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Original Investigation

Longitudinal Associations Between Exclusive and Dual Use of Electronic Nicotine Delivery Systems and Cigarettes and Self-Reported Incident Diagnosed Cardiovascular Disease Among Adults

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Abstract

Introduction: The cardiovascular health effects of electronic nicotine delivery systems (ENDS) use are not well characterized, making it difficult to assess ENDS as a potential harm reduction tool for adults who use cigarettes.

Aims and Methods: Using waves 1–5 of the Population Assessment of Tobacco and Health Study (2013–2019), we analyzed the risk of self-reported incident diagnosed myocardial infarction (MI; 280 incident cases) and stroke (186 incident cases) associated with ENDS and/or cigarette use among adults aged 40 + using discrete time survival models. We employed a time-varying exposure lagged by one wave, defined as exclusive or dual established use of ENDS and/or cigarettes every day or some days, and controlled for demographics, clinical factors, and past smoking history.

Results: The analytic samples (MI = 11 031; stroke = 11 076) were predominantly female and non-Hispanic White with a mean age of 58 years. At baseline, 14.2% of respondents exclusively smoked cigarettes, 0.6% exclusively used ENDS, and 1.0% used both products. Incident MI and stroke were rare during follow-up (< 1% at each wave). Compared to no cigarette or ENDS use, exclusive cigarette use increased the risk of MI (aHR 1.99, 95% CI = 1.40–2.84) and stroke (aHR 2.26, 95% CI = 1.51–3.39), while exclusive ENDS use (MI: aHR 0.61, 95% CI = 0.12–3.04; stroke: aHR 1.74, 95% CI = 0.55–5.49) and dual use (MI: aHR 1.84, 95% CI = 0.64–5.30; stroke: aHR 1.12, 95% CI = 0.33–3.79) were not significantly associated with the risk of either outcome.

Conclusions: Compared to non-use, exclusive cigarette use was associated with an increased risk of self-reported incident diagnosed cardiovascular disease over a 5-year period, while ENDS use was not associated with a statistically significant increase in the outcomes.

Implications: Existing literature on the health effects of ENDS use has important limitations, including potential reverse causation and improper control for cigarette smoking. We accounted for these issues by using a prospective design and adjusting for current and former smoking status and cigarette pack-years. In this context, we did not find that ENDS use was associated with a statistically significant increase in self-reported incident diagnosed myocardial infarction or stroke over a 5-year period. While more studies are needed, this analysis provides an important foundation and key methodological considerations for future research on the health effects of ENDS use.

Introduction

Cigarette use is a leading risk factor for cardiovascular disease, increasing the risk of myocardial infarction and stroke.[1] Although smoking is declining in the U.S., 14.0% of adults reported current cigarette use in 2019.[2] Conversely, electronic nicotine delivery systems (ENDS) use has increased in recent years, with 4.5% of adults reporting current ENDS use in 2019.[2] Given the numerous health hazards of cigarettes, it has been argued that ENDS may serve as a harm reduction tool for individuals who smoke cigarettes and cannot otherwise quit.[3,4] Abrams et al.[4] state, "It is not that e-cigarettes are completely safe, or even the safest nicotine-containing product available, but that they are much safer than smoking".

However, the cardiovascular impact of ENDS use is not well characterized, given the relatively recent introduction of ENDS to the nicotine product marketplace. Cardiovascular effects of ENDS use are theoretically plausible, as there is evidence of ENDS-induced cardiac dysfunction in animal

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models.[5] Potential cardiovascular risks of ENDS use may be attributable to nicotine,[6] as recent ENDS products contain as much nicotine as cigarettes.[7,8] Additionally, ENDS aerosol itself, independent of nicotine, may pose risks due to its toxicity.[6,8]

A number of epidemiological studies have identified an association between ENDS use and cardiovascular disease among adults.[9–13] However, these studies are predominately cross-sectional[9–13] and therefore subject to reverse causation,[14–16] as adults who smoke cigarettes may start using ENDS after being diagnosed with cardiovascular disease.[17] Additionally, although most adults who use ENDS have a history of cigarette use,[18] many of these studies do not adequately account for past smoking history. Furthermore, the rapid rise in ENDS use among youth[19] and young adults[20] has led to concerns about the long-term health effects of ENDS use among people who have never smoked.

Longitudinal studies on the health effects of ENDS use, including cardiovascular disease, are essential for characterizing health risks, relative to people who do and do not smoke cigarettes. We thus need to document the risks associated with ENDS use to situate ENDS within the risk continuum of nicotine and tobacco products and characterize risks for people who do not smoke cigarettes. Our objective for this study is to assess prospective associations between exclusive and dual use of ENDS and cigarettes with myocardial infarction and stroke among U.S. adults using a longitudinal, nationally representative study, adjusting for past cigarette smoking history.

Methods

Study Sample

We used restricted data on adults from Waves 1–5 (2013–2019) of the Population Assessment of Tobacco and Health (PATH) Study, a nationally representative longitudinal study of the U.S. civilian, non-institutionalized population ages 12 and older.[21] PATH collected data annually from Waves 1–4 before moving to biannual data collection in Wave 5 (Wave 1: September 2013—December 2014 (response rate (RR): 74.8% among those who completed the household screener [54.1%]); Wave 2: October 2014—October 2015 (RR among Wave 1 cohort: 82.8%); Wave 3: October 2015—October 2016 (RR among Wave 1 cohort: 78.0%); Wave 4: December 2016—January 2018 (RR among Wave 1 cohort: 72.9%); Wave 5: December 2018—November 2019 (RR among Wave 1 cohort: 69.4%). PATH oversamples people who use tobacco, young adults, and Black adults. Further details on the PATH design[22] and accessing restricted data files[21] are available elsewhere.

We analyzed incidence of myocardial infarction (MI) and stroke over follow-up waves 2–5. Given that MI is rare in young adults, PATH suppressed MI outcomes for respondents under age 40 beginning in Wave 4. We thus restricted the analytic sample to respondents aged 40 or older at Wave 1 for consistency across waves. Additionally, since the majority of lifetime MI and stroke events reported at baseline occurred before ENDS were available, we excluded respondents who reported an MI or stroke at baseline to minimize the potential for reverse causation.[15] A flowchart summarizing the sample selection procedure is available in the supplemental material (Supplementary Figures S1 and S2).

Measures

We examined incidence of self-reported diagnosed MI and stroke at each follow-up interview using these questions: "In the past 12 months, has a doctor, nurse, or other health professional told you that you had a heart attack (or needed bypass surgery)?" and "In the past 12 months, has a doctor, nurse, or other health professional told you that you had a stroke?" Both outcomes were coded as dichotomous variables (0 = no, 1 = yes), with "don't know" responses treated as missing (n = 11 for MI; n = 25 for stroke; see Supplementary Figures S1 and S2).

In Waves 2 and 3, all respondents answered questions about MI and stroke in the past 12 months. However, in Waves 4 and 5, PATH updated a skip pattern so that only respondents who reported seeing a health professional in the past 12 months answered these questions. For Waves 2 and 3, we classified all respondents who reported an MI or stroke as having the relevant outcome regardless of whether they saw a health professional in the past 12 months. In Waves 4 and 5, we classified respondents who did not see a health professional in the past 12 months, and were therefore not asked about MI or stroke, as not having either outcome.

We defined ENDS use as established (ever used ENDS fairly regularly) current use every day or some days, and cigarette use as established (smoked 100 or more cigarettes in lifetime) current use every day or some days. We developed a four-category exposure variable and included it as a time-varying exposure: non-current use of either product (including never use or former use), exclusive cigarette use, exclusive ENDS use, or dual use of cigarettes and ENDS. We imputed missing exposure data (about 2.5%) from a previous wave to reduce exposure missingness to less than 0.2% for any given wave. To ensure that the cigarette/ENDS exposure preceded the outcome, we lagged the exposure variable by one wave (t-1) and evaluated its association with the corresponding outcome at wave (t).

We included age (continuous), sex (female, male), race/ethnicity [Hispanic, Non-Hispanic (NH) White, NH Black, Another race/ethnicity], and educational attainment (high school or less, some college/associate degree, bachelor degree, graduate degree) as baseline sociodemographic covariates. We also adjusted for baseline clinical risk factors, including family history of premature heart disease (i.e., a biological family member with MI before age 50), diagnosed hypertension, and diagnosed diabetes.

To account for potential confounding by historical cigarette smoking, we included baseline indicators for former established smoking (smoked at least 100 cigarettes in lifetime, but no current use) and cigarette pack-years (CPY) for adults who currently/formerly smoked cigarettes. We calculated CPY by multiplying the baseline self-reported duration of cigarette smoking in years by the average cigarette packs smoked per day by Wave 1. We coded people who never smoked as having zero CPY and removed respondents with implausible values (more than 10 packs per day; n = 239–247 across samples) from the analysis.

Statistical Analysis

We produced weighted descriptive statistics at baseline overall and by tobacco use group, using Chi-square or Fischer's exact tests to assess differences between groups. We also estimated

the unadjusted weighted hazard of MI and stroke at each discrete time interval (wave) using life tables.

Using multivariable discrete time survival models, we estimated prospective associations between exclusive and dual use of ENDS and cigarettes and newly diagnosed MI and stroke across follow-up (Wave 2–Wave 5). Discrete time survival models are appropriate when the exact timing of an event is not known,[23] and are analogous to continuous time survival models when the data are restructured so each respondent has a separate row of data for each risk period (wave) until they experience the event or are right censored.[24] This allowed us to examine the conditional probability of MI and stroke at each discrete time interval. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) with the complimentary log–log link function on the person-period data set, running separate models with both non-current use and exclusive cigarette use as the referent category.

We used Wave 1 weights to ensure representativeness of the non-institutionalized U.S. adult population at baseline and to minimize biases associated with PATH longitudinal weights that drop respondents who did not complete a survey at every wave. To assess the impact of attrition, we compared baseline characteristic for censored (n = 2605–2658) and non-censored (n = 8418–8426) respondents. As sensitivity analyses, we estimated three additional multivariable discrete time models adjusting for the potential confounding of other tobacco product use [i.e., other combustibles (including traditional cigars, filtered cigars, cigarillos, hookah, and pipes) and smokeless tobacco], time since quitting cigarettes, and duration of ENDS use among adults who had established ENDS use at baseline. All analyses estimated variance using the balanced repeated replication methods with Fay's adjustment set to 0.3,[25,26] and were conducted using Stata 16.1.[27] Given the use of secondary de-identified data, this study was deemed not regulated as human subjects research by the University of Michigan Institutional Review Board.

Results

Our analytic samples differed slightly for MI (n = 11 031) and stroke (n = 11 076; Table 1), primarily due to differences in the number of respondents with MI or stroke prior to baseline who were excluded from the analysis (Supplementary Figures S1 and S2). As the samples are very similar, we present rounded descriptive statistics for simplicity (full details available in Tables 1 and 2). At baseline (2013–14), respondents had a mean age of 58 years and were predominantly female (55%) and NH White (71%) with at least some college education (59%). Most respondents did not currently use cigarettes or ENDS (84%), with the remaining 14% exclusively smoking cigarettes, 0.6% exclusively using ENDS, and 1% using both products at baseline (breakdown of time-varying ENDS/cigarette use available in Supplementary Table S1). Nearly one quarter (24%) of baseline respondents formerly smoked cigarettes. In terms of health history, 10% of respondents had a family history of premature MI, 39% had diagnosed hypertension, and 20% had diagnosed diabetes.

Table 2 presents sample characteristics at baseline by tobacco exposure category. Compared to respondents who exclusively smoked cigarettes (mean age 54 years) or exclusively used ENDS (mean age 54 years), respondents who did not currently use either product were older (mean age 58 years), while respondents who used both products were slightly younger (mean age 52 years). Respondents who exclusively smoked cigarettes were more likely to be male (51%), NH Black (16%), and have a high school degree or less (58%) versus respondents with other use profiles. Respondents who used ENDS, with or without cigarettes, were more likely to be female and NH White than respondents who exclusively smoked cigarettes or did not use either product. Notably, more than three-fourths of respondents exclusively using ENDS had previously smoked cigarettes. Mean CPYs ranged from 6 among adults who did not currently use ENDS or cigarettes to 29 among adults who exclusively used ENDS, highlighting that all groups included adults who either formerly or currently smoked cigarettes. Respondents who did not use either product had a higher prevalence of both diagnosed hypertension (40%) and diabetes (20%) than respondents with other use profiles.

The annual incidence of MI and stroke across the follow-up period was rare, accounting for less than 1% of the analytic sample for each outcome (Table 3; MI = 0.66% [n = 280], Stroke = 0.53% [n = 256]). The hazard, which measures the conditional probability of experiencing the outcomes at each discrete time interval, was similar across all time intervals for MI (F = .11, p = .95) and stroke (F = 1.85, p = .14), meaning that the probability of these outcomes did not significantly change as a function of time.

Myocardial Infarction

Table 4 presents the results of unadjusted and adjusted models examining the risk of incident MI and stroke diagnosis across the 5-year follow-up period. In the unadjusted model, respondents who exclusively smoked cigarettes had 63% higher risk of MI in subsequent waves compared to respondents who did not currently use cigarettes or ENDS (HR 1.63, 95% CI = 1.23–2.16). The risk of MI for respondents who used ENDS exclusively (HR 0.59, 95% CI = 0.12–2.62) or in combination with cigarettes (HR 1.12, 95% = 0.41–3.09) did not significantly differ from respondents who did not currently use either product. Results were similar after adjusting for sociodemographic factors, smoking history, and baseline risk factors, although the association with exclusive cigarette use was strengthened slightly (Adjusted Hazard Ratio [aHR] 1.99, 95% CI = 1.40–2.84). Past smoking history was not associated with the risk of MI after adjusting for other covariates. When using exclusive cigarette use as the referent group (Supplementary Table S2), the risk of MI for respondents who used ENDS exclusively (aHR 0.30, 95% CI = 0.06–1.59) or with cigarettes (aHR 0.93, 95% CI = 0.35–2.48) did not significantly differ from the risk for respondents who exclusively smoked cigarettes.

Stroke

In the unadjusted model, respondents who exclusively smoked cigarettes had 2.37 times higher risk of stroke in subsequent waves compared to respondents who did not use cigarettes or ENDS (Table 4; 95% CI = 1.76–3.19). Compared to respondents who did not currently use either product, the risk of stroke did not significantly differ for respondents who used ENDS exclusively (HR 1.45, 95% CI = 0.48–4.36) or in combination with cigarettes (HR 0.94, 95% CI = 0.28–3.14). In the fully adjusted model, exclusive cigarette use (aHR 2.26, 95% CI = 1.51–3.39) was associated with increased risk of stroke, while other use profiles were not. Past smoking history was not associated

Table 1. Sample characteristics for respondents, Population Assessment of Tobacco and Health (Wave 1, 2013–14)

	Myocardial infarction (n = 11 031)			Stroke (n = 11 076)		
	n	%	95% CI	*n*	%	95% CI
Sociodemographic factors						
Mean age (SD)	11 031	57.5 (11.7)		11 076	57.7 (11.8)	
Sex						
Female	5708	55.1	54.3–55.8	5651	54.3	53.6–55.1
Male	5323	44.9	44.2–45.7	5425	45.7	44.9–46.4
Race/ethnicity						
NH White	7410	71.3	70.5–72.1	7498	71.9	71.0–72.7
Hispanic	1331	11.5	10.8–12.2	1322	11.4	10.7–12.1
NH Black	1652	11.1	10.6–11.6	1626	10.8	10.3–11.3
Another race/ethnicity	638	6.1	5.6–6.6	630	5.9	5.5–6.7
Education						
High school or less	4769	41.2	40.5–41.8	4770	41.2	40.6–41.8
Some college/associates degree	3523	28.9	28.4–29.5	3565	29.2	28.6–29.7
Bachelor degree	1607	17.6	17.0–18.1	1615	17.5	17.0–18.1
Graduate degree	1132	12.3	11.9–12.7	1126	12.1	11.8–12.5
Cigarette/ENDS use						
Non-current use	6798	84.3	83.6–84.9	6813	84.2	83.5–84.8
Exclusive cigarette use	3785	14.2	13.6–14.7	3810	14.2	13.6–14.8
Exclusive ENDS use	174	0.6	0.52–0.74	172	0.6	0.53–0.73
Dual use	274	0.9	0.84–1.11	281	1.0	0.87–1.2
Smoking history at baseline						
Former established smoking	2173	23.5	22.3–24.8	2206	23.8	22.6–25.1
Cigarette pack-years						
Zero pack-years (never smoking)	4976	62.5	61.1–64.0	4960	62.2	60.7–63.6
Non-zero pack-years (former/current smoking)	6055	37.5	36.0–38.9	6116	37.8	36.4–39.3
Mean pack-years among former/current smoking (SD)	6055	26.0 (27.5)		6116	26.4 (27.7)	
Baseline risk factors						
Family history of premature MI[a]	1248	10.2	9.4–11.1	1291	10.5	9.8–11.3
Hypertension diagnosis	4205	39.0	37.8–40.2	4248	39.3	38.1–40.5
Diabetes diagnosis	2127	19.8	18.6–21.0	2162	19.9	18.8–21.1

Unweighted counts and weighted percentages presented.
ENDS = electronic nicotine delivery systems; MI = myocardial infarction.
[a]Prior to age 50.

with the risk of stroke after adjusting for other covariates. When using exclusive cigarette use as the referent group (Supplementary Table S2), the risk of stroke for respondents who used ENDS exclusively (aHR 0.77, 95% CI = 0.25–2.38) or with cigarettes (aHR 0.50, 95% CI 0.15–1.60) did not significantly differ from the risk for respondents who exclusively smoked cigarettes.

Attrition and Sensitivity Analyses

The results from an attrition analysis comparing baseline characteristics for respondents with complete and incomplete follow-up data are available in Supplementary Table S3. Compared to non-censored respondents, censored respondents were older and more likely to be male, NH White, have a high school degree or less, and have diagnosed hypertension at baseline. Additionally, censored respondents had a higher mean CPY value than non-censored respondents and were more likely to exclusively smoke cigarettes. However, the prevalence of exclusive ENDS use and dual use of cigarettes and ENDS were nearly identical between censored and non-censored cases.

We conducted several sensitivity analyses to assess the robustness of our findings. The interpretation and statistical significance of the cigarette/ENDS exposure variable did not change after adjusting for time-varying additional tobacco product use (other combustible products including traditional cigars, filtered cigars, cigarillos, hookah, and pipe; smokeless tobacco), time since quitting cigarettes (less than 2 years vs. 2 years or more), or duration of ENDS use among adults with established ENDS use at baseline (data not shown).

Discussion

This study examines prospective associations between exclusive and dual use of ENDS and cigarettes and cardiovascular disease using Waves 1–5 (2013–2019) of the PATH study, a nationally representative longitudinal survey. Exclusive

Table 2. Sample characteristics by cigarette/ENDS use, Population Assessment of Tobacco and Health (Wave 1, 2013–14)

	Myocardial infarction sample (n = 11 031)					Stroke sample (n = 11 076)				
	Non-current use	Cigarette use	ENDS use	Dual use	p-value	Non-current use	Cigarette use	ENDS use	Dual use	p-value
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)		% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	
Sociodemographic factors										
Mean age (SD)	58.3 (10.2)	53.5 (14.3)	53.5 (14.5)	51.5 (12.8)	***	58.4 (10.3)	53.6 (14.3)	53.8 (15.1)	51.9 (13.2)	***
Sex					***					***
Female	56.0 (55.1–56.8)	49.2 (47.5–50.9)	59.9 (52.6–66.9)	60.6 (54.8–66.1)		55.2 (54.3–56.1)	48.5 (46.8–50.2)	58.3 (51.1–65.1)	61.5 (55.6–67.1)	
Male	44.0 (43.2–44.9)	50.8 (49.1–52.5)	40.1 (33.1–47.4)	39.4 (33.9–45.2)		44.8 (43.9–45.6)	51.5 (49.8–53.2)	41.7 (34.9–48.9)	38.5 (32.9–44.4)	
Race/ethnicity					***					***
NH White	71.4 (70.4–72.4)	69.7 (67.9–71.6)	80.9 (72.5–86.6)	80.5 (74.5–85.3)		72.0 (71.0–73.0)	70.3 (68.4–72.2)	81.2 (73.2–87.2)	80.9 (75.1–85.5)	
Hispanic	12.0 (11.3–12.9)	9.2 (8.1–10.3)	5.1 (2.7–9.3)	4.1 (2.3–7.3)		11.9 (11.1–12.7)	9.1 (8.1–10.2)	5.1 (2.7–9.3)	3.9 (2.2–7.1)	
NH Black	10.2 (9.6–10.8)	16.3 (15.1–17.5)	8.2 (5.0–14.5)	10.9 (7.4–15.9)		9.9 (9.4–10.6)	16.0 (14.8–17.3)	8.3(4.8–14.1)	10.9 (7.4–15.7)	
Another race/ethnicity	6.4 (5.8–7.0)	4.8 (4.1–5.7)	5.8 (2.9–11.1)	4.5 (2.8–7.1)		6.2 (5.6–6.8)	4.6 (3.8–5.5)	5.4 (2.7–10.7)	4.3 (2.8–6.6)	
Education					***					***
High school or less	38.2 (37.4–4.4)	58.5 (56.6–60.4)	46.2 (38.7–53.5)	42.9 (36.3–49.7)		38.2 (37.5–38.9)	58.4 (56.5–60.2)	45.8 (38.4–53.4)	43.3 (36.9–49.9)	
Some college	28.4 (27.8–29.1)	30.9 (29.3–32.6)	38.1 (31.5–45.8)	38.7 (32.1–45.7)		28.6 (28.0–29.3)	31.0 (29.4–32.8)	39.6 (32.6–47.1)	38.3 (31.7–45.4)	
Bachelor degree	19.3 (18.7–19.9)	7.9 (7.0–9.0)	10.5 (6.4–16.6)	12.2 (8.1–17.9)		19.3 (18.6–19.9)	7.9 (7.0–9.0)	9.5 (5.7–15.2)	12.7 (8.3–19.0)	
Graduate degree	14.1 (13.6–14.5)	2.7 (2.2–3.2)	5.2 (2.3–11.2)	6.2 (4.1–9.5)		13.9 (13.4–14.3)	2.6 (2.2–3.2)	5.1 (2.3–11.1)	5.7 (3.6–8.7)	
Smoking history at baseline										
Former established smoking	27.3 (25.9–28.9)	0.0[a]	76.9 (69.5–83.0)	0.0[a]	***	27.7 (26.2–29.3)	0.0[a]	78.3 (71.3–83.9)	0.0[a]	***
Mean pack–years (SD)	6.4 (13.7)	27.4 (34.2)	29.0 (44.1)	23.7 (34.3)	***	6.7 (14.0)	27.7 (34.8)	29.5 (43.6)	23.5 (34.0)	***
Baseline risk factors										
Family history of premature MI[b]	9.7 (8.9–10.6)	13.0 (11.7–14.7)	14.7 (9.9–21.4)	10.7 (7.5–15.1)	***	9.9 (9.1–10.7)	13.7 (12.4–15.1)	13.3 (8.8–19.4)	13.0 (9.0–18.6)	***
Hypertension diagnosis at baseline	39.6 (38.2–41.0)	36.3 (34.6–38.0)	35.3 (27.8–43.7)	33.9 (28.4–40.0)	*	39.8 (38.4–41.2)	36.5 (34.9–38.2)	36.8 (29.6–44.5)	36.2 (30.8–42.0)	**
Diabetes diagnosis at baseline	20.4 (19.0–21.8)	16.3 (15.2–17.4)	16.4 (11.3–23.3)	19.0 (15.0–23.8)	**	20.4 (19.1–21.9)	16.9 (15.8–18.1)	16.4 (11.4–23.1)	19.4 (15.2–24.4)	***

Weighted percentages presented.
ENDS = electronic nicotine delivery systems; MI = myocardial infarction.
*$p < .05$.
**$p < .01$.
***$p < .001$.
[a]By definition, category only has adults who formerly smoked.
[b]Prior to age 50.

Table 3. Incidence of myocardial infarction/stroke, Population Assessment of Tobacco, and Health (Waves 1–5, 2013–2019)

	Myocardial infarction					Stroke				
	Total	No diagnosis	Diagnosis	Censored	Hazard estimate[a]	Total	No diagnosis	Diagnosis	Censored	Hazard estimate[a]
Wave 1–2 (2013–15)	11031	10958	73	802	0.0066	11076	11008	68	816	0.0043
Wave 2–3 (2014–16)	10156	10086	70	794	0.0062	10192	10117	75	803	0.0061
Wave 3–4 (2015–17)	9292	9230	62	1009	0.0067	9314	9265	49	1039	0.0045
Wave 4–5 (2016–19)	8221	8146	75	8146	0.0071	8226	8162	64	8162	0.0053
Average annual incidence					0.0066					0.0053

Test for significant change in hazards: MI outcome $F = .11$, $p = .95$; Stroke outcome $F = 1.85$, $p = .14$.
[a]Hazard estimates were calculated with replicate weights.

cigarette use was associated with a statistically higher incident risk of self-reported diagnosed MI or stroke compared to no current cigarette or ENDS use. ENDS use, either exclusively or in combination with cigarettes, was not statistically associated with increased risk of self-reported diagnosed MI or stroke over the 5-year follow-up period.

Consistent with a large body of existing evidence,[1,28,29] we found that cigarette use increased the risk of cardiovascular disease. In our study, only exclusive cigarette use, and not dual use of cigarettes and ENDS, statistically increased the risk of self-reported diagnosed MI and stroke. In the fully adjusted model predicting MI, the hazard ratio point estimate for dual use was elevated, but this finding did not reach statistical significance. This may be due to a lack of power, since our dual use sample was relatively small ($n = 274$ at baseline). There is some evidence suggesting that cigarette and ENDS dual use might be associated with greater nicotine[13,30] and toxicant exposure[30] than exclusive cigarette use, but further studies are needed to understand potential variation with the actual dose of each product. Additionally, some cross-sectional studies have reported higher odds of cardiovascular disease for respondents using both cigarettes and ENDS versus respondents exclusively smoking cigarettes.[11,12] However, these studies did not account for cigarette smoking intensity nor cumulative pack-years of exposure. In our study, respondents using both cigarettes and ENDS had slightly lower mean cigarettes pack-years (CPY) at baseline (23.5–23.7) than respondents exclusively using cigarettes (27.4–27.7) or ENDS (29.0–29.5). Furthermore, respondents using both cigarettes and ENDS were younger and had less diagnosed hypertension and less family history of premature MI than respondents exclusively using cigarettes or ENDS. If adults who smoke cigarettes are using ENDS as a cigarette cessation or reduction tool, and any potential cardiovascular risk associated with ENDS use is lower than the risk associated with current or past cigarette use, we would not necessarily expect a prospective association between dual use and cardiovascular disease.

We did not find a statistically significant association between exclusive ENDS use and risk of self-reported incident diagnosed MI or stroke, although the direction of the point estimates differed for the two outcomes. The adjusted hazard ratio for exclusive ENDS use and incident MI was less than one (0.61, 95% CI = 0.12–3.04), while the adjusted hazard ratio for exclusive ENDS use and stroke was greater than one (1.74, 95% CI = 0.55–5.49). These estimates had wide CIs, likely due to the relatively small number of respondents exclusively using ENDS ($n = 172$–174 at baseline). Nevertheless, the lack of an association between exclusive ENDS use and incident MI or stroke is consistent with several recent studies reporting no cross-sectional association between exclusive ENDS use and cardiovascular disease.[11,12] This finding is also noteworthy given that three-fourths of respondents in our study who exclusively used ENDS at baseline had formerly smoked cigarettes, although former smoking status at baseline was not associated with the outcomes in the fully adjusted models. A study from Italy reported a reduction in blood pressure among participants with hypertension who switched from cigarettes to ENDS,[31] suggesting that ENDS may be an important harm reduction tool for cardiovascular disease. However, as evidenced by our overlapping CIs, we did not find that adults who use ENDS were at a statistically lower risk for self-reported MI or stroke relative to adults who exclusively use cigarettes. Given the plausibility of ENDS as a cardiovascular risk factor based on animal models[5] and toxicity,[6,8] future studies with longer follow-up periods are needed to assess any potential harm reducing effect of ENDS relative to cigarette use as chronic cardiovascular conditions may take longer to develop than considered in our study.

Limitations

This study is among the first to examine prospective associations between ENDS use and cardiovascular disease while formally accounting for current and historical cigarette use. Despite this contribution to the literature, there are several limitations. First, these results are based on self-reported data from a prospective longitudinal study and should be interpreted with the same level of caution as all studies with self-reported data. Second, the PATH study does not yet have the follow-up period needed to fully examine risks of developing chronic conditions such as cardiovascular disease due to ENDS use because ENDS are relatively new products and PATH currently has only five waves of data. In the absence of this information, we have provided preliminary evidence that ENDS use does not statistically increase the risk of self-reported incident diagnosed MI or stroke over a 5-year period. Third, we were unable to account for nonrandom attrition among respondents who suffered debilitating or fatal cardiovascular events. However, for this to

Table 4. Discrete time survival analysis predicting incident myocardial infarction/stroke, Population Assessment of Tobacco, and Health (Waves 1–5, 2013–2019)

	Myocardial infarction				Stroke			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI	Hazard	95% CI	Hazard	95% CI
Time-varying cigarettes/ENDS use								
Non-current use	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Exclusive cigarette use	1.63**	1.23–2.16	1.99***	1.40–2.84	2.37***	1.76–3.19	2.26***	1.51–3.39
Exclusive ENDS use	0.59	0.12–2.62	0.61	0.12–3.04	1.45	0.48–4.36	1.74	0.55–5.49
Dual use	1.12	0.41–3.09	1.84	0.64–5.30	0.94	0.28–3.14	1.12	0.33–3.79
Sociodemographic factors								
Age	1.05***	1.04–1.06	1.04***	1.03–1.06	1.04***	1.03–1.06	1.04***	1.03–1.06
Sex								
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.53*	1.07–2.20	1.71**	1.18–2.46	1.14	0.85–1.53	1.21	0.89–1.64
Race/ethnicity								
NH White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Hispanic	0.76	0.45–1.26	0.84	0.50–1.42	0.64	0.34–1.22	0.65	0.35–1.23
NH Black	1.10	0.71–1.69	0.94	0.60–1.48	1.57*	1.10–2.25	1.29	0.92–1.82
Another race/ethnicity	0.39*	0.19–0.82	0.52	0.25–1.10	0.75	0.42–1.30	0.98	0.59–1.63
Education								
High school or less	3.60***	1.99–6.54	2.89**	1.56–5.36	3.98***	1.79–8.85	2.79*	1.24–6.26
Some college/associates degree	2.04*	1.08–3.86	1.86	0.98–3.56	2.41***	1.10–5.32	1.96	0.87–4.43
Bachelor degree	0.99	0.45–2.20	1.10	0.49–2.44	1.16	0.43–3.08	1.24	0.46–3.35
Graduate degree	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Smoking history at baseline								
Former established smoking	1.60*	1.09–2.35	1.43	0.91–2.24	0.80	0.47–1.38	0.70	0.39–1.25
Cigarette pack-years[a]	1.13***	1.08–1.17	0.98	0.92–1.04	1.12**	1.04–1.19	1.02	0.93–1.11
Baseline risk factors								
Family history of premature MI[b]	2.85***	2.00–4.04	2.68***	1.84–3.90	2.50***	1.74–3.60	2.25***	1.59–3.18
Hypertension diagnosis	2.52***	1.79–3.54	1.56*	1.01–2.40	2.21***	1.64–2.99	1.29	0.90–1.86
Diabetes diagnosis	2.22***	1.55–3.19	1.45	0.95–2.25	2.58***	1.77–3.74	1.85**	1.21–2.82

Myocardial infarction persons n = 11 031, person-years = 38 700; Stroke persons n = 11 076, person-years n = 38,808.
ENDS = electronic nicotine delivery systems; MI = myocardial infarction.
*$p < .05$.
**$p < .01$.
***$p < .001$.
[a]Rescaled to 10 pack-year intervals for models.
[b]Prior to age 50.

substantively change the non-significant ENDS use finding, the respondents who experienced these cardiovascular events would have to be adults who disproportionately use ENDS products. We examined differences between censored and uncensored cases and found that attrition was higher among adults who used cigarettes but not those who used ENDS. Nevertheless, this potential bias cannot be fully eliminated. Additionally, without linking to mortality data we may be underestimating the risk of cardiovascular disease. However, cardiovascular-related fatalities are likely most prevalent among older people who currently smoke. Fourth, beginning in wave 4, PATH only asked questions about diagnosed MI or stroke to respondents who reported visiting a health professional in the past 12 months. Although we may be missing individuals with MI or stroke who did not visit a health professional in the past 12 months in waves 4 and 5, we expect this is unlikely given the severity of the outcomes. Fifth, the small number of respondents using ENDS at each wave may have limited power to detect an association between ENDS use and cardiovascular disease. Although limiting our ENDS use definition to established use reduced the number of respondents classified as having ENDS use, it isolated any health effects associated with regular, rather than experimental or transient, ENDS use. Finally, ENDS products are changing rapidly, and the concomitant risks associated with ENDS use may also be changing. Further research with a larger number of adults who use ENDS will be needed to better understand any long-term cardiovascular health effects associated with prolonged ENDS use.

Conclusion

Using nationally representative prospective data among U.S. adults aged 40+, we found that exclusive

cigarette use statistically increased the risk of self-reported incident diagnosed cardiovascular disease over a 5-year period compared to no current cigarette or ENDS use, while ENDS use did not. Most adults who used ENDS had a history of cigarette smoking, and the results from this study underscore the importance of adjusting for smoking history when assessing the independent health effects of ENDS use on cardiovascular disease. The harm reducing potential of switching from cigarettes to ENDS will require further study, but the well-known harm producing effect of continued cigarette use on cardiovascular health has been re-affirmed in our study. Convincing adults who smoke cigarettes to stop smoking remains an important public health challenge with clear implications for cardiovascular health.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

The authors have no competing interests to declare.

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None.

Data Availability Statement

Public use files for the Population Assessment of Tobacco & Health (PATH) Study are available for direct download at https://www.icpsr.umich.edu/web/NAHDAP/studies/36498. The PATH restricted files used in this analysis are available via application at https://www.icpsr.umich.edu/web/NAHDAP/studies/36231.

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