	<0.001
Diabetes mellitus				
Yes	1.24 (0.76, 2.03)	0.384	1.49 (1.09, 2.03)	0.013
Age in years	1.06 (1.04, 1.07)	<0.001	1.07 (1.06, 1.08)	<0.001
Body Mass Index	1.02 (1.01, 1.03)	<0.001	1.02 (1.00, 1.03)	0.016
Sex				
Female	0.33 (0.21, 0.53)	<0.001	0.27 (0.18, 0.39)	<0.001
Poverty level/income				
At or above poverty	0.76 (0.45, 1.28)	0.307	0.72 (0.49, 1.04)	0.086
Race/ethnicity				
White	Reference		Reference	
Black	1.03 (0.65, 1.64)	0.903	0.86 (0.63, 1.16)	0.324
Asian	0.18 (0.03, 1.24)	0.086	0.31 (0.07, 1.38)	0.127
Other	1.67 (0.78, 3.56)	0.189	1.37 (0.83, 2.25)	0.226
Education				
Less than high school	1.63 (0.80, 3.33)	0.185	1.49 (1.05, 2.13)	0.030
High school or equivalent	Reference		Reference	
Some college and associate	1.21 (0.74, 1.95)	0.447	0.97 (0.72, 1.29)	0.814
Bachelor and advanced degree	0.65 (0.37, 1.13)	0.131	0.62 (0.44, 0.87)	0.007
Sample size	31,815		32,320	
Number of MI's (total)	284		699	
Number of MI's (among ecig users)	Never =181 Former= 61 Some day =10 Every day =6		Never =433 Former= 128 Some day =19 Every day =19	
VIF	<1.2		<1.1	

Adjusted Odds Ratio adjusts for cigarette smoking (former, some day and every day), age, body mass index, sex, poverty level, race/ethnicity, education, and clinical variables.
VIF: Variance Inflation Factor

Figure S1. Flow diagram for sample.