



Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers

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ABSTRACT

BACKGROUND: The prevalence of e-cigarette use in the United States has increased rapidly. However, the association between e-cigarette use and cardiovascular disease remains virtually unknown. Therefore, we aimed to examine the association between e-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers.

METHODS: We pooled 2016 and 2017 data from the Behavioral Risk Factor Surveillance System (BRFSS), a large, nationally representative, cross-sectional telephone survey. We included 449,092 participants with complete self-reported information on all key variables. The main exposure, e-cigarette use, was further divided into daily or occasional use, and stratified by combustible-cigarette use (never and current). Cardiovascular disease, the main outcome, was defined as a composite of self-reported coronary heart disease, myocardial infarction, or stroke.

RESULTS: Of 449,092 participants, there were 15,863 (3.5%) current e-cigarette users, 12,908 (2.9%) dual users of e-cigarettes + combustible cigarettes, and 44,852 (10.0%) with cardiovascular disease. We found no significant association between e-cigarette use and cardiovascular disease among never combustible-cigarette smokers. Compared with current combustible-cigarette smokers who never used e-cigarettes, dual use of e-cigarettes + combustible cigarettes was associated with 36% higher odds of cardiovascular disease (odds ratio 1.36; 95% confidence interval, 1.18-1.56); with consistent results in subgroup analyses of premature cardiovascular disease in women <65 years and men <55 years old.

CONCLUSION: Our results suggest significantly higher odds of cardiovascular disease among dual users of e-cigarettes + combustible cigarettes compared with smoking alone. These data, although preliminary, support the critical need to conduct longitudinal studies exploring cardiovascular disease risk associated with e-cigarette use, particularly among dual users.

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KEYWORDS: Cardiovascular disease; Combustible cigarettes; Dual use; E-cigarettes

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INTRODUCTION

E-cigarettes were introduced in the United States market more than a decade ago, and since then, the prevalence of e-cigarette use in the United States has grown rapidly.¹⁻³ A recent study estimated that 10.8 million US adults used e-cigarettes in 2016.² Dual use of e-cigarettes and combustible cigarettes remains the dominant use pattern, followed by e-cigarette use among former smokers, with sole e-cigarette use in the absence of any history of tobacco product use the smallest group.²

Although there is a paucity of data on the long-term cardiovascular health effects of e-cigarettes, a few acute exposure studies suggest potential cardiovascular toxicity, as reflected by an increase in heart rate, blood pressure, and systemic oxidative stress.^{1,4-9} These findings reinforce the critical need to study the potential impact of e-cigarette use on adverse cardiovascular health outcomes; however, the long-term health effects of e-cigarettes are difficult to study, primarily because e-cigarettes have been on the market for only a few years.⁴ Nonetheless, cross-sectional associations with cardiovascular disease have been reported from a relatively smaller survey of people aged ≥ 18 years, using data from the National Health Interview Survey in 2014 and 2016.¹⁰

Prior analyses of e-cigarettes and cardiovascular disease have been limited by pooling of all e-cigarette users together, despite their varying combustible-cigarette-smoking backgrounds.¹⁰ Importantly, it is unclear how dual use of e-cigarettes and combustible cigarettes affects cardiovascular disease risk. This is particularly important given the widespread prevalence of dual use^{2,11} and current controversies surrounding this pattern of use. Some studies cite dual use as a marker of ongoing efforts at smoking cessation, whereas others argue that dual use may be a persistent state that reinforces nicotine addiction and tobacco abuse potential.^{2,12-14}

To understand the relationship between e-cigarette use and cardiovascular disease, we studied the association between e-cigarette use and cardiovascular disease outcomes among never and current combustible-cigarette smokers in the largest US survey of e-cigarette use to date.

METHODS

Using pooled data from Behavioral Risk Factor Surveillance System (BRFSS) 2016 and 2017 surveys, we conducted a cross-sectional analysis of e-cigarette use and self-reported cardiovascular disease. The BRFSS is the largest nationally representative health survey with data on health-related risk

behaviors and chronic medical conditions.¹⁵ The median survey response rate for all states, territories, and Washington, DC in 2016 was 47.0% and ranged from 30.7% to 65.0%.¹⁶ The median survey response rate in 2017 was 45.1% and ranged from 30.6% to 64.1. We studied a total of 449,092 never and current combustible-cigarette smokers with complete information on all key variables in our study.

CLINICAL SIGNIFICANCE

- While some cite e-cigarettes as a smoking cessation tool, others argue that dual use of e-cigarettes and combustible cigarettes may reinforce nicotine addiction and abuse potential. Dual use of both products remains common in current clinical practice.
- Clinicians should exercise caution in recommending e-cigarettes as a smoking cessation strategy, and should recommend traditional evidence-based smoking cessation strategies until sufficient evidence establishing safety/harm of e-cigarettes is obtained from longitudinal studies.

E-Cigarette Use

Participants were first asked, “Have you ever used an e-cigarette or other electronic ‘vaping’ product, even just one time, in your entire life?” Those who answered “yes” were then asked a follow-up question: “Do you now use e-cigarettes or other electronic ‘vaping’ products every day, some days, or not at all?” Those who answered in the affirmative to the first question were categorized as ever e-cigarette users, those who responded “no” were considered never e-cigarette users. Ever e-cigarette users who responded “every day” and “some days” to the follow-up question were categorized as daily or occasional e-cigarette users, respectively.

Cigarette Smoking

Participants who responded “yes” to “Have you smoked at least 100 cigarettes in your entire life?” were classified as ever combustible-cigarette smokers, and those who responded “no” were considered never smokers. Ever smokers who responded “every day” or “some days” to the question “Do you now smoke cigarettes every day, some days, or not at all?” were classified as current combustible-cigarette smokers.

Cardiovascular Disease Assessment

Participants who responded “yes” to “Has a doctor, nurse, or other health professional ever told you that you had a stroke, myocardial infarction or coronary heart disease?” were classified as having cardiovascular disease. Additionally, we defined premature cardiovascular disease as cardiovascular disease in women ages < 65 years and men < 55 years.

Covariate Assessment

The income variable from BRFSS was adjusted using the federal poverty levels in the United States for 2016 and 2017.¹⁸ In generating this variable, the number of adults and children in a household and state of residence were considered. This was categorized into participants below the 100% federal poverty level, between 100% and 200% poverty level, and above 200% poverty level.

Heavy alcohol intake was defined as adult men having more than 14 drinks per week and adult women having more than 7 drinks per week. Demographic factors such as age, race, sex, and level of education, as well as risk factors such as history of diabetes, hypertension, high cholesterol, body mass index, and level of physical activity were self-reported.

Statistical Analysis

The BRFSS employs appropriate weighting methodology to improve the representativeness of the data. Details of this weighting methodology are available elsewhere.¹⁹ Baseline characteristics were compared across e-cigarette use categories (never and current). The association of e-cigarette use with cardiovascular disease was assessed using multivariable logistic regression models stratified by combustible-cigarette smoking status (never and current). Models were adjusted for age, sex, race, educational status, income, physical activity, body mass index, diabetes, and heavy alcohol drinking. Sensitivity analyses adjusting additionally for hypertension and high cholesterol (in BRFSS 2017) and models with limited adjustments are available as [Supplementary Tables 1-4](#) (available online).

Additionally, given the popularity of e-cigarettes among younger adults, coupled with the previous studies establishing harm of combustible-cigarette smoking on younger individuals,^{20,21} we repeated the analysis in a subgroup of women <65 years of age and men <55 years to evaluate any association between e-cigarette use and premature cardiovascular disease. We adopted the definition of premature cardiovascular disease from the 2018 Guideline on Management of Blood Cholesterol,²² which constitutes atherosclerotic vascular disease in males aged <55 years or females <65 years.²² Former combustible-cigarette smokers were excluded from these analyses because data on combustible-cigarette smoking intensity or burden (pack-years), which can confound the association between e-cigarette use and cardiovascular disease in this subgroup, were not systematically available. All analyses were conducted using Stata statistical software (version 15.0; StataCorp LLC, College Station, Texas).

RESULTS

Of 449,092 participants, there were 15,863 (3.5%) current e-cigarette users, 58,789 (13.1%) current combustible-cigarette smokers, 12,908 (2.9%) dual users of e-cigarettes + combustible cigarettes, and 44,852 (10.0%) participants with self-reported cardiovascular disease. The median age group of current e-cigarette users was 30-34 years ([Table 1](#)). Compared with never e-cigarette users, current e-cigarette users were more likely to be men, white, heavy alcohol consumers, and current combustible-cigarette users, but were less likely to have diabetes. (See [Table 1](#))

While there currently appears to be no significant association between e-cigarette use and cardiovascular disease among never combustible-cigarette smokers, we noted statistically significant associations between e-cigarette use and cardiovascular disease among current combustible-cigarette

smokers. Compared with current combustible-cigarette smokers who never used e-cigarettes, dual users had 36% higher odds of cardiovascular disease (odds ratio [OR] 1.36; 95% confidence interval [CI], 1.18-1.56), with daily use of e-cigarettes among current combustible-cigarette smokers associated with the highest odds (OR 1.59; 95% CI, 1.20-2.08). (See [Table 2](#))

Consistent results were noted in the analysis of premature cardiovascular disease. There was a graded increase in odds of cardiovascular disease among dual users, with daily e-cigarette users having higher odds of cardiovascular disease than occasional users. Compared with never combustible-cigarette smokers who never used e-cigarettes ([Figure](#)) dual users had the highest odds of cardiovascular disease (OR 2.44; 95% CI, 2.14-2.78).

Table 1 Baseline Characteristics of the Study Population According to E-Cigarette Use Status

Variables	BRFSS 2016 & 2017 N = 449,092	
	E-Cigarette Use Status	
	Current (n = 15,863)	Never (n = 433,229)
Median age group, years	30-34	45-49
Women (%)	41.2	55.2
Race		
White (%)	69.7	60.5
Blackf (%)	9.1	12.4
Asian (%)	3.7	6.5
Hispanic (%)	12.1	17.9
Others (%)	5.4	2.7
Diabetes (%)	7.9	10.4
Heavy alcohol intake (%)	12.8	4.2
Body mass index (BMI)		
< 18.5 kg/m ² (%)	3.2	2.0
18.5 to < 25 kg/m ² (%)	37.9	33.7
25 to < 30 kg/m ² (%)	31.5	34.9
30 kg/m ² (%)	27.4	29.4
Education		
Less than high school diploma (%)	15.5	12.4
High school diploma (%)	36.0	25.6
Some college (%)	48.5	62.0
Physically active in past 30 days (%)	74.9	76.0
Federal poverty line		
< 100% (%)	19.6	13.9
100%-200% (%)	24.6	19.6
> 200% (%)	55.8	66.5
Current combustible-cigarette use (%)	73.7	10.3
Cardiovascular disease (%)	7.6	7.2

BRFSS = Behavioral Risk Factor Surveillance System.
 * American Indian or Alaskan native only, Native Hawaiian or other Pacific Islander only, multiracial (non-Hispanic), other race only (non-Hispanic).
 † Heavy alcohol intake was defined as adult men having more than 14 drinks per week and adult women having more than 7 drinks per week.

Table 2 Association Between E-Cigarette Use and Cardiovascular Disease According to Combustible-Cigarette Smoking Among US Adults

E-Cigarette Use Status	Cardiovascular Disease (Pooled BRFSS 2016 & 2017)* OR (95% CI)		Premature Cardiovascular Disease (Females <65 Y Males <55 Y) (Pooled BRFSS 2016 & 2017)* OR (95% CI)	
	Combustible-Cigarette Smoking Status		Combustible-Cigarette Smoking Status	
	Never Smoker (n = 390,303)	Current Smoker (n = 58,789)	Never Smoker (n = 218,820)	Current Smoker (n = 35,296)
Never e-cigarette users	Ref	Ref	Ref	Ref
Current e-cigarette users	1.04 (0.63-1.72)	1.36 (1.18-1.56)	1.01 (0.56-1.83)	1.45 (1.20-1.74)
Occasional use	0.95 (0.50-1.82)	1.30 (1.12-1.52)	0.97 (0.47-2.02)	1.36 (1.11-1.66)
Daily use	1.35 (0.74-2.46)	1.59 (1.20-2.08)	1.16 (0.56-2.41)	1.84 (1.32-2.56)

BRFSS = Behavioral Risk Factor Surveillance System; CI = confidence interval; OR = odds ratio.

* Adjusted for age, sex, race, educational status, income, physical activity, body mass index, diabetes and heavy drinking.

DISCUSSION

In this cross-sectional study, we found that dual use of e-cigarettes + combustible cigarettes was associated with significantly higher odds of cardiovascular disease compared with smoking alone. We also found a graded increase in odds of cardiovascular disease with increasing frequency of e-cigarette exposure among current combustible-cigarette smokers. These results have distinct implications for clinicians, public health officials, and for tobacco product regulation.

Recently, using data from the National Health Interview Survey, Alzahrani et al¹⁰ showed that daily e-cigarette users have 1.79 higher odds (95% CI, 1.20-2.66) of reporting myocardial infarction compared with never users. While finding a similar overall point estimate for the prevalence odds ratio, our

study investigated this relationship in greater detail across combustible-cigarette status groups. We fill an important knowledge gap by adding that the association between e-cigarette use and cardiovascular disease is most consistent among dual users, an observation further supported by our subgroup analyses.

The current lack of significant association between e-cigarette use and cardiovascular disease among never combustible-cigarette smokers may be due to the younger age of this group. In a recent study, 60% of e-cigarette users without a history of combustible-cigarette smoking are younger than 25 years, and therefore may not have had sufficient time to develop clinically significant cardiovascular disease.²³ Also, occasional use of e-cigarettes is the predominant pattern in never smokers, leading to low intensity of use, making it less likely to detect any potential cardiovascular harm.

While the potential cardiovascular toxicity of e-cigarettes is important, it will also be important to consider the magnitude of potential harm compared with traditional cigarette smoking. Some pathophysiologic studies suggest lower cardiovascular risk of e-cigarettes compared with traditional combustible-cigarette use. For example, Carnevale et al⁸ showed that both e-cigarettes and combustible cigarettes have undesirable effects on markers of flow-mediated dilation and oxidative stress after single use, although e-cigarettes had a lesser effect compared with combustible cigarettes. Nocella et al²⁴ also showed that both traditional and e-cigarettes have short-term effects on platelet activation, with less impact among nonsmokers who used e-cigarettes. Keith et al²⁵ showed that sole use of electronic nicotine delivery devices may be associated with lower volatile organic compounds exposure compared with cigarette smoking. Accordingly, it is possible that dual users who reduce daily use of combustible cigarettes may benefit in terms of clinical cardiovascular outcomes in comparison with sole users of traditional cigarettes.

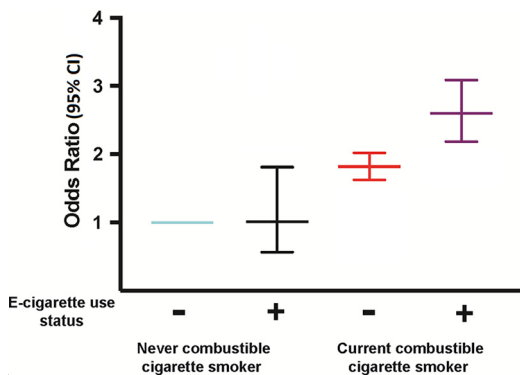


Figure Association between e-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers using never combustible-cigarette smokers who never use e-cigarettes as reference group. - Never e-cigarette use. + Current e-cigarette use.

E-cigarette use may also have a differential impact compared with heat-not-burn products; however, limited studies address the health effects of heat-not-burn products. Heat-not-burn tobacco products heat tobacco to generate nicotine, compared with e-cigarettes, which heat e-liquid.^{26–28} Heat-not-burn tobacco products may be marketed as healthier than traditional cigarettes and appeal to consumers who demand the “throat-hit” delivered by traditional cigarettes but not by electronic cigarettes.²⁶ It is critical that studies assessing the potential risk of these products be performed as interest in these products continues to rise.^{26,27}

While our study highlights associations between e-cigarettes and cardiovascular disease, future studies must also consider other domains of potential risk, including pulmonary disease and cancers. There is evidence that switching completely from regular use of combustible cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems.²⁹ Some studies suggest that e-cigarette use may markedly reduce number of combustible cigarettes smoked per day, reducing exposure to toxicants and ameliorating adverse pulmonary disease.³⁰ However, other acute exposure studies indicate that e-cigarette use may be associated with increased odds of pulmonary disease compared with no e-cigarette use.^{31,32}

Whereas our results have potential public health and regulatory implications, they should be considered preliminary and hypothesis-generating. The exposures and outcomes in the study were self-reported, and both may be misclassified in a nonrandom fashion. Our study was cross-sectional, limiting causal inferences. The potential for reverse causation cannot be excluded; current smokers with cardiovascular disease are more likely to attempt cessation, and e-cigarette use may be a marker of attempted cessation. For example, in a randomized trial of e-cigarettes vs nicotine-replacement therapy, Hajek et al³³ showed that e-cigarettes were more effective for smoking cessation compared with nicotine-replacement therapy, when both products were combined with behavioral support.

In addition, data on combustible-cigarette smoking intensity or burden (pack-years), duration, and intensity of e-cigarette use (puffs/day) were not systematically available in BRFSS. Hence, we cannot exclude the possibility that dual use is a proxy for intensity of cigarette consumption rather than representing a distinct hazard from e-cigarettes per se.

Despite these limitations, the BRFSS provides the largest sample size with enough power to stratify e-cigarette use by combustible-cigarette smoking status, and as one of the best nationally representative datasets on health-related risk behaviors available for the study of e-cigarettes, is an important first step in the study of potential e-cigarette-related cardiovascular toxicity.

CONCLUSION

It has been well established that cigarette smoke triggers an inflammatory response within coronary arteries.³⁴ These

preliminary findings from a large, representative US health survey support significantly higher odds of cardiovascular disease among dual users of e-cigarettes + combustible cigarettes compared with combustible-cigarette smoking alone. Our findings emphasize the critical need to conduct longitudinal studies exploring potential cardiovascular disease risks associated with e-cigarettes, particularly in dual users.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in online version at <https://doi.org/10.1016/j.amjmed.2019.02.016>.

APPENDIX A

Supplementary Table 1 Association Between E-Cigarette Use and Cardiovascular Disease According to Combustible-Cigarette Smoking Among US Adults

E-Cigarette Use Status	Cardiovascular Disease (Pooled BRFSS 2016 & 2017) OR (95% CI)		Cardiovascular Disease (Pooled BRFSS 2016 & 2017) OR (95% CI)	
	Model 1*		Model 2†	
	Combustible-Cigarette Smoking Status		Combustible-Cigarette Smoking Status	
	Never smoker (n = 390,303)	Current smoker (n = 58,789)	Never smoker (n = 390,303)	Current smoker (n = 58,789)
Never e-cigarette users	Ref	Ref	Ref	Ref
Current e-cigarette users	1.11 (0.67-1.84)	1.36 (1.18-1.57)	1.04 (0.63-1.72)	1.36 (1.18-1.56)
• Occasional use	1.01 (0.52-1.94)	1.31 (1.13-1.53)	0.95 (0.50-1.82)	1.30 (1.12-1.52)
• Daily use	1.48 (0.82-2.67)	1.57 (1.18-2.07)	1.35 (0.74-2.46)	1.59 (1.20-2.08)

BRFSS = Behavioral Risk Factor Surveillance System; CI = confidence interval; OR = odds ratio.

* Adjusted for age, sex, and race.

† Adjusted for age, sex, race, educational status, income, physical activity, body mass index, diabetes and heavy drinking.

Supplementary Table 2 Association Between E-Cigarette Use and Premature Cardiovascular Disease According to Combustible-Cigarette Smoking Among US Adults

E-cigarette Use Status	Premature Cardiovascular Disease (Females <65 Y Males <55 Y) (Pooled BRFSS 2016 & 2017)* OR (95% CI)		Premature Cardiovascular Disease (Females <65 Y Males <55 Y) (Pooled BRFSS 2016 & 2017)† OR (95% CI)	
	Model 1*		Model 2†	
	Combustible-Cigarette Smoking Status		Combustible-Cigarette Smoking Status	
	Never smoker (n = 218,820)	Current smoker (n = 35,296)	Never smoker (n = 218,820)	Current smoker (n = 35,296)
Never E-cigarette users	Ref	Ref	Ref	Ref
Current E-cigarette users	1.11 (0.61-2.03)	1.43 (1.18-1.73)	1.01 (0.56-1.83)	1.45 (1.20-1.74)
• Occasional use	1.05 (0.49-2.22)	1.35 (1.10-1.66)	0.97 (0.47-2.02)	1.36 (1.11-1.66)
• Daily use	1.36 (0.67-2.77)	1.74 (1.23-2.46)	1.16 (0.56-2.41)	1.84 (1.32-2.56)

BRFSS = Behavioral Risk Factor Surveillance System; CI = confidence interval; OR = odds ratio.

* Adjusted for age, sex, and race.

† Adjusted for age, sex, race, educational status, income, physical activity, body mass index, diabetes and heavy drinking.

Supplementary Table 3 Association Between E-Cigarette Use and Cardiovascular Disease According to Combustible-Cigarette Smoking Among US Adults Stratified By Calendar Year

E-cigarette Use Status	Cardiovascular Disease (Pooled BRFSS 2016)* OR (95% CI)		Cardiovascular Disease (Pooled BRFSS 2017)† OR (95% CI)	
	Combustible-Cigarette Smoking Status		Combustible-Cigarette Smoking Status	
	Never smoker (n = 214,398)	Current smoker (n = 32,851)	Never smoker (n = 165,251)	Current smoker (n = 23,447)
Never E-cigarette users	Ref	Ref	Ref	Ref
Current E-cigarette users	0.72 (0.45-1.16)	1.31 (1.12-1.53)	1.70 (0.68-4.23)	1.45 (1.12-1.88)
• Occasional use	0.70 (0.41-1.19)	1.25 (1.06-1.47)	1.55 (0.44-5.42)	1.43 (1.08-1.89)
• Daily use	0.79 (0.28-2.21)	1.57 (1.14-2.15)	2.13 (0.91-4.94)	1.53 (0.91-2.58)

BRFSS = Behavioral Risk Factor Surveillance System; CI = confidence interval; OR = odds ratio.

*Adjusted for age, sex, race, educational status, income, physical activity, body mass index, diabetes and heavy drinking.

†Models additionally adjusted for hypertension and high cholesterol (only available in BRFSS 2017).

Supplementary Table 4 Association Between E-Cigarette Use and Premature Cardiovascular Disease According to Combustible-Cigarette Smoking Among US Adults

E-cigarette Use Status	Premature Cardiovascular Disease (Pooled BRFSS 2016)* OR (95% CI)		Premature Cardiovascular Disease (Pooled BRFSS 2017)† OR (95% CI)	
	Combustible-Cigarette Smoking Status		Combustible-Cigarette Smoking Status	
	Never smoker (n = 121,591)	Current smoker (n = 19,835)	Never smoker (n = 88,863)	Current smoker (n = 13,512)
Never E-cigarette users	Ref	Ref	Ref	Ref
Current E-cigarette users	0.70 (0.40-1.23)	1.46 (1.19-1.79)	1.63 (0.54-4.92)	1.48 (1.07-2.04)
• Occasional use	0.68 (0.36-1.27)	1.37 (1.10-1.70)	1.66 (0.43-6.40)	1.42 (1.00-2.01)
• Daily use	0.77 (0.23-2.58)	1.89 (1.29-2.76)	1.51 (0.52-4.44)	1.72 (0.91-3.25)

BRFSS = Behavioral Risk Factor Surveillance System; CI = confidence interval; OR = odds ratio.

*Adjusted for age, sex, race, educational status, income, physical activity, body mass index, diabetes and heavy drinking†

†Models additionally adjusted for hypertension and high cholesterol (only available in BRFSS 2017)