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An association between electronic nicotine delivery systems use and a history of stroke using the 2016 behavioral risk factor surveillance system

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Abstract

Electronic nicotine delivery systems (ENDS) are growing in use and many of the health implications with these devices remain unknown. This study aims to assess, using a survey representative of the USA general population, if an association exists between a history of ENDS use and a history of stroke.

This cross-sectional study was a secondary data analysis using the 2016 behavioral risk factor surveillance system survey. The main exposure variable of the study was a self-reported history of ENDS use. The main outcome was a self-reported history of stroke. Covariates included sex, race, traditional cigarette use, smokeless tobacco use, chronic kidney disease, diabetes, myocardial infarction, and coronary artery disease. Unadjusted and adjusted logistic regression analyses were done. Adjusted odds ratios (AOR) and their corresponding 95% confidence intervals (CI) were calculated.

Of the 486,303 total behavioral risk factor surveillance system survey participants, 465,594 met the inclusion criteria for this study of ENDS use and stroke. This study shows that current ENDS use was positively associated with a history of stroke. AOR of some daily ENDS use with stroke was 1.28 (95% CI: 1.02–1.61) and AOR of current daily ENDS use with stroke was 1.62 (95% CI: 1.18–2.31). The majority (55.9%) of current daily ENDS users reported former traditional cigarette smoking. Female sex, non-white ethnicity, elderly age, chronic kidney disease, coronary artery disease, diabetes, and traditional cigarette use characteristics were all also associated with increased odds of reporting a stroke.

This study found a statistically significant and positive association between ENDS use and a history of stroke. Further research is warranted to investigate the reproducibility and temporality of this association. Nevertheless, this study contributes to the growing body of knowledge about the potential cardiovascular concerns related to ENDS use and the need for large cohort studies.

Abbreviations: AOR = adjusted odds ratio, BMI = body mass index, BRFSS = behavioral risk factor surveillance system, CAD = coronary artery disease, CDC = Centers for Disease Control, CKD = chronic kidney disease, CVD = cardiovascular disease, DM = diabetes mellitus, EDU = every day ENDS use, ENDS = electronic nicotine delivery systems, FU = former ENDS use, MACE = major adverse cardiac events, NU = never ENDS use, SDU = nondaily ENDS use, TC = traditional cigarettes.

Keywords: association, behavioral risk factor surveillance system, cerebrovascular, electronic cigarette, electronic nicotine delivery systems, stroke

1. Introduction

Electronic nicotine delivery systems (ENDS) have grown in popularity as an alternative to the known harmful effects of traditional cigarettes (TC). ENDS are especially growing amongst teenagers, with one study finding that from 2011 to 2018 ENDS use had grown from 1.5% to 20.8% of teenagers.[1–4] Yet, little is known about long term health effects of ENDS, including effects on cerebrovascular disease. In 2018, there were 147,810 fatal

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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strokes in the United States, and stroke was the fifth most common cause of death.[5] Per the American Heart Association 2021 Update on heart disease and stroke statistics, "the cardiovascular disease (CVD) risks associated with e-cigarette use are not known."[5]

Several theoretical frameworks exist that could make ENDS a possible risk factor for stroke. First, TCs have been found to be major risk factor for stroke with many studies demonstrating a 2 to 4 times increased risk.[6–8] While considered by some studies to be less toxic than TCs, ENDS share some similarities to them including nicotine, inhalation at high temperatures, and some overlap in ingested chemicals.[9,10] Substances such as acrolein and formaldehyde, emitted in both TCs and ENDS, have been associated with cardiotoxicity in rodents ranging from bradycardia to cardiomyopathy.[11,12] Second, numerous studies have evaluated possible biochemical mechanisms which may link ENDS to CVD and neural disease.[13–15] For example, ENDS may have transient effects on increasing heart rate.[16] Its aerosol contents may cause reactive damage and inflammation or impair platelet function.[17,18] Albeit less than TCs, one study found ENDS to increase unfavorable markers of vascular function including oxidative stress and flow-mediated dilation.[18] Its use may impair glucose uptake in the ischemic brain.[19]

Some population based cross-sectional studies have looked into ENDS use and cardiovascular diseases. At least 2 studies have found an association between ENDS use and myocardial infarction.[20,21] However, the data for ENDS use and stroke are particularly limited with 1 study in young adults thus far not showing an overall association.[22] Thus, using a large US population-based survey, the objective of this study (Study) is to investigate if there is a statistical association between ENDS use and stroke history.

2. Methods

2.1. Study design and population

This cross-sectional study was a secondary data analysis using the 2016 Centers for Disease Control (CDC)'s behavioral risk factor surveillance system (BRFSS). The CDC conducts the BRFSS surveys annually in the general American population. Throughout 2016, CDC interviewers collected data through a series of randomized phone calls to landlines and cellular phones across all 50 states, Puerto Rico, District of Columbia, and the US Virgin Islands.[23] In a standardized script, interviewers asked interviewees a series of questions. Interviews took an average of 27 minutes.[23] The sampled population interviewed was designed and statistically weighted by the BRFSS to have similar baseline characteristics to the general American population. This Study's authors downloaded the publicly available data in 2018 from the BRFSS section within the CDCs website.

This study includes patients only if they answered all of the following questions from the 2016 BRFSS questionnaire.[24] For Question 6.3, participants were asked: "Were you ever told that you had a stroke?" Participants must have answered "yes" or "no." For Question 10.1, they were asked, have you ever used an electronic cigarette product. For Question 10.2, they were also asked: "Do you now use electronic cigarette or other electronic 'vaping' products every day, some days, or not at all?" Participants must have answered "yes" or "no" to 10.1. If participants answered "yes" to 10.1, they must have answered "every day," "some days," or "not at all" to 10.2. Participants were excluded from the study if they answered "don't know/not sure" or "refuse to answer" to any of the above questions regarding ENDS use or stroke. A participant was still included in the study if they answered appropriately to ENDS use and stroke but answered "don't know/not sure" or "refuse to answer" to any of the 9 covariates: sex, age, race, body mass index (BMI), coronary artery disease (CAD), chronic kidney disease (CKD), diabetes mellitus (DM), smokeless tobacco use, and TC use. Missing data points from unanswered covariate data were excluded from this Study's multivariate analysis.

2.2. Criteria for assessing data

The main independent variable of this study was self-reported ENDS use, defined as electronic cigarettes and other electronic "vaping" products including electronic hookas, vape pens, e-cigars, and others. ENDS use was categorized as "current every-day use (EDU)," "nondaily or some-days use (SDU)," "former use (FU)," and "never use (NU)." FU was defined as having used ENDS in the past but not currently using. The dependent variable, and main outcome variable, is a self-reported history of stroke, reported as "yes" or "no."

This study evaluated the 9 covariates (sex, age, race, BMI, CAD, CKD, DM, smokeless tobacco use, and TC use) as follows. Sex was defined as "male" or "female." Age was categorized as "18–24," "25–34," "35–44," "45–54," "55–64," and "65+." Race was categorized as "non-Hispanic white" and "other," which included African American, Asian American, Hispanic, or other. Self-reported BMI was categorized as "<25" or non-overweight, and "≥ 25" or overweight in accordance with CDC guidelines.[25] Self-reported diagnoses of CAD, CKD, and DM were categorized as "yes" or "no." Smokeless tobacco was differentiated as "current use" versus "not current use." "Current use" encompassed participants who answered "every day" and "some day" use. TC use was categorized into the following categories: "current-every day," "some-days," "former," and "never." "Former" TC use encompassed having smoked at least 100 cigarettes in one's life, but none currently. If <100 lifetime TCs were used, and not currently using, they were categorized as "never."

This study analyzed the BRFSS data using STATA 3D.[26] Initially, a descriptive analysis was performed to assess baseline characteristics of ENDS use with covariates and stroke. Then, analysis of variance testing was used to obtain P-values across each category. Next, collinearity diagnostics were done to ensure that none of the independent variables or covariates were correlated with each other ($r > 0.6$ or $r < -0.6$). Finally, logistic regression analyses were performed to calculate unadjusted and adjusted odds ratios (AOR) and their corresponding 95% confidence intervals (CI).

2.3. Ethical considerations

This study used de-identified data and was classified by the Florida International University Internal Review Board as non-human subject research. The authors have no conflicts of interest to disclose. The research was performed without any funding.

3. Results

This study's population included 465,594 (95.7%) of the 2016 BRFSS survey of 486,303 participants. It excluded 20,709 (4.3%) participants due to missing data on history of stroke or

ENDS usage. Within this study's population, 5010 (1.5%) participants reported EDU, 10,169 (3.0%) reported SDU, 58,834 (17.1%) reported FU, and 391,581 (78.4%) reported NU. 20,045 (3.2%) reported a history of stroke, and 445,549 (96.8%) denied a history of stroke.

Table 1 outlines the baseline characteristics of ENDS use in this study. Participants with stroke histories represented 3.5% of total EDU versus 3.3% of total SDU versus 2.8% of total FU versus 3.3% of total NU ($P=.02$). Demographically, EDU was more associated with male sex, non-Hispanic white race, and younger age compared with NU. Men accounted for 64.5% of EDU versus 46.5% of NU ($P<.01$). Eighteen to 24-year-olds accounted for 21.2% of EDU versus 9.6% of NU, while 65+ participants made up just 5.3% of EDU versus 24.1% of NU ($P<.01$). Non-Hispanic Whites represented 79.1% of EDU but only 63.0% of NU. Participants with EDU were less likely than with NU to suffer from comorbidities including BMI $\geq$25 kg/m^2, CAD, and DM. BMI $\geq$25 was seen in 63.4% of EDU versus 66.1% of NU ($P<.01$). CAD accounted for 5.4% of EDU versus 7% of NU ($P<.01$). Likewise, DM was with 7.5% of EDU versus 11.9% of NU ($P<.01$). CKD, however, was recorded with 3.5% of EDU, 2.3% of SDU, 2.2% of FU, and 3.1% of NU ($P<.01$). Regarding tobacco, current daily TC use was seen with 18% of EDU versus 4.8% of NU ($P<.01$). Of note, the 55.9% of EDU was seen with former TC use. Currently smokeless tobacco use was seen in 6.4% of EDU versus 2.8% of NU ($P<.01$).

Table 2 shows the adjusted odds ratios (AOR) between the covariates and a history of stroke. Among demographic covariates, female sex was positively associated with a history of stroke versus men (AOR: 1.2, [95% CI: 1.1–1.3]). "Other" race was also positively associated versus non-Hispanic white (1.2, [1.1–1.3]). With age 25 to 34 chosen as the reference, age >65 was strongly associated with stroke (7.3, [5.7–9.3]). Among demographic covariates, BMI $\geq$25 was not significantly associated with stroke versus a normal BMI (0.98, [0.90–1.05]). However, reporting a history of CKD (2.1, [1.8–2.3]), CAD (4.3, [3.9–4.6]), and DM (1.8, [1.6–1.9]) were all associated with a stroke history. Within tobacco covariates, current every-day TC use (2.1, [1.9–2.4]), current someday TC use (1.8, [1.6–2.1]), and former TC use (1.3, [1.2–1.4]) were associated with stroke versus never TC use. In this sample, current smokeless tobacco use was not statistically associated with stroke versus non-current use (1.2, [0.997–1.5]).

Table 1

Baseline characteristics of 2016 BRFSS participants according to electronic nicotine delivery system use.

Electronic nicotine delivery system use									
Characteristic	Current every day		Current some day		Former		Never		P value*
	N	%	N	%	N	%	N	%	
Sex									<.01
Male	2778	64.5	5018	57.8	29014	55.6	164605	46.5	
Female	2229	35.5	5151	42.2	29815	44.4	226937	53.5	
Race									<.01
Non-Hispanic White	4109	79.1	7658	68.2	44074	66.3	298948	63	
Other[a]	818	20.9	2357	31.8	13791	33.7	86135	37	
Age, y									<.01
18–24	640	21.2	1681	28.3	7972	23.6	15029	9.6	
25–34	1030	28.3	1897	23.4	12373	27.5	30815	14.6	
35–44	873	17.9	1536	17.5	9235	17.2	40707	15.9	
45–54	900	15.9	1873	15	10281	14.7	60616	17.7	
55–64	953	11.5	2050	11.3	11259	11.3	88737	18.3	
65+	614	5.3	1132	4.5	7714	5.8	155677	24.1	
Body mass index, kg/m^2									<.01
>25	3113	63.4	5957	58.6	35341	60.9	245605	66.1	
<25	1710	36.6	3817	41.4	20733	39.1	119420	33.9	
Kidney disease									<.01
Yes	177	3.5	342	2.3	1828	2.2	15306	3.1	
No	4812	96.5	9789	97.7	56833	97.8	375153	96.9	
Coronary artery disease									<.01
Yes	416	5.4	872	5.4	4877	5.4	37152	7	
No	4561	94.6	9214	94.6	53529	94.6	351482	93	
Diabetes									<.01
Yes	473	7.5	1019	7	5759	6.8	56145	11.9	
No	4528	92.5	9128	93	52978	93.2	334941	88.1	
Traditional cigarette									<.01
Current every day	1031	18	4849	41.3	23533	34	19342	4.8	
Current some days	705	16.2	2158	20.9	7348	12.4	9331	2.8	
Former	2878	55.9	1612	15.2	13970	22.5	115336	24.5	
Never	375	9.8	1497	22.5	13698	31	245427	67.9	
Smokeless tobacco									<.01
Yes	271	6.4	751	8.1	3646	6.3	10498	2.8	
No	4732	93.6	9400	91.9	55113	93.7	380506	97.2	

[a] Hispanic White, African American, Asian American, and other.

* P value: performed by chi-squared test.

Table 2

Unadjusted and adjusted odds ratios between covariates and a history of stroke using the 2016 BRFSS survey.

History of stroke				
Covariate	**Unadjusted**		**Adjusted**	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Sex				
Male	Reference		Reference	
Female	1.03 (0.97–1.09)	.37	1.2 (1.1–1.3)	<.01
Race				
Non-Hispanic White	Reference		Reference	
Other[a]	0.8 (0.76–0.88)	<.01	1.2 (1.1–1.3)	<.01
Age				
25–34	Reference		Reference	
18–24	0.4 (0.2–0.7)	.04	0.5 (0.3–0.95)	.03
35–44	1.9 (1.5–2.5)	<.01	2.0 (1.5–2.6)	<.01
45–54	3.6 (2.9–4.5)	<.01	3.2 (2.5–4.1)	<.01
55–64	6.0 (4.9–7.5)	<.01	4.7 (3.7–6.0)	<.01
65+	10.4 (8.4–12.8)	<.01	7.3 (5.7–9.3)	<.01
Body mass index, kg/m^2				
<25	Reference		Reference	
≥25	1.3 (1.2–1.4)	<.01	0.98 (0.90–1.05)	.52
Kidney disease				
No	Reference		Reference	
Yes	5.1 (4.6–5.6)	<.01	2.1 (1.8–2.3)	<.01
Coronary artery disease				
No	Reference		Reference	
Yes	9.1 (8.5–9.7)	<.01	4.3 (3.9–4.6)	<.01
Diabetes				
No	Reference		Reference	
Yes	4.1 (3.8–4.3)	<.01	1.8 (1.6–1.9)	<.01
Traditional cigarette				
Never	Reference		Reference	
Current every day	2.4 (2.2–2.6)	<.01	2.1 (1.9–2.4)	<.01
Current some days	1.8 (1.6–2.0)	<.01	1.8 (1.6–2.1)	<.01
Former	2.2 (2.0–2.3)	<.01	1.3 (1.2–1.4)	<.01
Smokeless tobacco				
No	Reference		Reference	
Yes	1.07 (0.8–1.3)	.49	1.2 (0.997–1.5)	.053

[a] Other: Hispanic White, African American, Asian American, and other.

Table 3 demonstrates the primary endpoint, the association between ENDS use and stroke history. After adjusting for the 9 covariates above, EDU use was independently, positively associated with stroke versus NU (1.62, [1.18–2.31]). SDU use was also positively associated (1.28, [1.02–1.61]). FU was not significantly associated with stroke (AOR 1.09, [0.98–1.23]).

4. Discussion

The data from this study revealed a positive association between ENDS use and a history of stroke. EDU and SDU were both associated with an increased likelihood compared with NU of reporting stroke. The association with EDU was greater than with SDU consistent with a dose dependent relationship.

Overall, this study's associations between covariates and stroke aligned relatively closely to those found in other large population-based studies with differences sometimes in the magnitude of the AORs. Female sex, old age, non-Caucasian race, DM, CKD, and TC use have all been accepted as risk factors for stroke.[5] This study's female sex association is very similar to the Framingham study which noted a 1 in 5 lifelong risk of stroke for women versus 1 in 6 for men.[27] For race, this study echoes

Table 3

Unadjusted and adjusted odds ratios of electronic nicotine delivery system (ENDS) use and a history of stroke using the 2016 BRFSS survey.

Stroke				
ENDS use	**Unadjusted**		**Adjusted**	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Never	Reference		Reference	
Current everyday	1.08 (0.80–1.47)	.61	1.62 (1.18–2.31)	.01
Current some days	1.02 (0.84–1.24)	.84	1.28 (1.02–1.61)	.03
Former	0.86 (0.79–0.94)	<.01	1.09 (0.98–1.23)	.11

other studies with non-Caucasian race as a risk factor.[28–30] However, this study's strength of association was less than in the REGARDS cohort, which compared stroke to black versus white ethnicity.[28] This study found that diabetes nearly doubled the risk of reporting stroke, similar to a prior study consisting of 775,385 people.[31] Most studies showed that reduced glomerular filtration rate was associated with an increased odds of reporting stroke, however this study's associations were stronger than in some other studies.[32–34] A meta analysis with 280,000 pooled patients found a lower risk ratio.[32] This study did not account for hypertension which may overestimate this AOR compared with the other studies which were able to account for it. Finally, this study found daily TC use to double the odds of reporting stroke, in line with previous research.[6–8] Overall, the similarity of this study's multifactorial analysis of covariates to stroke compared with those reported in other large studies adds validity to this study's key finding of a statistically significant association between ENDS use and stroke.

Furthermore, several cross-sectional based studies have looked at the association between ENDS and myocardial infarction. One 2018 study of 70,000 participants using the National Health Interview Surveys found that current ENDS users had a statistically significant increased odds of reporting an MI compared with NUs (AOR = 1.8; 95% CI 1.2–2.7).[20] A second study published in 2019, looking at about 60,000 participants in the 2016 to 2017 National Health Interview Surveys, found no statistically significant association between daily ENDS use and MI (AOR 1.35, 95% CI: 0.80–2.27).[21] While their study did not find statistical significance, only 714 participants reported EDU, compared with this Study of which 5010 reported EDU. It is possible that if a larger sample was used, statistical significance would have been found. This study found a large association between MI and stroke. The positive associations found between ENDS and MI bolster the possibility of a true association between ENDS and stroke due to overlaps in pathogenesis between MI and stroke.

Finally, one recently published study using pooled data from the 2016 to 2017 BRFSS sought to examine the risk of stroke with ENDS use in young adults.[22] Amongst 150,000 participants aged 18 to 44, their results found that dual use of ENDS and TCs was associated with a 2.91 AOR (1.62–5.25) of stroke versus nonusers, and a 1.83 AOR (1.06–3.17) of stroke with dual use versus only TCs. Compared with nonsmokers, ENDS use did not show significantly different odds of stroke versus non ENDS or TC users (AOR 0.69, 0.34–1.32).[22] Parekh et al's findings differs from this study's as their study examined at a younger subset and utilized subgroup analyses to look at single ENDS use and dual ENDS use with TC use. Meanwhile this study had a different focus, to find a global independent association between ENDS use and stroke, across all age groups. It included participants of any adult age, including participants older than 65, who are far more likely to report a stroke.

Naturally, this study has some limitations. First, ENDS were initially introduced around 2007 and this study's data were collected in 2016.[35] Hence, there is a relatively short time period in which a person could have ingested enough ENDS doses for ENDS to be a risk factor. Second, while this study accounted for 9 important covariates, it missed valuable modifiable risk factors including hypertension, hyperlipidemia, and alcohol use. The BRFSS did not include these variables in their 2016 questionaire.[24] Third, this study lacked the resolution to further differentiate levels of ENDS use beyond the categories of "EDU," "SDU," and "FU." "SDU" is a potentially vague classification and might not precisely reflect ENDS use. Fourth these data were self-reported which is subject its own inaccuracies.

Lastly, this study's most important limitation is its cross-sectional design. This study could not determine the temporality of the association between ENDS use and a history of stroke. Rather than ENDS use being the exposure variable, and a history of stroke as the outcome variable as intended, it could be that a history of stroke is a risk factor for a participant starting ENDS. This Study found that most every day ENDS users are former TC users and over 90% of every day ENDS users have smoked at least 100 lifetime cigarettes. In other studies, such as the National Center for Health Statistics data brief, among former TC users who quit within the last year, 25.2% of them were current ENDS users. Meanwhile, among current TC users, only 9.7% of them were current ENDS users.[36] Similarly, current TC users with a history of CVD who attempted to quit TC use in the past year had 1.97 times the odds of current ENDS use compared with all TC smokers (including the non-CVD population), who did not attempt to quit TC use within the past year.[37] Some evidence has suggested that TC users may be more prone to stop smoking TCs after a major adverse cardiac event (MACE).[38,39]

However, whether TC users after MACE actually switch to ENDS in a greater frequency than patients without MACE remains to be proven. One study, using 2013 to 2015 Population Assessment of Tobacco and Health data, determined that post MI patients who smoked TCs were not significantly more likely to adopt non-combustible cigarettes than those without an MI.[40] Nevertheless, even if stroke and other MACE were found to be independent risk factors for ENDS, this would still have important healthcare implications. The FDA has yet to approve ENDS for smoking cessation, let alone in those with MACE. The CDC and American Heart Association lack clear statements on ENDS use in patients after MACE, such as stroke.

This study's positive association could be due to either ENDS use as the exposure with stroke as the outcome, or stroke as the exposure with ENDS use as the outcome—both scenarios with important public health implications. The validity of this study's positive association is supported by the similarity of this study's covariates to stroke AORs versus the AORs found in other large studies. It is further supported by the existence of reported positive associations between ENDS use and CAD found in a recent study. Thus, this study's statistical association cannot be ignored and its existence compels the need for future cohort studies to best analyze a relationship between ENDS use and stroke.

5. Conclusion

This study, consisting of over 450,000 people responding to the 2016 BRFSS survey, found an independent positive association between ENDS use and stroke. It is among the first population-based studies to assess for this association. Further research, particularly cohort studies, is needed to assess the reproducibility and temporality of the positive association found in this study.

Author contributions

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