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Running Head: ENDS AND HYPERTENSION AMONG US ADULTS

The time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study

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Abstract

Objective: Electronic Nicotine Delivery Systems (ENDS) products have emerged as the most popular alternative to combustible cigarettes. However, ENDS products contain potentially dangerous toxicants and chemical compounds, and little is known about their health effects. The aim of the present study was to examine the prospective association between cigarette and ENDS use on self-reported incident hypertension.

Design and Methods: Using adult data from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco and Health Study, we examined the risk of self-reported incident hypertension associated with ENDS use using discrete-time survival models. To distinguish the role of cigarettes and ENDS, we constructed a time-varying tobacco exposure, lagged by one wave, defined as no use, exclusive established use (daily or some days) of ENDS or cigarettes, and dual use. We controlled for demographics (age, sex, race/ethnicity, household income), clinical risk factors (family history of heart attack, obesity, diabetes, binge drinking) and smoking history (cigarette pack-years).

Results: The self-reported incidence of hypertension was 3.7% between Waves 2-5. At baseline, 18.0% of respondents exclusively smoked cigarettes, 1.1% exclusively used ENDS, and 1.7% were dual users. In adjusted models, exclusive cigarette use was associated with an increased risk for self-reported incident hypertension compared to non-use (aHR=1.21, 95% CI: 1.06-1.38), while exclusive ENDS use (aHR=1.00, 95% CI: 0.68-1.47) and dual use (aHR=1.15, 95% CI: 0.87-1.52) were not.

Conclusions: We found that smoking increased the risk of self-reported hypertension but ENDS use did not. These results highlight the importance of using prospective longitudinal data to examine the health effects of ENDS use.

Keywords: ENDS, cigarettes, hypertension, cardiovascular disease

Strengths and limitations of this study

- To our knowledge, this is the first study to examine the time-varying association between cigarette smoking and ENDS use on the incidence of hypertension among a nationally representative sample of US adults.
- By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.
- We also controlled for the potential confounding of past smoking history, measured as cigarette pack-years, which important because most adults who use ENDS are either currently smoking cigarettes or have smoked cigarettes in the past.
- Our study was limited by relying on self-reported hypertension, as systolic and diastolic blood pressure measures were not available.
- Our non-randomized data means that our results could be affected by unmeasured confounding, and the results should be interpreted with the same level of caution required in all prospective longitudinal studies.

Introduction

Cigarette smoking is the leading cause of premature mortality in the US,[1,2] and a significant proportion of smoking-attributable deaths are related to cardiovascular disease.[3,4] Smoking is known to cause an acute rise in blood pressure,[5] contribute to arterial stiffness,[6] and has been associated with an increased risk of developing hypertension.[5,7-10] Hypertension, in turn, is an important risk factor for most downstream cardiovascular diseases.[11-13] The health hazards of smoking on cardiovascular disease underscore the importance of further reducing smoking prevalence in the general population, and the continued need to promote smoking cessation among adults who smoke.

Electronic Nicotine Delivery Systems (ENDS) products became widely available around 2010, and they refer to a broad range of devices that produce an aerosol from heating an e-liquid. ENDS products quickly emerged as the most popular alternative to combustible cigarettes in the US, as their prevalence doubled among young adults between 2014-2018,[14] and more than 5.6 million U.S. adults reported ENDS use in 2018-2019.[15] Some adults use ENDS products as a way to help them quit smoking,[15,16] and because they are generally believed to be less harmful than combustible cigarettes,[17,18] and it has been argued that their use should be encouraged as part of a harm minimization strategy.[17] However, non-smoking youth are also using ENDS products,[19] raising concerns about tobacco use renormalization. Furthermore, ENDS contain toxicants and chemical compounds that are potentially dangerous, including aldehydes, carbonyl, nicotine, and flavoring additives.[20,21] Very little is known about the health consequences of ENDS product use,[21] and we need reliable and rigorous estimates of their health effects.

One potential consequence of ENDS product use may be an increased risk of hypertension. Evidence of a short-term elevation in both systolic blood pressure and diastolic

blood pressure from ENDS product use have been found in experimental studies,[22] and a recent epidemiological study found evidence of a cross-sectional association between ENDS product use and self-reported hypertension among adults.[23] However, cross-sectional research on the cardiovascular risks of ENDS use has resulted in a contentious debate,[24-28] largely centered around the issue of reverse causation.[27] Without information on the timing of both the ENDS use and the disease outcome, it is simply not possible to know whether ENDS use came before or after the disease outcome. The latter is likely common given the use of ENDS by some smokers trying to quit after being diagnosed with a cardiovascular disease.[29] Therefore, the results from these cross-sectional studies need to be interpreted with caution. Researchers have highlighted the need for prospective longitudinal data to better understand the temporal ordering between ENDS use and cardiovascular disease endpoints.[22,28]

In this study, we use data from a nationally representative prospective cohort study to examine the time-varying association between cigarette and ENDS use on the incidence of self-reported hypertension among respondents without any self-reported heart conditions at baseline. By restricting our sample to respondents without any pre-existing heart conditions and examining the incidence of hypertension, we limit potential concerns with reverse causation. In addition, we developed a composite exposure variable combining current cigarette and ENDS use to examine the relative contribution of exclusive cigarette use, exclusive ENDS use, and dual cigarette/ENDS use, compared to no use. We also adjust for past cigarette smoking history.

Methods

Data

We used data on adults from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available data set. However, this analysis used the Restricted Use Files[30] in order to use variables such as continuous age, and cigarette pack-years. These variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

The PATH study is a nationally representative longitudinal study of the civilian, non-institutionalized population in the United States. Date were collected from September, 2013 to December, 2014 for Wave 1(response rate among screened households, 74.0%); October, 2014 to October, 2015 for Wave 2 (response rate, 83.2%); October, 2015 to October, 2016 for Wave 3 (response rate, 78.4%); December, 2016 to January, 2018 for Wave 4 (response rate, 73.5%); and December, 2018 to November 2019 for Wave 5 (response rate, 69.4%). Further details about the design of the PATH Study are available elsewhere.[31]

The analytic sample for the current study was restricted to adult respondents (18+) at baseline (Wave 1) who reported no history of *any* cardiovascular outcome and participated in at least one follow-up interview through Waves 2-5. Respondents who did not get diagnosed were right censored at their last observation point. The final analytic sample consisted of 17,539 respondents. A flowchart summarizing the analytic sample is provided in the appendix (Figure A1).

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Self-Reported Hypertension

We examined the incidence of self-reported hypertension at follow-up among respondents who reported they had never been diagnosed with hypertension at baseline. In Wave 2 and Wave 3, *all* respondents were asked, *"In the past 12 months, has a doctor, nurse or other health professional told you that you had high blood pressure?"* Due to a change in the skip pattern in Wave 4 and Wave 5, this question was *only* asked to respondents who reported they saw a *"medical doctor, nurse, or other health professional"* during the past 12 months. We adopted an inclusive measurement strategy because self-reported hypertension is known to have low sensitivity (i.e., it is underestimated) in epidemiological studies,[32] especially among females[33] and Non-Hispanic Black adults.[34] To minimize this bias, we classified respondents who answered 'yes' to the blood pressure question as having self-reported hypertension regardless of whether they reported seeing a doctor during the past year. In Wave 4 and 5, we classified respondents who did not report seeing a doctor during the past year as not having self-reported hypertension.

To better approximate clinical hypertension and minimize potential false positive errors in self-reported hypertension, we also included a measure of medicated hypertension as a sensitivity analysis. Respondents who self-reported hypertension and responded 'yes' when asked, "*In the past 12 months, did you take heart or blood pressure medication regularly,"* were considered to have medicated hypertension.

Cigarette/ENDS Exposure Variable

Our exposure variable was based on answers to questions about established cigarette (100 or more cigarettes smoked in lifetime) and ENDS (ever fairly regularly used ENDS) use, as well as every day or someday use of cigarettes and ENDS (current use). Based on these variables, we developed a four-category exposure variable: non-current user (of either product, which included people who never used either product), exclusive cigarette smoker, exclusive ENDS user, and dual user of cigarettes and ENDS. This variable was constructed at each wave and was included as a time-varying exposure. To minimize missing values for a given wave, we imputed missing tobacco exposure data borrowing information from a previous wave. To ensure that the tobacco product use exposure preceded the hypertension diagnosis, we lagged our time-varying exposure by one wave. The descriptive statistics of the time-varying tobacco use exposure can be found in the appendix (Table A1).

Covariates

We included age (continuous ages 18-90) sex (0=female, 1=male), race/ethnicity (Hispanic, Non-Hispanic [NH] White, NH Black, NH Asian, NH Other), and household income (less than $49,999, more than $50,000, missing) as baseline sociodemographic variables. Missing values for baseline sociodemographic variables were updated with data from other waves when available to reduce item non-response. We also included baseline risk factors to control for potential confounding, including familial history of heart attack/bypass surgery, obesity (BMI >30), diabetes mellitus, and regular binge drinking (five or more drinks in one sitting on at least five separate days during the past month).

To account for the potential confounding effect of lifetime cigarette smoking, two additional covariates were included. First, we included a dichotomous predictor for former

established smokers (smoked at least 100 cigarettes in lifetime but reports no current use at baseline). Second, we included cigarette pack-years as a measure of lifetime cigarette smoking at baseline. Pack-years were calculated by multiplying the duration of cigarette smoking by the average number of packs of cigarettes smoked per day while individuals smoked. Respondents who reported smoking more than 200 cigarettes per day (10 packs per day) were considered implausible and were set to missing (n=99).

Statistical Analysis

Descriptive statistics were first calculated for sociodemographic characteristics, cigarette/ENDS use, and hypertension risk factors at baseline. The sample characteristics were then calculated according to respondent's cigarette/ENDS use at baseline. Chi-square tests or Fisher's exact tests were used to test for statistically significant differences between groups. Lifetables were then used to describe the distribution of the incident hypertension outcomes at follow-up (Wave 2-Wave 5). The hazard estimates reflect the weighted conditional probability for self-reported hypertension for respondents in the risk set at each discrete time interval.[35]

We used discrete time survival models to analyze the incidence of self-reported hypertension across Wave 2-Wave 5 of follow-up (approximately 5 years). Discrete time survival models are appropriate when the exact timing until an event is not known.[35] The data was fit to an unbalanced person-period data set where each individual contributed a number of rows equal to the time period until they were diagnosed with hypertension or were right censored.[36] As such, all 17,539 respondents in the self-reported hypertension sample had a separate row of data for each period, with a maximum of four rows per respondent, resulting in a person-period data set with 59,367 observations. The structure of the reorganized person-period dataset allowed for an examination of the conditional probability of self-reported and medicated

incident hypertension at each discrete time interval. All discrete-time survival models were estimated using a complimentary log-log (cloglog) link function on the person-period dataset.

Data were weighted using Wave 1 (W1) weights, including full-sample and 100 replicate weights, to ensure that our respondents were representative of the non-institutionalized adult population in the United States at baseline. To assess the impact of attrition, we compared baseline characteristics for censored and non-censored respondents (Appendix, Table A2). Because the censored respondents had a slightly different sociodemographic profile than the non-censored respondents, as a sensitivity analysis, we estimated the discrete time models using the 'all waves weights', which account for this type of attrition[31] and restricts the analysis to a longitudinal cohort of respondents who participated in all waves of the PATH study (person n=11,437 risk period n=45,250). Additionally, we conducted another sensitivity analysis in which all discrete time models were estimated using medicated hypertension as the outcome to better approximate clinical hypertension and minimize potential false positive errors in self-reported hypertension (person n=14,868, risk period n=52,818). For all analyses, variances were computed using the balanced repeated replication methods with Fay's adjustment set to 0.3 as recommended by the PATH study.[37,38] All analyses were conducted using Stata 16.1.[39]

Results

The weighted baseline sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for the self-reported hypertension (n=17,539) analytic sample are outlined in Table 1. At baseline, respondents had a mean age of 39 years (SD=15.4) and were predominately female (53.9%), NH White (63.0%), and reported a household income of less than $50,000 (56.0%). Most respondents were not current cigarette or ENDS users at baseline (79.2%) while a similar

percentage of respondents were exclusive ENDS users (1.1%) or dual users (1.7%). Current cigarette use was the most common tobacco use status at baseline (18.0%). 13.4% of respondents were former established smokers at baseline, among current or former established smokers, the average cigarette pack-years was 13.9 (SD=20.0). In terms of baseline hypertensive risk factors, approximately one quarter of respondents reported a family history of heart attack (27.7%) and obesity (24.6%), while diabetes mellitus (4.7%) and regular binge drinking (4.5%) were reported less frequently.

Table 2 presents the sample characteristics stratified by our tobacco exposure variable at baseline. Compared to all other groups, respondents who exclusively smoked cigarettes were the most likely to be NH Black (12.6%), most likely to report household incomes under $50,000 (74.3%). Compared to exclusive cigarette users, exclusive ENDS users at baseline were younger (33.2 (SD=16.7) vs. 37.1 (SD=17.7) years), reported higher household incomes (33.2% vs. 23.8%), and were more likely to report a family history of heart attack (31.7% vs. 29.4%) and obesity (33.2% vs. 23.8%). Importantly, nearly two thirds of exclusive ENDS users were former established smokers at baseline (63.7%). The average pack-years value for exclusive ENDS users who were former established smokers (17.9, SD=23.6) was higher than for current exclusive cigarette users (14.1, SD=22.4) at baseline. Dual users shared similar sociodemographic characteristics with exclusive ENDS users, except dual users were more likely to be NH White (76.7%-vs. 69.3%), to have diabetes mellitus (5.1% vs 3.2%) and reported more regular binge drinking (12.1% vs. 10.5%-10.3%). The average pack-years values for dual users (11.1, SD=16.9), on the other hand, was lower than exclusive cigarette users (14.1, SD=22.4), and for former smokers who were non-current users (13.9, SD=15.3) or exclusive ENDS users (17.9, SD=23.61) at baseline.

Table 1. Weighted sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for adult respondents (18+) at baseline, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	N	%^	95% CI
Age (mean, sd)	17,539	38.97 (15.42)	
Sex			
Female	9,073	53.9	53.2-54.6
Male	8,466	46.1	45.4-46.8
Race/Ethnicity			
NH White	10,250	63	62.2-63.8
Hispanic	3,446	17.6	17.0-18.2
NH Black	2,422	11	10.5-11.5
NH Asian	526	5.8	5.3-6.3
NH Other	895	2.6	2.4-2.9
Household Income			
<$50,000	11,481	56	54.6-57.3
>$50,000	5,699	41.8	40.4-43.1
missing	359	2.2	1.9-2.7
Cigarette/ecigarette baseline exposure			
Non user	11,063	79.2	78.5-79.9
Cigarette only	5,570	18	17.3-18.7
E-cigarette only	336	1.1	.92-1.2
Dual user	570	1.7	1.6-2.0
Family history of heart attack			
No	12,852	72.3	71.2-73.3
Yes	4,687	27.7	26.7-28.8
Obesity (BMI >30)			
No	13,318	75.4	74.3-76.5
Yes	4,221	24.6	23.5-25.7
Diabetes diagnosis at baseline			
No	16,848	95.3	94.8-95.8
Yes	691	4.7	4.2-5.2
Regular Binge drinking			
No	16,297	95.5	95.1-95.8
Yes	1,242	4.5	4.2-4.9
Former established smoker at baseline			
No	15,618	86.6	85.8-87.5
Yes	1,921	13.4	12.5-14.2
Pack-years among current/former smokers (mean, sd)^^	8,061	13.9 (20.0)	

ENDS = electronic nicotine delivery systems

^ Percentages were calcuated using W1 weights

^^mean pack years value for ever established (both current and former) smokers.

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Table 2. Sample characteristics by baseline cigarette/ENDS use, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	Non-user	Exclusive Cigarette user	Exclusive ENDS user	Dual User
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Age (mean, sd)	39.6 (14.2)	37.1 (17.7)	33.2 (16.7)	33.2 (16.6)
Sex				
Female	55.9 (55.1-56.8)	45.9 (44.5-47.3)	45.9 (39.9-52.1)	47.5 (43.4-51.6)
Male	44.1 (43.2-44.9)	54.1 (52.7-55.5)	54.1 (47.9-60.1)	52.5 (48.4-56.6)
Race/Ethnicity				
NH White	61.2 (60.1-62.4)	68.9 (67.3-70.5)	69.3 (63.0-75.0)	76.6 (72.7-80.4)
Hispanic	19 (18.2-19.7)	12.6 (11.7-13.6)	12.3 (9.1-16.5)	10.2 (7.5-13.0)
NH Black	10.8 (10.2-11.4)	12.6 (11.5-13.7)	8.5 (5.6-12.5)	6.2 (3.8-8.7)
NH Asian	6.6 (6.1-7.3)	2.4 (1.8-3.2)	5.7 (2.7-11.5)	2.7 (1.0-4.9)
NH Other	2.4 (2.1-2.7)	3.5 (3.1-3.9)	4.2 (2.4-7.1)	5.3 (3.8-7.2)
Household Income				
<$50,000	51.4 (49.9-52.9)	74.3 (72.7-75.9)	65.2 (59.3-70.7)	66.2 (61.0-70.9)
>$50,000	46.2 (44.7-47.7)	23.8 (22.3-25.3)	33.2 (27.4-39.5)	32.5 (27.5-37.3)
missing	2.4 (2.0-2.9)	1.9 (1.5-2.3)	1.6 (.65-3.7)	1.3 (.80-3.2)
Family history of heart attack				
No	72.8 (71.6-74.0)	70.6 (69.2-72.0)	68.3 (63.3-73.0)	65.7 (61.0-70.3)
Yes	27.2 (26.0-28.4)	29.4 (28.0-30.8)	31.7 (27.0-36.7)	34.3 (29.7-39.0)
Obesity (BMI >30)				
No	75.5 (74.1-76.8)	75.3 (73.8-76.7)	72 (65.7-77.5)	76.5 (72.2-79.8)
Yes	24.5 (23.2-25.9)	24.7 (23.3-26.2)	28 (22.5-34.3)	23.5 (20.2-27.8)
Diabetes diagnosis at baseline				
No	95.3 (94.6-95.8)	95.5 (94.9-96.0)	96.8 (94.3-98.2)	94.8 (92.3-96.6)
Yes	4.7 (4.2-5.4)	4.5 (4.0-5.1)	3.2 (1.8-5.7)	5.2 (3.4-7.7)
Regular Binge drinking				
No	97.2 (96.8-97.5)	89 (88.0-89.9)	89.5 (85.1-92.7)	87.8 (84.6-90.6)

Yes	2.8 (2.5-3.2)	11 (10.1-12.0)	10.5 (7.3-14.9)	12 (9.4-15.4)
Former established smoker at baseline				
No	84 (82.9-85.0)	100	36.3 (30.3-42.9)	100
Yes	16 (15.0-17.1)	0	63.7 (57.1-69.7)	0
Pack-years smoking at baseline (mean, sd)^	13.9 (15.3)	14.1 (22.4)	17.9 (23.6)	11.1 (16.9)

ENDS = electronic nicotine delivery systems

^mean pack years value for ever established (both current and former) smokers.

Lifetables describing the conditional probability for self-reported incident hypertension are displayed in Table 3. Hypertension was self-reported by 1930 respondents in the analytic sample, with an annual incidence hazard of 3.7% (range 2.9% to 4.6% between W2 and W5). The hazard estimates were similar across all discrete time intervals, with slight increases between Wave 4-Wave 5, reflecting a two-year time interval between waves.

Table 3. Life tables describing the incidence of self-reported hypertension among adults (18+), Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

Interval	Total	Diagnosis	Censored	Hazard Estimate^
Period 1 (W1-W2)	17539	652	1230	0.039
Period 2 (W2-W3)	15660	464	1137	0.033
Period 3 (W3-W4)	14067	334	1632	0.029
Period 4 (W4-W5)	12101	480	11612	0.046

^ hazard estimates were calculated using W1 weights

Table 4 presents discrete time hazard models examining the risk of self-reported incident hypertension. In the unadjusted model, respondents who exclusively smoked cigarettes had a significantly higher risk of self-reported incident hypertension compared to those who did not currently use cigarettes or ENDS products (hazard ratio [HR] 1.28, 95% CI:1.15-1.42). The risk did not statistically differ for respondents who used ENDS, either exclusively (HR 0.84, 95% CI: 0.68-1.47) or with cigarettes (HR 1.00, 95% CI: 0.77-1.30), from respondents who did not use either product. After adjusting for sociodemographic risk factors, baseline risk factors, and smoking history variables, the results were very similar as exclusive cigarette use was associated with a 21 percent higher risk of self-reported incident hypertension (95% CI: 1.06-1.38), while exclusive ENDS use (adjusted hazard ratio [aHR] 1.0, 95% CI: 0.68-1.47) and dual use (aHR 1.15, 95% CI:0.87-1.52) were not. Other hypertensive risk factors associated with an increased

risk of self-reported hypertension included being older age, male sex, NH Black (vs. NH White) race/ethnicity, lower (vs. higher) household income, family history of heart attack, obesity, diabetes diagnosis and regular binge drinking at baseline in adjusted (multivariable) models.

Sensitivity Analyses

The discrete-time models were estimated using the longitudinal cohort with the 'all waves' weights,' which resulted in a reduced sample size because respondents were only included in the analysis if they participated in all five waves (see Table A3, Appendix). The substantive results were nearly identical to the results obtained using the Wave 1 weights as exclusive cigarette use increased the risk of self-reported incident hypertension (aHR 1.26, 95% CI: 1.07-1.49) while exclusive ENDS use (aHR 1.07, 95% CI: .70-1.63) and dual use (aHR 1.25, 95% CI: .89-1.75) were not. As a secondary sensitivity analysis, discrete-time models were also estimated for the medicated hypertension outcome (see Table A4, Appendix). This more restrictive definition resulted in a reduced sample size because many self-reported hypertensive respondents did not report being prescribed medication. Still, the substantive results were nearly identical to the self-reported hypertension results. Exclusive cigarette use was associated with risk of medicated incident hypertension in the fully adjusted model, as exclusive cigarette use (aHR 1.25, 95% CI: 1.02-1.53) was the only tobacco product exposure significantly associated with the incidence of medicated hypertension. In contrast to the self-reported hypertension outcome, for medicated hypertension, baseline cigarette pack-years was associated with an increased risk of incident medicated hypertension in the fully adjusted model.

Table 4. Discrete time survival analysis predicting incidence of self-reported hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.28	1.15-1.42	1.21	1.06-1.38
Exclusive ENDS use	0.84	.58-1.21	1	.68-1.47
Dual use	1	.77-1.30	1.15	.87-1.52
Sociodemographic Risk factors				
Age (mean)^	1.03	1.03-1.04	1.03	1.03-1.04
Sex (Male=1)	1.28	1.11-1.48	1.33	1.16-1.53
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	0.83	.71-.98	0.99	.84-1.17
NH Black	1.44	1.24-1.68	1.62	1.38-1.90
NH Asian	0.38	.23-.64	0.55	.33-.94
NH Other	1.03	.73-1.44	1.06	.76-1.49
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	0.8	.70-.92	0.83	.72-.96
missing	0.67	.32-1.39	0.58	.27-1.22
Baseline Risk Factors				
Family History of heart attack	1.43	1.24-1.66	1.27	1.08-1.49
Obesity (BMI>30)	1.89	1.66-2.15	1.71	1.50-1.96
Diabetes diagnosis	2.48	2.0-3.06	1.74	1.37-2.21
Binge Drinking	1.22	.99-1.50	1.25	1.01-1.56
Smoking History Variables				
Former Established smoker	1.42	1.18-1.72	1.03	.83-1.27
Pack years (intervals of 10)^	1.17	1.13-1.21	1.03	.98-1.08

Notes: Person N=17,539 ; Risk Period N=59,367
^for interpretation, pack-years were rescaled to intervals of 10 packyears

Discussion

To our knowledge, this is the first study to examine the time-varying association between cigarette smoking and ENDS use on the incidence of self-reported hypertension among a nationally representative sample of US adults. We found that exclusive cigarette use was associated with an increased risk of incident hypertension in both unadjusted and fully adjusted models. While the association between chronic cigarette use and hypertension is complex,[40] and the causal link is still debated,[40,41] this finding aligns with previous research indicating a modest association between current cigarette smoking and the risk of incident hypertension.[5,8,10,42,43] Moreover, this finding is consistent with hypertension risk prediction models that include current cigarette smoking as a covariate,[7] and with the findings from the 2014 Surgeon General's report, which concluded that cigarette smoking is directly associated with coronary heart disease, including hypertension.[9] In contrast, studies examining the effects of ENDS use on hypertension have only recently been published,[22] and we found that ENDS use was not associated with incident hypertension, at least after relatively short-term follow-up of approximately 5 years.

Dual use of cigarettes and ENDS was not associated with the incidence of hypertension, although the direction of the hazard estimates was positive in fully adjusted models for both self-reported and medicated hypertension outcomes. However, it is important to note that dual users were different from exclusive cigarette smokers, and the non-significant association between dual use and incident hypertension may be partially explained by residual confounding by sociodemographic characteristics and tobacco use histories of dual users. In our study, dual users were younger, more likely to be NH White, and reported higher household incomes than exclusive cigarette smokers. These characteristics are all correlated with lower risk for

hypertension.[8,44,45] In addition, dual users had lower pack-years values than exclusive cigarette users, with pack-years values very similar to exclusive ENDS users. The different smoking histories between exclusive cigarette and dual users is consistent with other research finding that dual use is associated with reduced cigarette consumption,[46-48] and may represent part of a transitional state as smokers move away from smoking cigarettes.[48,49] It is possible that dual users may have a different risk profile than exclusive cigarette users, which may then translate into a lower risk of disease relative to exclusive cigarette users. Studies with a larger number of ENDS users are needed to better understand the risk of incident hypertension among dual users.

Taken together, the results from this study do not support an association between ENDS use and self-reported incident hypertension. By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.[27] This is the most likely reason why our findings differ from a recent cross-sectional examination of the lifetime prevalence of hypertension using PATH data,[23] where the authors did not account for the relative timing of the ENDS exposure and hypertension. In addition, we also controlled for the potential confounding of past cigarettes smoking history, measured as pack-years, which is important given that 64% of exclusive adult ENDS users at baseline were former established cigarette smokers. The substantial history of cigarette use among the majority of exclusive ENDS users further highlights the importance of controlling for their past cigarette smoking history when trying to estimate the independent effect of ENDS use on hypertension and other health outcomes.

Limitations

Our study has several important limitations that need to be considered. First, the results from this study are based on observational data from a prospective longitudinal study, and the results should be interpreted with the same level of caution required in all self-reported studies. Our non-randomized data means that our results could be affected by unmeasured confounding, and while we included a measure of medicated hypertension as a sensitivity analysis, both our hypertensive outcomes are self-reported. Since systolic and diastolic blood pressure measures are not available in the PATH study, the reported incidence may underestimate the true incidence of hypertension,[32,33] particularly for some sociodemographic groups.[32] Future research would benefit from including measured hypertension instead of self-reported hypertension where possible. Second, while the PATH study was representative of the US population at baseline, the loss to follow-up was significant and respondent attrition may not have been random. While we examined differences between censored and uncensored cases and conducted a sensitivity analysis with weights meant to adjust for attrition, this problem cannot be fully eliminated, as is true of most longitudinal studies. The discrete-time survival approach, which allows us to include all available information from respondents at each time interval, is a way to maximize information on the longitudinal sample. Third, while PATH has the biggest representative sample of longitudinal tobacco use and health in the US, ENDS use was only reported by a relatively small number of participants, limiting the power to detect statistical associations between ENDS use and incident hypertension. Fourth, if some respondents used ENDS to quit smoking cigarettes, it is possible that these respondents also made other lifestyle changes that may have concomitantly reduced the impact of ENDS use on incident hypertension. Similarly, some might have decided to switch in response to symptoms or health issues. Future research is

needed to better understand the characteristics of respondents who transition from cigarettes to ENDS use, their reasons for doing so, and the future health outcomes of these transitions. Finally, ENDS products have only been widely available in the US for little more than a decade.[50]The findings from our study are based on approximately five years of longitudinal follow-up, so this analysis will need to be updated as more longitudinal data on long-termer term ENDS use becomes available. Moreover, additional studies will be needed to understand the risks of new products entering the marketplace, and as ENDS products continue to rapidly evolve.

Conclusions

Using nationally representative prospective longitudinal data among US adults, we found that time-varying cigarette smoking increased the risk of self-reported incident hypertension, but time-varying ENDS use did not. These results highlight the importance of using prospective longitudinal data to disentangle the temporal ordering between cigarette and ENDS use and the need to control for the potential confounding effect of cigarette smoking histories among ENDS users. This type of longitudinal analysis can be extended in future research examining the cardiovascular health effects of ENDS use, as longer-term data becomes available.

Contributorship statement: SC conducted the data analysis and drafted and revised the manuscript. JH and NF initiated the research project in collaboration with RM and DL. IB and RM provided statistical consultation, and GB and DA provided medical expertise and helped interpret the findings. EM, AP, and JJ created the measures used in the analysis. All co-authors revised the draft of the paper, and NF revised the final draft prior to submission.

Ethics statement: This study used de-identified data an no personal identifying information is included in the manuscript. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

Competing interest statement: All authors report no conflicts of interest or disclosures.

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Data sharing statement: Data may be obtained from a third party and are not publicly available. Data are derived from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available de-identified data set. However, this analysis used the Restricted Use Files to use variables such as continuous age, and cigarette pack-years. These variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21.

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Appendix

Figure A1. Flowchart of Sample Selection for Analytic Sample, Self-Reported Hypertension Outcome

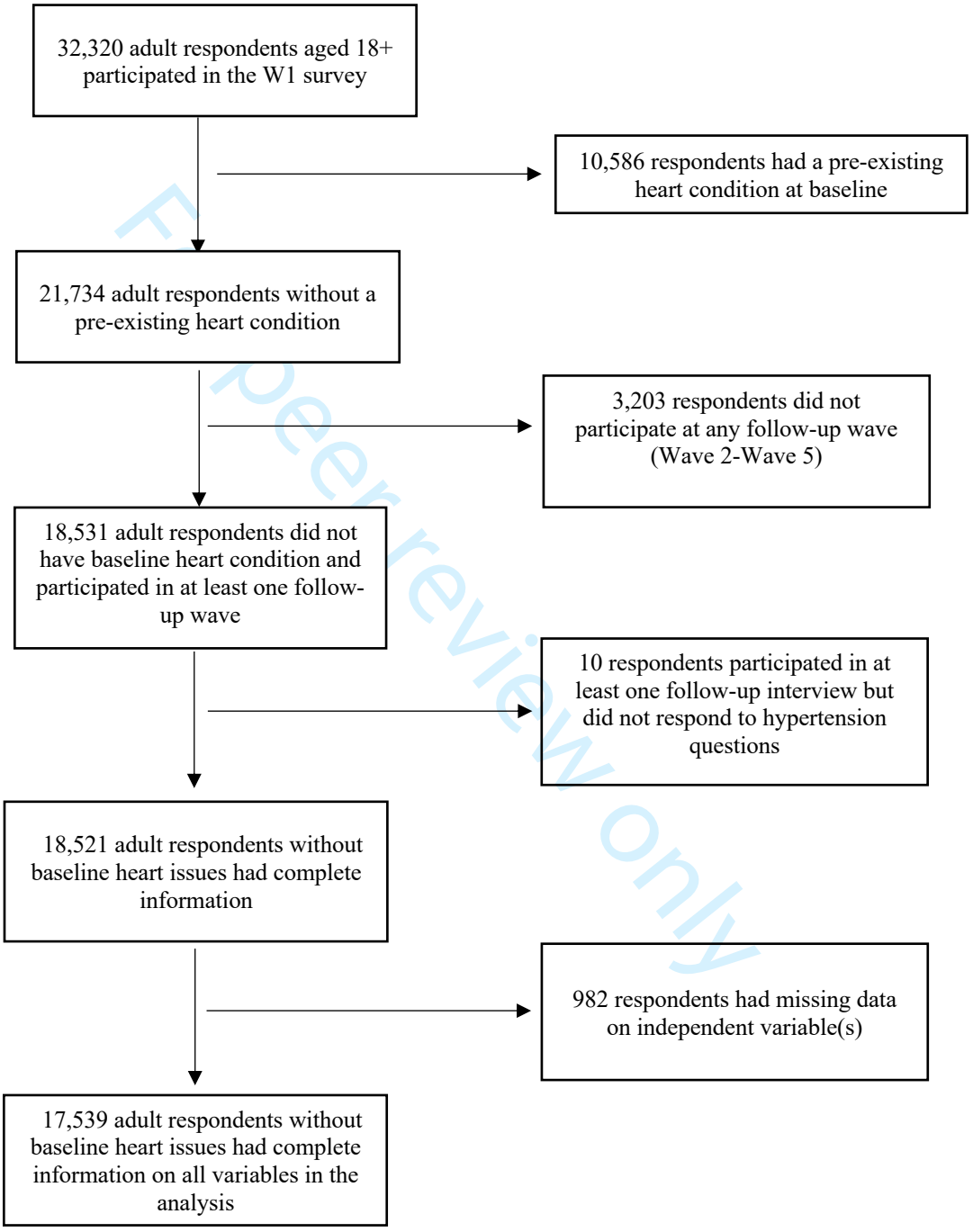

Table A1. Descriptive Statistics for Time-Varying Cigarette/ENDS Use, Established Adult Cigarette Smokers, Population Assessment of Tobacco & Health Study

	Follow-Up Interview*							
	Wave 1		Wave 2		Wave 3		Wave 4	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Time varying cigarettes/ENDS use								
Non use	79.2	78.5-79.9	78.6	77.9-79.4	79	78.2-79.7	79.9	79.0-80.6
Exclusive cigarette use	18	17.3-18.7	17.8	17.1-18.5	17.5	16.9-18.3	16.9	16.2-17.7
Exclusive ENDS use	1.1	0.92-1.96	1.3	1.2-1.5	1.4	1.3-1.6	1.5	1.3-1.7
Dual use	1.7	1.6-2.0	2.2	2.0-2.5	2.1	1.8-2.3	1.8	1.6-2.0

*time-varying covariates were lagged by one wave to limit issues with reverse causation

Table A2. Analysis of Censored Cases, Self-reported hypertension

	Non-censored	Censored	P
Age (mean)	39.2	38	**
Sex			***
Female	55.5%	47.9%	
Male	44.5%	52.1%	
Baseline cigarettes/ENDS exposure			***
Non use	80.1%	75.7%	
Exclusive cigarette use	17.2%	20.9%	
Exclusive ENDS use	1.1%	1.1%	
Dual use	1.6%	2.3%	
Race/Ethnicity			**
NH White	62.7%	63.9%	
Hispanic	17.8%	16.9%	
NH Black	1150.0%	9.2%	
NH Asian	530.0%	7.4%	
NH Other	260.0%	2.6%	
Household Income			***
<$50,000	56.5%	54.1%	
>$50,000	42.3%	39.9%	
missing	1.2%	6.0%	
Family history of heart attack			NS
No	71.7%	74.2%	
Yes	28.3%	25.8%	
Obesity (BMI >30)			**
No	74.5%	78.7%	
Yes	25.5%	21.3%	
Diabetes diagnosis at baseline			NS
No	95.2%	95.6%	
Yes	4.8%	4.4%	
Binge drinking			***
No	95.6%	94.9%	
Yes	4.4%	5.1%	
Former established smoker at baseline			NS
No	86.4%	87.7%	
Yes	13.6%	12.3%	
Pack-years at baseline (10 PY intervals)	0.453	0.458	NS

*p<0.05, **p<0.01, ***p<0.001

Table A3. Discrete time survival analysis predicting incidence of hypertension among adults using longitudinal cohort 'all waves weights', Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.35***	1.18-1.55	1.26**	1.07-1.49
Exclusive ENDS use	0.95	.63-1.41	1.07	.70-1.63
Dual use	1.11	.81-1.51	1.25	.89-1.75
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.03	1.03***	1.02-1.03
Sex (Male=1)	1.36***	1.16-1.59	1.45***	1.23-1.70
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.78*	.65-.94	0.92	.76-1.10
NH Black	1.53***	1.31-1.79	1.65***	1.39-1.96
NH Asian	.34***	.21-.53	.49**	.30-.81
NH Other	1	.69-1.47	1.07	.72-1.59
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.82*	.70-.97	0.85	.72-1.01
missing	1	.36-2.82	0.79	.26-2.38
Baseline Risk Factors				
Family History of heart attack	1.45***	1.22-1.71	1.29**	1.07-1.56
Obesity (BMI>30)	2.05***	1.77-2.36	1.81***	1.54-2.13
Diabetes diagnosis	2.61***	2.05-3.32	1.98***	1.54-2.55
Binge Drinking	1.19	.93-1.54	1.19	.91-1.55
Smoking History Variables				
Former Established smoker	1.48**	1.19-1.83	1.09	.86-1.38
Pack years (intervals of 10)^	1.17***	1.12-1.21	1.04	.99-1.09

Person N=11,437 ; Risk Period N =45,250

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table A4. Discrete time survival analysis predicting incidence of medicated hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Medicated Hypertension			
	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.29**	1.10-1.51	1.25*	1.02-1.53
Exclusive ENDS use	0.62	.36-1.08	0.88	.51-1.50
Dual use	0.85	.61-1.18	1.07	.73-1.57
Sociodemographic Risk factors				
Age (mean)^	1.04***	1.04-1.05	1.04***	1.04-1.05
Sex (Male=1)	1.23*	1.04-1.47	1.23*	1.04-1.46
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.81*	.66-.99	1.03	.83-1.28
NH Black	1.41***	1.17-1.70	1.71***	1.39-2.10
NH Asian	.32*	.13-.77	0.52	.21-2.10
NH Other	0.71	.44-1.15	0.81	.52-1.26
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.78**	.66-.92	0.85	.72-1.03
missing	0.78	.29-2.08	0.57	.21-1.54
Baseline Risk Fators				
Family History of heart attack	1.34**	1.10-1.62	1.12	.91-1.38
Obesity (BMI>30)	1.86***	1.59-2.18	1.68***	1.41-2.00
Diabetes diagnosis	3.21***	2.51-4.11	2.12***	1.62-2.78
Binge Drinking	1.11	.84-1.47	1.27	.95-1.68
Smoking History Variables				
Former Established smoker	1.42**	1.14-1.77	0.88	.68-1.13
Pack years (intervals of 10)^	1.20***	1.15-1.24	1.06*	1.00-1.12

Person N=14,868 ; Risk Period N =52,818

*p<0.05, **p<0.01, ***p<0.001

^tested for nonlinearity but the quadratic term was not significant

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	(a)-1 (b)-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	Fig A1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	(a)-9-10 (c, d, e) -10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Fig A1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

The time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study

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Running Head: ENDS AND HYPERTENSION AMONG US ADULTS

The time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study

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Abstract

Objective: Electronic Nicotine Delivery Systems (ENDS) products have emerged as the most popular alternative to combustible cigarettes. However, ENDS products contain potentially dangerous toxicants and chemical compounds, and little is known about their health effects. The aim of the present study was to examine the prospective association between cigarette and ENDS use on self-reported incident hypertension.

Design and Methods: Using adult data from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco and Health Study, we examined the risk of self-reported incident hypertension associated with ENDS use among 17,539 adults aged 18+ using discrete-time survival models. To distinguish the role of cigarettes and ENDS, we constructed a time-varying tobacco exposure, lagged by one wave, defined as no use, exclusive established use (daily or some days) of ENDS or cigarettes, and dual use. We controlled for demographics (age, sex, race/ethnicity, household income), clinical risk factors (family history of heart attack, obesity, diabetes, binge drinking) and smoking history (cigarette pack-years).

Results: The self-reported incidence of hypertension was 3.7% between Waves 2-5. At baseline, 18.0% (n=5,570) of respondents exclusively smoked cigarettes, 1.1% (n=336) exclusively used ENDS, and 1.7% (n=570) were dual users. In adjusted models, exclusive cigarette use was associated with an increased risk for self-reported incident hypertension compared to non-use (aHR=1.21, 95% CI: 1.06-1.38), while exclusive ENDS use (aHR=1.00, 95% CI: 0.68-1.47) and dual use (aHR=1.15, 95% CI: 0.87-1.52) were not.

Conclusions: We found that smoking increased the risk of self-reported hypertension but ENDS use did not. These results highlight the importance of using prospective longitudinal data to examine the health effects of ENDS use.

Keywords: ENDS, cigarettes, hypertension, cardiovascular disease

Strengths and limitations of this study

- In this study, we examine the time-varying association between cigarette smoking and ENDS use on the incidence of hypertension among a nationally representative sample of US adults.
- By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.
- We also controlled for the potential confounding of past smoking history, measured as cigarette pack-years, which important because most adults who use ENDS are either currently smoking cigarettes or have smoked cigarettes in the past.
- Our study was limited by relying on self-reported hypertension, as systolic and diastolic blood pressure measures were not available.
- Our non-randomized data means that our results could be affected by unmeasured confounding, and the results should be interpreted with the same level of caution required in all prospective longitudinal studies.

Introduction

Cigarette smoking is the leading cause of premature mortality in the US,[1, 2] and a significant proportion of smoking-attributable deaths are related to cardiovascular disease.[3, 4] Smoking is known to cause an acute rise in blood pressure,[5] contribute to arterial stiffness,[6] and has been associated with an increased risk of developing hypertension.[5, 7-10] Hypertension, in turn, is an important risk factor for most downstream cardiovascular diseases.[11-13] The health hazards of smoking on cardiovascular disease underscore the importance of further reducing smoking prevalence in the general population, and the continued need to promote smoking cessation among adults who smoke.

Electronic Nicotine Delivery Systems (ENDS) products became widely available around 2010, and they refer to a broad range of devices that produce an aerosol from heating an e-liquid. ENDS products quickly emerged as the most popular alternative to combustible cigarettes in the US, as their prevalence doubled among young adults between 2014-2018,[14] and more than 5.6 million U.S. adults reported ENDS use in 2018-2019.[15] Some adults use ENDS products as a way to help them quit smoking,[15, 16] and because they are generally believed to be less harmful than combustible cigarettes,[17, 18] and it has been argued that their use should be encouraged as part of a harm minimization strategy.[17] However, non-smoking youth are also using ENDS products,[19] raising concerns about tobacco use renormalization. Furthermore, ENDS contain toxicants and chemical compounds that are potentially dangerous, including aldehydes, carbonyl, nicotine, and flavoring additives.[20, 21] Very little is known about the health consequences of ENDS product use,[21] and we need reliable and rigorous estimates of their health effects.

One potential consequence of ENDS product use may be an increased risk of hypertension. Evidence of a short-term elevation in both systolic blood pressure and diastolic blood pressure from ENDS product use have been found in experimental studies,[22] and a recent epidemiological study found evidence of a cross-sectional association between ENDS product use and self-reported hypertension among adults.[23] However, cross-sectional research on the cardiovascular risks of ENDS use has resulted in a contentious debate,[24-28] largely centered around the issue of reverse causation.[27] Without information on the timing of both the ENDS use and the disease outcome, it is simply not possible to know whether ENDS use came before or after the disease outcome. The latter is likely common given the use of ENDS by some smokers trying to quit after being diagnosed with a cardiovascular disease.[29] Therefore, the results from these cross-sectional studies need to be interpreted with caution. Researchers have highlighted the need for prospective longitudinal data to better understand the temporal ordering between ENDS use and cardiovascular disease endpoints.[22, 28]

In this study, we use data from a nationally representative prospective cohort study to examine the time-varying association between cigarette and ENDS use on the incidence of self-reported hypertension among respondents without any self-reported heart conditions at baseline. By restricting our sample to respondents without any pre-existing heart conditions and examining the incidence of hypertension, we limit potential concerns with reverse causation. In addition, we developed a composite exposure variable combining current cigarette and ENDS use to examine the relative contribution of exclusive cigarette use, exclusive ENDS use, and dual cigarette/ENDS use, compared to no use. We also adjust for past cigarette smoking history.

Methods

Data

We used data on adults from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available data set. However, this analysis used the Restricted Use Files[30] in order to use variables such as continuous age, and cigarette pack-years. These variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

The PATH study is an ongoing, nationally representative cohort study of the civilian, non-institutionalized population in the United States. A four-stage stratified area probability sample was used for recruitment at baseline, and a two-staged design was used for sampling the adult cohort.[31]African-Americans and tobacco users were oversampled related to population proportions, and weighting procedures adjusted for oversampling and non-response based on US Census Bureau Data. Data were collected from September, 2013 to December, 2014 for Wave 1(response rate among screened households, 74.0%); October, 2014 to October, 2015 for Wave 2 (response rate, 83.2%); October, 2015 to October, 2016 for Wave 3 (response rate, 78.4%); December, 2016 to January, 2018 for Wave 4 (response rate, 73.5%); and December, 2018 to November 2019 for Wave 5 (response rate, 69.4%). All PATH survey interviews were completed in-person, using Audio-Assisted Self-Interviewing (ACASI) administrations, available in English or Spanish. Data collection protocols were used to ensure that follow-up

interviews were close to the anniversary of their participation in the previous wave.[32] Further details about the design and methods of the PATH Study have been published elsewhere.[31-34]

The analytic sample for the current study was restricted to adult respondents (18+) (Wave 1, n=32,320) who reported no self-reported heart condition at baseline (n=21,734). A total of 3203 respondents were excluded as they did not participate at any follow-up interview, and respondents who did not report a hypertension diagnosis were right censored at their last observation point. Respondents with missing variable information (n=992; 5.3%) were excluded from the analysis using listwise deletion. The final analytic sample consisted of 17,539 respondents. A flowchart summarizing the analytic sample is provided in the appendix (Figure A1).

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Self-Reported Hypertension

We examined the incidence of self-reported hypertension at follow-up among respondents who reported they had never been diagnosed with hypertension at baseline. The reliability and concurrent validity of self-reported hypertension has been established in a previous study using PATH Study data.[32] In Wave 2 and Wave 3, <u>all</u> respondents were asked, *"In the past 12 months, has a doctor, nurse or other health professional told you that you had high blood pressure?"* Due to a change in the skip pattern in Wave 4 and Wave 5, this question was <u>only</u> asked to respondents who reported they saw a *"medical doctor, nurse, or other health professional"* during the past 12 months. We adopted an inclusive measurement strategy because self-reported hypertension is known to have low sensitivity (i.e., it is underestimated) in

epidemiological studies,[35] especially among females[36] and Non-Hispanic Black adults.[37] To minimize this bias, we classified respondents who answered 'yes' to the blood pressure question as having self-reported hypertension regardless of whether they reported seeing a doctor during the past year. In Wave 4 and 5, we classified respondents who did not report seeing a doctor during the past year as not having self-reported hypertension.

Cigarette/ENDS Exposure Variable

Our exposure variable was based on answers to questions about established cigarette (100 or more cigarettes smoked in lifetime) and ENDS (ever fairly regularly used ENDS) use, as well as every day or someday use of cigarettes and ENDS (current use). Based on these variables, we developed a four-category exposure variable: non-current user (of either product, which included people who never used either product), exclusive cigarette smoker, exclusive ENDS user, and dual user of cigarettes and ENDS. This variable was constructed at each wave and was included as a time-varying exposure. To minimize missing values for a given wave, we imputed missing tobacco exposure data borrowing information from a previous wave. To ensure that the tobacco product use exposure preceded the hypertension diagnosis, we lagged our time-varying exposure by one wave. The descriptive statistics of the time-varying tobacco use exposure can be found in the appendix (Table A1).

Covariates

We included age (continuous ages 18-90) sex (0=female, 1=male), race/ethnicity (Hispanic, Non-Hispanic [NH] White, NH Black, NH Asian, NH Other), and household income (less than $49,999, more than $50,000, missing) as baseline sociodemographic variables. Missing values for baseline sociodemographic variables were updated with data from other

waves when available to reduce item non-response. We also included baseline risk factors to control for potential confounding, including familial history of heart attack/bypass surgery, obesity (BMI >30), diabetes mellitus, and regular binge drinking (five or more drinks in one sitting on at least five separate days during the past month).

To account for the potential confounding effect of lifetime cigarette smoking, two additional covariates were included. First, we included a dichotomous predictor for former established smokers (smoked at least 100 cigarettes in lifetime but reports no current use at baseline). Second, we included cigarette pack-years as a measure of lifetime cigarette smoking at baseline. Pack-years were calculated by multiplying the duration of cigarette smoking by the average number of packs of cigarettes smoked per day while individuals smoked. Respondents who reported smoking more than 200 cigarettes per day (10 packs per day) were considered implausible and were set to missing (n=99).

Statistical Analysis

Descriptive statistics were first calculated for sociodemographic characteristics, cigarette/ENDS use, and hypertension risk factors at baseline. The sample characteristics were then calculated according to respondent's cigarette/ENDS use at baseline. Chi-square tests or Fisher's exact tests were used to test for statistically significant differences between groups. Lifetables were then used to describe the distribution of the incident hypertension outcomes at follow-up (Wave 2-Wave 5). The hazard estimates reflect the weighted conditional probability for self-reported hypertension for respondents in the risk set at each discrete time interval.[38]

We used discrete time survival models to analyze the incidence of self-reported hypertension across Wave 2-Wave 5 of follow-up (approximately 5 years). Discrete time survival models are appropriate when the exact timing until an event is not known.[38] The data

was fit to an unbalanced person-period data set where each individual contributed a number of rows equal to the time period until they were diagnosed with hypertension or were right censored.[39] As such, all 17,539 respondents in the self-reported hypertension sample had a separate row of data for each period, with a maximum of four rows per respondent, resulting in a person-period data set with 59,367 observations. The structure of the reorganized person-period dataset allowed for an examination of the conditional probability of self-reported and medicated incident hypertension at each discrete time interval. All discrete-time survival models were estimated using a complimentary log-log (cloglog) link function on the person-period dataset. Data were weighted using Wave 1 (W1) weights, including full-sample and 100 replicate weights, to ensure that our respondents were representative of the non-institutionalized adult population in the United States at baseline.

Several sensitivity analyses were included as robustness checks. First, to assess the impact of attrition, we compared baseline characteristics for censored and non-censored respondents (Table S2). Because the censored respondents had a slightly different sociodemographic profile than the non-censored respondents, as a sensitivity analysis, we estimated the discrete time models using the 'all waves weights,' which account for this type of attrition[31] and restricts the analysis to a longitudinal cohort of respondents who participated in all waves of the PATH study (Table S3). Third, to better approximate clinical hypertension and minimize potential false positive errors in self-reported hypertension, we also included a measure of medicated hypertension as a sensitivity analysis. Respondents who self-reported hypertension and responded 'yes' when asked, "*In the past 12 months, did you take heart or blood pressure medication regularly,"* were considered to have medicated hypertension (Table S4). Fourth, to examine whether more frequent cigarette/ENDS use was associated with incident hypertension,

we included a more frequent cigarette/ENDS use exposure (measured as 10+ days in the past 30 days) as a sensitivity analysis (Table S5). Fifth, to more clearly distinguish between adults who never smoked cigarettes from former smokers, we created a revised exposure with adults who reported 'never established smoking' as the reference group, with the following use categories: (1) former cigarette, no ENDS; (2) current cigarette, no ENDS; (3) former cigarette, current ENDS; (4) current cigarette and ENDS; (5) exclusive ENDS (see Table S6). Finally, we restricted our analysis to adults who reported they had never smoked 100 cigarettes in their lifetime at baseline and examined the association between ENDS use and hypertension among respondents who had never smoked (Table S7). For all analyses, variances were computed using the balanced repeated replication methods with Fay's adjustment set to 0.3 as recommended by the PATH study.[33, 40] All analyses were conducted using Stata 16.1.[41]

Results

The weighted baseline sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for the self-reported hypertension (n=17,539) analytic sample are outlined in Table 1. At baseline, respondents had a mean age of 39 years (SD=15.4) and were predominately female (53.9%), NH White (63.0%), and reported a household income of less than $50,000 (56.0%). Most respondents were not current cigarette or ENDS users at baseline (n=11,063; 79.2%) while a similar percentage of respondents were exclusive ENDS users (n=336; 1.1%) or dual users (n=570; 1.7%). Current cigarette use was the most common tobacco use status at baseline (n=5,570; 18.0%). 13.4% of respondents were former established smokers at baseline, among current or former established smokers, the average cigarette pack-years was 13.9 (SD=20.0). In terms of baseline hypertensive risk factors, approximately one quarter of respondents reported a

family history of heart attack (27.7%) and obesity (24.6%), while diabetes mellitus (4.7%) and regular binge drinking (4.5%) were reported less frequently.

Table 2 presents the sample characteristics stratified by our tobacco exposure variable at baseline. Compared to all other groups, respondents who exclusively smoked cigarettes were the most likely to be NH Black (12.6%), most likely to report household incomes under $50,000 (74.3%). Compared to exclusive cigarette users, exclusive ENDS users at baseline were younger (33.2 (SD=16.7) vs. 37.1 (SD=17.7) years), reported higher household incomes (33.2% vs. 23.8%), and were more likely to report a family history of heart attack (31.7% vs. 29.4%) and obesity (33.2% vs. 23.8%). Importantly, nearly two thirds of exclusive ENDS users were former established smokers at baseline (63.7%). The average pack-years value for exclusive ENDS users who were former established smokers (17.9, SD=23.6) was higher than for current exclusive cigarette users (14.1, SD=22.4) at baseline. Dual users shared similar sociodemographic characteristics with exclusive ENDS users, except dual users were more likely to be NH White (76.7%-vs. 69.3%), to have diabetes mellitus (5.1% vs 3.2%) and reported more regular binge drinking (12.1% vs. 10.5%-10.3%). The average pack-years values for dual users (11.1, SD=16.9), on the other hand, was lower than exclusive cigarette users (14.1, SD=22.4), and for former smokers who were non-current users (13.9, SD=15.3) or exclusive ENDS users (17.9, SD=23.61) at baseline.

Table 1. Weighted sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for adult respondents (18+) at baseline, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	N	%^	95% CI
Age (mean, sd)	17,539	38.97 (15.42)	
Sex			
Female	9,073	53.9	53.2-54.6
Male	8,466	46.1	45.4-46.8
Race/Ethnicity			
NH White	10,250	63	62.2-63.8
Hispanic	3,446	17.6	17.0-18.2
NH Black	2,422	11	10.5-11.5
NH Asian	526	5.8	5.3-6.3
NH Other	895	2.6	2.4-2.9
Household Income			
<$50,000	11,481	56	54.6-57.3
>$50,000	5,699	41.8	40.4-43.1
missing	359	2.2	1.9-2.7
Cigarette/ecigarette baseline exposure			
Non user	11,063	79.2	78.5-79.9
Cigarette only	5,570	18	17.3-18.7
E-cigarette only	336	1.1	.92-1.2
Dual user	570	1.7	1.6-2.0
Family history of heart attack			
No	12,852	72.3	71.2-73.3
Yes	4,687	27.7	26.7-28.8
Obesity (BMI >30)			
No	13,318	75.4	74.3-76.5
Yes	4,221	24.6	23.5-25.7
Diabetes diagnosis at baseline			
No	16,848	95.3	94.8-95.8
Yes	691	4.7	4.2-5.2
Regular Binge drinking			
No	16,297	95.5	95.1-95.8
Yes	1,242	4.5	4.2-4.9
Former established smoker at baseline			
No	15,618	86.6	85.8-87.5
Yes	1,921	13.4	12.5-14.2

Pack-years among current/former smokers (mean, sd)^^	8,061	13.9 (20.0)

ENDS = electronic nicotine delivery systems

^ Percentages were calcuated using W1 weights

^^mean pack years value for ever established (both current and former) smokers.

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Table 2. Sample characteristics by baseline cigarette/ENDS use, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	Non-user	Exclusive Cigarette user	Exclusive ENDS user	Dual User
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Age (mean, sd)	39.6 (14.2)	37.1 (17.7)	33.2 (16.7)	2 (16.6)
Sex				
Female	55.9 (55.1-56.8)	45.9 (44.5-47.3)	45.9 (39.9-52.1)	(43.4-51.6)
Male	44.1 (43.2-44.9)	54.1 (52.7-55.5)	54.1 (47.9-60.1)	(48.4-56.6)
Race/Ethnicity				
NH White	61.2 (60.1-62.4)	68.9 (67.3-70.5)	69.3 (63.0-75.0)	(72.7-80.4)
Hispanic	19 (18.2-19.7)	12.6 (11.7-13.6)	12.3 (9.1-16.5)	(7.5-13.0)
NH Black	10.8 (10.2-11.4)	12.6 (11.5-13.7)	8.5 (5.6-12.5)	(3.8-8.7)
NH Asian	6.6 (6.1-7.3)	2.4 (1.8-3.2)	5.7 (2.7-11.5)	.2 (1.0-4.9)
NH Other	2.4 (2.1-2.7)	3.5 (3.1-3.9)	4.2 (2.4-7.1)	5 (3.8-7.2)
Household Income				
<$50,000	51.4 (49.9-52.9)	74.3 (72.7-75.9)	65.2 (59.3-70.7)	66. (61.0-70.9)
>$50,000	46.2 (44.7-47.7)	23.8 (22.3-25.3)	33.2 (27.4-39.5)	32. (27.5-37.3)
missing	2.4 (2.0-2.9)	1.9 (1.5-2.3)	1.6 (.65-3.7)	1 (.80-3.2)
Family history of heart attack				
No	72.8 (71.6-74.0)	70.6 (69.2-72.0)	68.3 (63.3-73.0)	65. (61.0-70.3)
Yes	27.2 (26.0-28.4)	29.4 (28.0-30.8)	31.7 (27.0-36.7)	34. (29.7-39.0)
Obesity (BMI >30)				
No	75.5 (74.1-76.8)	75.3 (73.8-76.7)	72 (65.7-77.5)	76. (72.2-79.8)
Yes	24.5 (23.2-25.9)	24.7 (23.3-26.2)	28 (22.5-34.3)	23. (20.2-27.8)
Diabetes diagnosis at baseline				
No	95.3 (94.6-95.8)	95.5 (94.9-96.0)	96.8 (94.3-98.2)	94. (92.3-96.6)
Yes	4.7 (4.2-5.4)	4.5 (4.0-5.1)	3.2 (1.8-5.7)	5 (3.4-7.7)
Regular Binge drinking				
No	97.2 (96.8-97.5)	89 (88.0-89.9)	89.5 (85.1-92.7)	87. (84.6-90.6)

Yes	2.8 (2.5-3.2)	11 (10.1-12.0)	10.5 (7.3-14.9)	12 (9.4-15.4)
Former established smoker at baseline				
No	84 (82.9-85.0)	100	36.3 (30.3-42.9)	100
Yes	16 (15.0-17.1)	0	63.7 (57.1-69.7)	0
Pack-years smoking at baseline (mean, sd)^	13.9 (15.3)	14.1 (22.4)	17.9 (23.6)	11.1 (16.9)

ENDS = electronic nicotine delivery systems

^mean pack years value for ever established (both current and former) smokers.

Lifetables describing the conditional probability for self-reported incident hypertension are displayed in Table 3. Hypertension was self-reported by 1930 respondents in the analytic sample, with an annual incidence hazard of 3.7% (range 2.9% to 4.6% between W2 and W5). The hazard estimates were similar across all discrete time intervals, with slight increases between Wave 4-Wave 5, reflecting a two-year time interval between waves.

Table 3. Life tables describing the incidence of self-reported hypertension among adults (18+), Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

Interval	Total	Diagnosis	Censored	Hazard Estimate^
Period 1 (W1-W2)	17539	652	1230	0.039
Period 2 (W2-W3)	15660	464	1137	0.033
Period 3 (W3-W4)	14067	334	1632	0.029
Period 4 (W4-W5)	12101	480	11612	0.046

^ hazard estimates were calculated using W1 weights

Table 4 presents discrete time hazard models examining the risk of self-reported incident hypertension. In the unadjusted model, respondents who exclusively smoked cigarettes had a significantly higher risk of self-reported incident hypertension compared to those who did not currently use cigarettes or ENDS products (hazard ratio [HR] 1.28, 95% CI:1.15-1.42). The risk did not statistically differ for respondents who used ENDS, either exclusively (HR 0.84, 95% CI: 0.68-1.47) or with cigarettes (HR 1.00, 95% CI: 0.77-1.30), from respondents who did not use either product. After adjusting for sociodemographic risk factors, baseline risk factors, and smoking history variables, the results were very similar as exclusive cigarette use was associated with a 21 percent higher risk of self-reported incident hypertension (95% CI: 1.06-1.38), while exclusive ENDS use (adjusted hazard ratio [aHR] 1.0, 95% CI: 0.68-1.47) and dual use (aHR 1.15, 95% CI:0.87-1.52) were not. Other hypertensive risk factors associated with an increased

risk of self-reported hypertension included being older age, male sex, NH Black (vs. NH White) race/ethnicity, lower (vs. higher) household income, family history of heart attack, obesity, diabetes diagnosis and regular binge drinking at baseline in adjusted (multivariable) models.

Sensitivity Analyses

As sensitivity analyses, discrete-time models were estimated using the longitudinal cohort who participated in all waves of follow-up (Table S3); with a medicated hypertension outcome (Table S4); and with cigarette/ENDS use measured as 10+ days in the past 30 days rather than every day or someday use (Table S5). Across these sensitivity analyses, the substantive results remained robust as exclusive cigarette use was associated with an increased risk of incident hypertension compared to non-use in both unadjusted and fully adjusted models. In contrast, compared to non-use, exclusive ENDS and dual use were not associated with increased hypertension risk in unadjusted or fully adjusted models in any of these analyses. Discrete-time models were also estimated with an expanded cigarette/ENDS exposure incorporating never and former smoking as a sensitivity analysis (Table S6). Compared to never smoking, current cigarette smoking and non-ENDS use (aHR 1.20, 95% CI 1.04, 1.38) was associated with an increased risk of incident hypertension while current ENDS use among respondents who had formerly smoked (aHR 1.01, 95% CI 0.64, 1.60) and dual ENDS and cigarette smoking (aHR 1.13, 95% CI 0.84, 1.52) were not associated with increased hypertension risk. Finally, respondents with established cigarette use patterns were removed from the analytic sample, and the association between ENDS use and hypertension was examined among respondents who never smoked as an additional sensitivity analysis (Table S7). Time-varying ENDS use was not associated with an increased risk of incident hypertension compared to non-ENDS use in either unadjusted (HR = 0.56, 95% CI 0.28, 1.13) or adjusted models (aHR=0.75, 95% CI 0.37, 1.52).

Table 4. Discrete time survival analysis predicting incidence of self-reported hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.28	1.15-1.42	1.21	1.06-1.38
Exclusive ENDS use	0.84	.58-1.21	1	.68-1.47
Dual use	1	.77-1.30	1.15	.87-1.52
Sociodemographic Risk factors				
Age (mean)^	1.03	1.03-1.04	1.03	1.03-1.04
Sex (Male=1)	1.28	1.11-1.48	1.33	1.16-1.53
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	0.83	.71-.98	0.99	.84-1.17
NH Black	1.44	1.24-1.68	1.62	1.38-1.90
NH Asian	0.38	.23-.64	0.55	.33-.94
NH Other	1.03	.73-1.44	1.06	.76-1.49
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	0.8	.70-.92	0.83	.72-.96
missing	0.67	.32-1.39	0.58	.27-1.22
Baseline Risk Factors				
Family History of heart attack	1.43	1.24-1.66	1.27	1.08-1.49
Obesity (BMI>30)	1.89	1.66-2.15	1.71	1.50-1.96
Diabetes diagnosis	2.48	2.0-3.06	1.74	1.37-2.21
Binge Drinking	1.22	.99-1.50	1.25	1.01-1.56
Smoking History Variables				
Former Established smoker	1.42	1.18-1.72	1.03	.83-1.27
Pack years (intervals of 10)^	1.17	1.13-1.21	1.03	.98-1.08

Notes: Person N=17,539 ; Risk Period N=59,367
^for interpretation, pack-years were rescaled to intervals of 10 packyears

Discussion

This study examined the time-varying association between cigarette smoking and ENDS use on the incidence of self-reported hypertension among a nationally representative sample of US adults. We found that exclusive cigarette use was associated with an increased risk of incident hypertension in both unadjusted and fully adjusted models. While the association between chronic cigarette use and hypertension is complex,[42] and the causal link is still debated,[42, 43] this finding aligns with previous research indicating a modest association between current cigarette smoking and the risk of incident hypertension.[5, 8, 10, 44, 45] Moreover, this finding is consistent with hypertension risk prediction models that include current cigarette smoking as a covariate,[7] and with the findings from the 2014 Surgeon General's report, which concluded that cigarette smoking is directly associated with coronary heart disease, including hypertension.[9] In contrast, studies examining the effects of ENDS use on hypertension have only recently been published,[22] and in a longitudinal follow-up of approximately five years, we found no evidence that short term and time-varying ENDS use was associated with an increased risk of incident hypertension.

Dual use of cigarettes and ENDS was not associated with the incidence of hypertension, although the direction of the hazard estimates was positive in fully adjusted models for both self-reported and medicated hypertension outcomes. However, it is important to note that dual users were different from exclusive cigarette smokers, and the non-significant association between dual use and incident hypertension may be partially explained by residual confounding by sociodemographic characteristics and tobacco use histories of dual users. In our study, dual users were younger, more likely to be NH White, and reported higher household incomes than exclusive cigarette smokers. These characteristics are all correlated with lower risk for

hypertension.[8, 46, 47] In addition, dual users had lower pack-years values than exclusive cigarette users, with pack-years values very similar to exclusive ENDS users. The different smoking histories between exclusive cigarette and dual users is consistent with other research finding that dual use is associated with reduced cigarette consumption,[48-50] and may represent part of a transitional state as smokers move away from smoking cigarettes.[50, 51] It is possible that dual users may have a different risk profile than exclusive cigarette users, which may then translate into a lower risk of disease relative to exclusive cigarette users. Studies with a larger number of ENDS users are needed to better understand the risk of incident hypertension among dual users.

Taken together, the results from this study do not support an association between ENDS use and self-reported incident hypertension. By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.[27] This is the most likely reason why our findings differ from a recent cross-sectional examination of the lifetime prevalence of hypertension using PATH data,[23] where the authors did not account for the relative timing of the ENDS exposure and hypertension. In addition, we also controlled for the potential confounding of past cigarettes smoking history, measured as pack-years, which is important given that 64% of exclusive adult ENDS users at baseline were former established cigarette smokers. The substantial history of cigarette use among the majority of exclusive ENDS users further highlights the importance of controlling for their past cigarette smoking history when trying to estimate the independent effect of ENDS use on hypertension and other health outcomes.

Limitations

Our study has several important limitations that need to be considered. First, the results from this study are based on observational data from a prospective longitudinal study, and the results should be interpreted with the same level of caution required in all self-reported studies. Our non-randomized data means that our results could be affected by unmeasured confounding, and while we included a measure of medicated hypertension as a sensitivity analysis, both our hypertensive outcomes are self-reported. Since systolic and diastolic blood pressure measures are not available in the PATH study, the reported incidence may underestimate the true incidence of hypertension,[35, 36] particularly for some sociodemographic groups.[35] Future research would benefit from including measured hypertension instead of self-reported hypertension where possible. Second, while the PATH study was representative of the US population at baseline, the loss to follow-up was significant and respondent attrition may not have been random. While we examined differences between censored and uncensored cases and conducted a sensitivity analysis with weights meant to adjust for attrition, this problem cannot be fully eliminated, as is true of most longitudinal studies. The discrete-time survival approach, which allows us to include all available information from respondents at each time interval, is a way to maximize information on the longitudinal sample. Third, while PATH has the biggest representative sample of longitudinal tobacco use and health in the US, ENDS use was only reported by a relatively small number of participants, limiting the power to detect statistical associations between ENDS use and incident hypertension. Fourth, if some respondents used ENDS to quit smoking cigarettes, it is possible that these respondents also made other lifestyle changes that

may have concomitantly reduced the impact of ENDS use on incident hypertension. Similarly, some might have decided to switch in response to symptoms or health issues. Future research is needed to better understand the characteristics of respondents who transition from cigarettes to ENDS use, their reasons for doing so, and the future health outcomes of these transitions. Finally, ENDS products have only been widely available in the US for little more than a decade.[52] The findings from our study are based on approximately five years of longitudinal follow-up, and longer exposure to ENDS products may be required to more fully understand the role of ENDS use on the risk of hypertension. Moreover, ENDS products continue to evolve, and more recent generations of ENDS products have more efficient nicotine delivery. This study did not adjust for cumulative exposure to ENDS or for nicotine level by product type. Future studies should seek to develop valid methods for better understanding exposure to ENDS products, and this analysis will need to be updated as more longitudinal data on long-termer term ENDS use becomes available.

Conclusions

Using nationally representative prospective longitudinal data among US adults, we found that time-varying cigarette smoking increased the risk of self-reported incident hypertension, but time-varying ENDS use did not. These results highlight the importance of using prospective longitudinal data to disentangle the temporal ordering between cigarette and ENDS use and the need to control for the potential confounding effect of cigarette smoking histories among ENDS users. This type of longitudinal analysis can be extended in future research examining the cardiovascular health effects of ENDS use, as longer-term data becomes available.

Contributorship statement: SC conducted the data analysis and drafted and revised the manuscript. JH and NF initiated the research project in collaboration with RM and DL. IB and RM provided statistical consultation, and GB and DA provided medical expertise and helped interpret the findings. EM, AP, and JJ created the measures used in the analysis. All co-authors revised the draft of the paper, and NF revised the final draft prior to submission.

Ethics statement: This study used de-identified data an no personal identifying information is included in the manuscript. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

Competing interest statement: All authors report no conflicts of interest or disclosures.

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Data sharing statement: Data may be obtained from a third party and are not publicly available. Data are derived from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available de-identified data set. However, this analysis used the Restricted Use Files to use variables such as continuous age, and cigarette pack-years. These variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21.

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Supplemental Material

Figure S1. Flowchart of Sample Selection for Analytic Sample, Self-Reported Hypertension Outcome

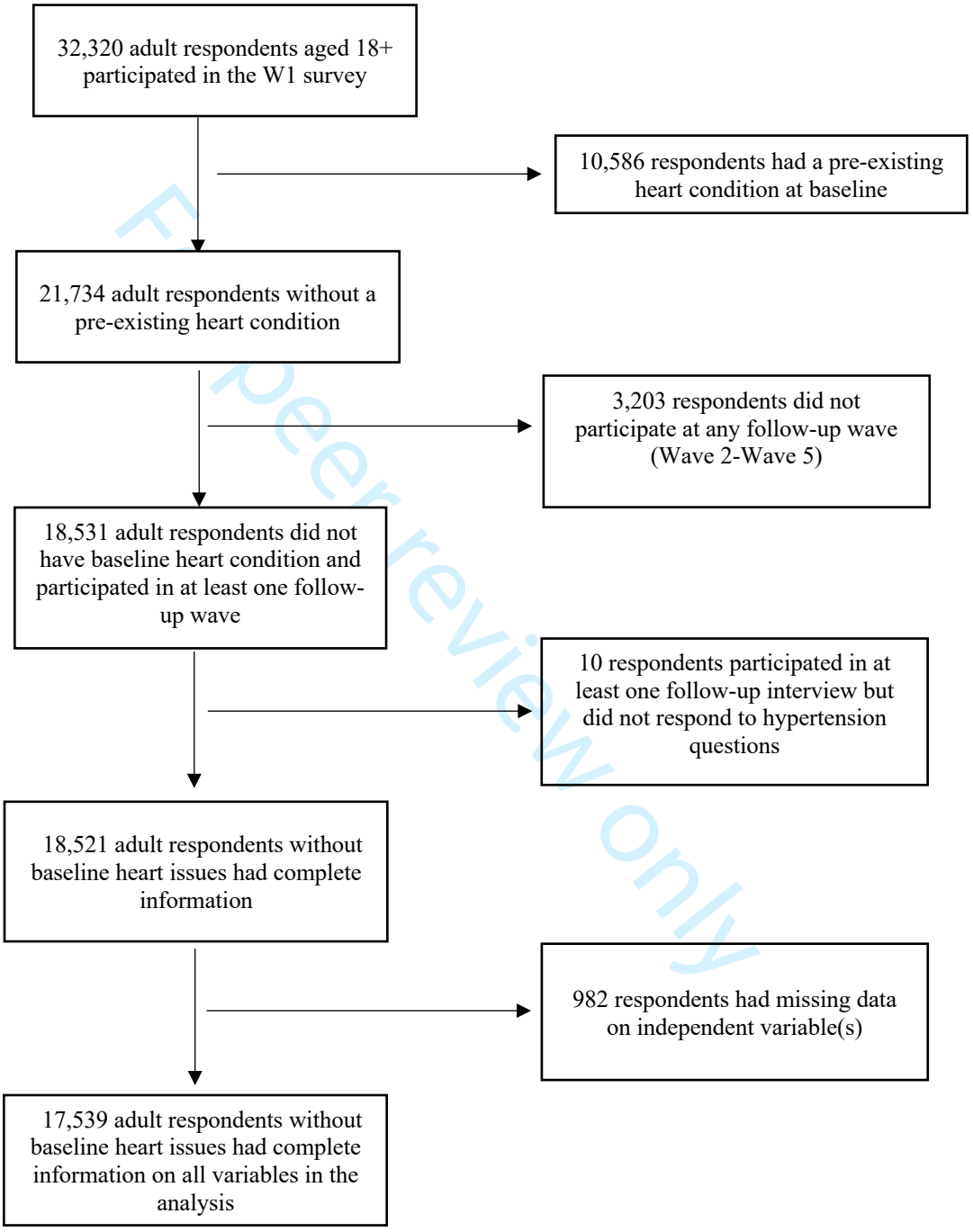

Table S1. Descriptive Statistics for Time-Varying Cigarette/ENDS Use, Established Adult Cigarette Smokers, Population Assessment of Tobacco & Health Study

	Follow-Up Interview*							
	Wave 1		Wave 2		Wave 3		Wave 4	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Time varying cigarettes/ENDS use								
Non use	79.2	78.5-79.9	78.6	77.9-79.4	79	78.2-79.7	79.9	79.0-80.6
Exclusive cigarette use	18	17.3-18.7	17.8	17.1-18.5	17.5	16.9-18.3	16.9	16.2-17.7
Exclusive ENDS use	1.1	0.92-1.96	1.3	1.2-1.5	1.4	1.3-1.6	1.5	1.3-1.7
Dual use	1.7	1.6-2.0	2.2	2.0-2.5	2.1	1.8-2.3	1.8	1.6-2.0

*time-varying covariates were lagged by one wave to limit issues with reverse causation

Table S2. Analysis of Censored Cases, Self-reported hypertension

	Non-censored	Censored	P
Age (mean)	39.2	38	**
Sex			***
Female	55.5%	47.9%	
Male	44.5%	52.1%	
Baseline cigarettes/ENDS exposure			***
Non use	80.1%	75.7%	
Exclusive cigarette use	17.2%	20.9%	
Exclusive ENDS use	1.1%	1.1%	
Dual use	1.6%	2.3%	
Race/Ethnicity			**
NH White	62.7%	63.9%	
Hispanic	17.8%	16.9%	
NH Black	1150.0%	9.2%	
NH Asian	530.0%	7.4%	
NH Other	260.0%	2.6%	
Household Income			***
<$50,000	56.5%	54.1%	
>$50,000	42.3%	39.9%	
missing	1.2%	6.0%	
Family history of heart attack			NS
No	71.7%	74.2%	
Yes	28.3%	25.8%	
Obesity (BMI >30)			**
No	74.5%	78.7%	
Yes	25.5%	21.3%	
Diabetes diagnosis at baseline			NS
No	95.2%	95.6%	
Yes	4.8%	4.4%	
Binge drinking			***
No	95.6%	94.9%	
Yes	4.4%	5.1%	
Former established smoker at baseline			NS
No	86.4%	87.7%	
Yes	13.6%	12.3%	
Pack-years at baseline (10 PY intervals)	0.453	0.458	NS

*p<0.05, **p<0.01, ***p<0.001

Table S3. Discrete time survival analysis predicting incidence of hypertension among adults using longitudinal cohort 'all waves weights', Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.35***	1.18-1.55	1.26**	1.07-1.49
Exclusive ENDS use	0.95	.63-1.41	1.07	.70-1.63
Dual use	1.11	.81-1.51	1.25	.89-1.75
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.03	1.03***	1.02-1.03
Sex (Male=1)	1.36***	1.16-1.59	1.45***	1.23-1.70
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.78*	.65-.94	0.92	.76-1.10
NH Black	1.53***	1.31-1.79	1.65***	1.39-1.96
NH Asian	.34***	.21-.53	.49**	.30-.81
NH Other	1	.69-1.47	1.07	.72-1.59
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.82*	.70-.97	0.85	.72-1.01
missing	1	.36-2.82	0.79	.26-2.38
Baseline Risk Factors				
Family History of heart attack	1.45***	1.22-1.71	1.29**	1.07-1.56
Obesity (BMI>30)	2.05***	1.77-2.36	1.81***	1.54-2.13
Diabetes diagnosis	2.61***	2.05-3.32	1.98***	1.54-2.55
Binge Drinking	1.19	.93-1.54	1.19	.91-1.55
Smoking History Variables				
Former Established smoker	1.48**	1.19-1.83	1.09	.86-1.38
Pack years (intervals of 10)^	1.17***	1.12-1.21	1.04	.99-1.09

Person N=11,437 ; Risk Period N =45,250

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S4. Discrete time survival analysis predicting incidence of medicated hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Medicated Hypertension			
	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.29**	1.10-1.51	1.25*	1.02-1.53
Exclusive ENDS use	0.62	.36-1.08	0.88	.51-1.50
Dual use	0.85	.61-1.18	1.07	.73-1.57
Sociodemographic Risk factors				
Age (mean)^	1.04***	1.04-1.05	1.04***	1.04-1.05
Sex (Male=1)	1.23*	1.04-1.47	1.23*	1.04-1.46
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.81*	.66-.99	1.03	.83-1.28
NH Black	1.41***	1.17-1.70	1.71***	1.39-2.10
NH Asian	.32*	.13-.77	0.52	.21-2.10
NH Other	0.71	.44-1.15	0.81	.52-1.26
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.78**	.66-.92	0.85	.72-1.03
missing	0.78	.29-2.08	0.57	.21-1.54
Baseline Risk Fators				
Family History of heart attack	1.34**	1.10-1.62	1.12	.91-1.38
Obesity (BMI>30)	1.86***	1.59-2.18	1.68***	1.41-2.00
Diabetes diagnosis	3.21***	2.51-4.11	2.12***	1.62-2.78
Binge Drinking	1.11	.84-1.47	1.27	.95-1.68
Smoking History Variables				
Former Established smoker	1.42**	1.14-1.77	0.88	.68-1.13
Pack years (intervals of 10)^	1.20***	1.15-1.24	1.06*	1.00-1.12

Person N=14,868 ; Risk Period N =52,818

*p<0.05, **p<0.01, ***p<0.001

^tested for nonlinearity but the quadratic term was not significant

Table S5. Discrete time survival analysis predicting incidence of self-reported hypertension among adults with 'regular' cigarette/ENDS use (10+ days), Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.28***	1.15-1.42	1.18**	1.05, 1.33
Exclusive ENDS use	0.84	.58-1.21	0.95	0.67, 1.35
Dual use	1	.77-1.30	1.14	0.80, 1.64
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.04	1.03***	1.03, 1.04
Sex (Male=1)	1.28**	1.11-1.48	1.33***	1.16,1 .54
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.83*	.71-.98	0.99	0.84, 1.17
NH Black	1.44***	1.24-1.68	1.62***	1.39, 1.90
NH Asian	.38***	.23-.64	0.55*	0.33, 0.93
NH Other	1.03	.73-1.44	1.06	0.76, 1.49
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.80**	.70-.92	0.83*	0.72, 0.96
missing	0.67	.32-1.39	0.58	0.27, 1.23
Baseline Risk Factors				
Family History of heart attack	1.43***	1.24-1.66	1.27**	1.08, 1.49
Obesity (BMI>30)	1.89***	1.66-2.15	1.71***	1.50, 1.96
Diabetes diagnosis	2.48***	2.0-3.06	1.74***	1.37, 2.20
Binge Drinking	1.22	.99-1.50	1.26*	1.02, 1.57
Smoking History Variables				
Former Established smoker	1.42***	1.18-1.72	1.02	0.83, 1.27
Pack years (intervals of 10)^	1.17***	1.13-1.21	1.04	0.99, 1.09

Notes: Person N=17,539 ; Risk Period N=59,367

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S6. Discrete time survival analysis predicting incidence of self-reported hypertension with revised cigarette/ENDS exposure, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Never established use	REF	REF	REF	REF
Former cigarettes, no ENDS	1.43**	1.17, 1.75	0.97	0.78, 1.21
Current cigarettes, no ENDS	1.38***	1.22, 1.56	1.20*	1.04, 1.38
Former cigarettes, current ENDS	1	0.64, 1.55	1.01	0.64. 1.60
Current cigarettes and ENDS	1.07	0.80, 1.41	1.13	0.84, 1.52
Exclusive ENDS	0.64	0.31, 1.32	0.86	0.41, 1.82
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.04	1.03***	1.03, 1.04
Sex (Male=1)	1.28**	1.11-1.48	1.33***	1.15, 1.53
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.83*	.71-.98	1	0.85, 1.17
NH Black	1.44***	1.24-1.68	1.61***	1.37, 1.89
NH Asian	.38***	.23-.64	0.56*	0.33, 0.94
NH Other	1.03	.73-1.44	1.05	0.75, 1.47
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.80**	.70-.92	0.83*	0.72, 0.96
missing	0.67	.32-1.39	0.58	0.27, 1.24
Baseline Risk Factors				
Family History of heart attack	1.43***	1.24-1.66	1.28**	1.09, 1.49
Obesity (BMI>30)	1.89***	1.66-2.15	1.72***	1.50, 1.98
Diabetes diagnosis	2.48***	2.0-3.06	1.76***	1.39, 2.22
Binge Drinking	1.22	.99-1.50	1.26*	1.01, 1.57
Smoking History Variables				
Pack years (intervals of 10)^	1.17***	1.13-1.21	1.04	0.99, 1.09

Notes: Person N=17,539 ; Risk Period N=59,367

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S7. Discrete time survival analysis predicting incidence of self-reported hypertension among never established cigarette smokers, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying ENDS use	0.56	0.28, 1.13	0.75	0.37, 1.52
Sociodemographic Risk factors				
Age (mean)^	1.04***	1.03, 1.04	1.04***	1.03, 1.04
Sex (Male=1)	1.25*	1.03, 1.52	1.31**	1.07, 1.60
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	0.84	0.67, 1.05	0.89	0.69, 1.14
NH Black	1.42**	1.17, 1.72	1.56***	1.25, 1.93
NH Asian	0.40**	0.21, 0.77	0.54	0.28, 1.05
NH Other	1.25	0.80, 1.97	1.34	0.81, 2.19
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	0.75**	0.62, 0.90	0.74**	0.60, 0.90
missing	0.71	0.27, 1.87	0.53	0.19, 1.43
Baseline Risk Factors				
Family History of heart attack	1.41**	1.16, 1.71	1.23	0.99, 1.52
Obesity (BMI>30)	2.09***	1.72, 2.53	1.80***	1.47, 2.20
Diabetes diagnosis	2.59***	1.95, 3.45	1.71**	1.23, 2.36
Binge Drinking	1.09	0.71, 168	1.4	0.89, 2.18

Notes: Person N=9478 ; Risk Period N=32,579

*p<0.05, **p<0.01, ***p<0.001

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	(a)-1 (b)-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	Fig A1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	(a)-9-10 (c, d, e) -10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Fig A1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study

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Running Head: ENDS AND HYPERTENSION AMONG US ADULTS

The time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study

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Abstract

Objective: Electronic Nicotine Delivery Systems (ENDS) products have emerged as the most popular alternative to combustible cigarettes. However, ENDS products contain potentially dangerous toxicants and chemical compounds, and little is known about their health effects. The aim of the present study was to examine the prospective association between cigarette and ENDS use on self-reported incident hypertension.

Design and Methods: Using adult data from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco and Health Study, we examined the risk of self-reported incident hypertension associated with ENDS use among 17,539 adults aged 18+ using discrete-time survival models. To distinguish the role of cigarettes and ENDS, we constructed a time-varying tobacco exposure, lagged by one wave, defined as no use, exclusive established use (daily or some days) of ENDS or cigarettes, and dual use. We controlled for demographics (age, sex, race/ethnicity, household income), clinical risk factors (family history of heart attack, obesity, diabetes, binge drinking) and smoking history (cigarette pack-years).

Results: The self-reported incidence of hypertension was 3.7% between Waves 2-5. At baseline, 18.0% (n=5,570) of respondents exclusively smoked cigarettes, 1.1% (n=336) exclusively used ENDS, and 1.7% (n=570) were dual users. In adjusted models, exclusive cigarette use was associated with an increased risk for self-reported incident hypertension compared to non-use (aHR=1.21, 95% CI: 1.06-1.38), while exclusive ENDS use (aHR=1.00, 95% CI: 0.68-1.47) and dual use (aHR=1.15, 95% CI: 0.87-1.52) were not.

Conclusions: We found that smoking increased the risk of self-reported hypertension but ENDS use did not. These results highlight the importance of using prospective longitudinal data to examine the health effects of ENDS use.

Keywords: ENDS, cigarettes, hypertension, cardiovascular disease

Strengths and limitations of this study

- In this study, we examine the time-varying association between cigarette smoking and ENDS use on the incidence of hypertension among a nationally representative sample of US adults.
- By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.
- We also controlled for the potential confounding of past smoking history, measured as cigarette pack-years, which important because most adults who use ENDS are either currently smoking cigarettes or have smoked cigarettes in the past.
- Our study was limited by relying on self-reported hypertension, as systolic and diastolic blood pressure measures were not available.
- Our non-randomized data means that our results could be affected by unmeasured confounding, and the results should be interpreted with the same level of caution required in all prospective longitudinal studies.

Introduction

Cigarette smoking is the leading cause of premature mortality in the US,[1,2] and a significant proportion of smoking-attributable deaths are related to cardiovascular disease.[3,4] Smoking is known to cause an acute rise in blood pressure,[5] contribute to arterial stiffness,[6] and has been associated with an increased risk of developing hypertension.[5,7-10] Hypertension, in turn, is an important risk factor for most downstream cardiovascular diseases.[11-13] The health hazards of smoking on cardiovascular disease underscore the importance of further reducing smoking prevalence in the general population, and the continued need to promote smoking cessation among adults who smoke.

Electronic Nicotine Delivery Systems (ENDS) products became widely available around 2010, and they refer to a broad range of devices that produce an aerosol from heating an e-liquid. ENDS products quickly emerged as the most popular alternative to combustible cigarettes in the US, as their prevalence doubled among young adults between 2014-2018,[14] and more than 5.6 million U.S. adults reported ENDS use in 2018-2019.[15] Some adults use ENDS products as a way to help them quit smoking,[15,16] and because they are generally believed to be less harmful than combustible cigarettes,[17,18] and it has been argued that their use should be encouraged as part of a harm minimization strategy.[17] However, non-smoking youth are also using ENDS products,[19] raising concerns about tobacco use renormalization. Furthermore, ENDS contain toxicants and chemical compounds that are potentially dangerous, including aldehydes, carbonyl, nicotine, and flavoring additives.[20,21] Very little is known about the health consequences of ENDS product use,[21] and we need reliable and rigorous estimates of their health effects.

One potential consequence of ENDS product use may be an increased risk of hypertension. Evidence of a short-term elevation in both systolic blood pressure and diastolic

blood pressure from ENDS product use have been found in experimental studies,[22] and a recent epidemiological study found evidence of a cross-sectional association between ENDS product use and self-reported hypertension among adults.[23] However, cross-sectional research on the cardiovascular risks of ENDS use has resulted in a contentious debate,[24-28] largely centered around the issue of reverse causation.[27] Without information on the timing of both the ENDS use and the disease outcome, it is simply not possible to know whether ENDS use came before or after the disease outcome. The latter is likely common given the use of ENDS by some smokers trying to quit after being diagnosed with a cardiovascular disease.[29] Therefore, the results from these cross-sectional studies need to be interpreted with caution. Researchers have highlighted the need for prospective longitudinal data to better understand the temporal ordering between ENDS use and cardiovascular disease endpoints.[22,28]

In this study, we use data from a nationally representative prospective cohort study to examine the time-varying association between cigarette and ENDS use on the incidence of self-reported hypertension, which limits potential concerns with reverse causation. In addition, we developed a composite exposure variable combining current cigarette and ENDS use to examine the relative contribution of exclusive cigarette use, exclusive ENDS use, and dual cigarette/ENDS use, compared to no use. We also adjust for past cigarette smoking history.

Methods

Data

We used data on adults from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available data set. However, this analysis used the Restricted Use Files[30] in order to use variables such as continuous age, and cigarette pack-years. These

variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

The PATH study is an ongoing, nationally representative cohort study of the civilian, non-institutionalized population in the United States. A stratified area probability design was used to sample geographical segments from 156 geographical primary sampling units. An address-based sampling frame was then used to randomly select households based on residential addresses derived from the United States Postal Service. Once households were identified, a two-phase sampling procedure was used to select adults within sampled households for in-person interviews.[31]African-Americans and tobacco users were oversampled related to population proportions, and weighting procedures adjusted for oversampling and non-response based on US Census Bureau Data. Data were collected from September, 2013 to December, 2014 for Wave 1(response rate among screened households, 74.0%); October, 2014 to October, 2015 for Wave 2 (response rate, 83.2%); October, 2015 to October, 2016 for Wave 3 (response rate, 78.4%); December, 2016 to January, 2018 for Wave 4 (response rate, 73.5%); and December, 2018 to November 2019 for Wave 5 (response rate, 69.4%). All PATH survey interviews were completed in-person, using Audio-Assisted Self-Interviewing (ACASI) administrations, available in English or Spanish. Data collection protocols were used to ensure that follow-up interviews were close to the anniversary of their participation in the previous wave.[32] Further details about the design and methods of the PATH Study have been published elsewhere.[31-34]

The analytic sample for the current study was restricted to adult respondents (18+) (Wave 1, n=32,320) with no self-reported heart condition (e.g., congestive heart failure, heart attack,

stroke) or previous diagnosis of hypertension or high cholesterol at baseline (n=21,734). A total of 3203 respondents were excluded as they did not participate at any follow-up interview, and respondents who did not report a hypertension diagnosis were right censored at their last observation point. Respondents with missing variable information (n=992; 5.3%) were excluded from the analysis using listwise deletion. The final analytic sample consisted of 17,539 respondents. A flowchart summarizing the analytic sample is provided in the appendix (Figure S1).

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Self-Reported Hypertension

We examined the incidence of self-reported hypertension at follow-up among respondents who reported they had never been diagnosed with hypertension at baseline. The reliability and concurrent validity of self-reported hypertension has been established in a previous study using PATH Study data.[32] In Wave 2 and Wave 3, *all* respondents were asked, *"In the past 12 months, has a doctor, nurse or other health professional told you that you had high blood pressure?"* Due to a change in the skip pattern in Wave 4 and Wave 5, this question was *only* asked to respondents who reported they saw a *"medical doctor, nurse, or other health professional"* during the past 12 months. We adopted an inclusive measurement strategy because self-reported hypertension is known to have low sensitivity (i.e., it is underestimated) in epidemiological studies,[35] especially among females[36] and Non-Hispanic Black adults.[37] To minimize this bias, we classified respondents who answered 'yes' to the blood pressure question as having self-reported hypertension regardless of whether they reported seeing a doctor during the past year.

In Wave 4 and 5, we classified respondents who did not report seeing a doctor during the past year as not having self-reported hypertension.

Cigarette/ENDS Exposure Variable

Our exposure variable was based on answers to questions about established cigarette (100 or more cigarettes smoked in lifetime) and ENDS (ever fairly regularly used ENDS) use, as well as every day or someday use of cigarettes and ENDS (current use). Based on these variables, we developed a four-category exposure variable: non-current user (of either product, which included people who never used either product), exclusive cigarette smoker, exclusive ENDS user, and dual user of cigarettes and ENDS. This variable was constructed at each wave and was included as a time-varying exposure. To minimize missing values for a given wave, we imputed missing tobacco exposure data borrowing information from a previous wave. To ensure that the tobacco product use exposure preceded the hypertension diagnosis, we lagged our time-varying exposure by one wave. The descriptive statistics of the time-varying tobacco use exposure can be found in the appendix (Table S1).

Covariates

We included age (continuous ages 18-90) sex (0=female, 1=male), race/ethnicity (Hispanic, Non-Hispanic [NH] White, NH Black, NH Asian, NH Other), and household income (less than $49,999, more than $50,000, missing) as baseline sociodemographic variables. Missing values for baseline sociodemographic variables were updated with data from other waves when available to reduce item non-response. We also included baseline risk factors to control for potential confounding, including familial history of heart attack/bypass surgery,

obesity (BMI >30), diabetes mellitus, and regular binge drinking (five or more drinks in one sitting on at least five separate days during the past month).

To account for the potential confounding effect of lifetime cigarette smoking, two additional covariates were included. First, we included a dichotomous predictor for former established smokers (smoked at least 100 cigarettes in lifetime but reports no current use at baseline). Second, we included cigarette pack-years as a measure of lifetime cigarette smoking at baseline. Pack-years were calculated by multiplying the duration of cigarette smoking by the average number of packs of cigarettes smoked per day while individuals smoked. Respondents who reported smoking more than 200 cigarettes per day (10 packs per day) were considered implausible and were set to missing (n=99).

Statistical Analysis

Descriptive statistics were first calculated for sociodemographic characteristics, cigarette/ENDS use, and hypertension risk factors at baseline. The sample characteristics were then calculated according to respondent's cigarette/ENDS use at baseline. Chi-square tests or Fisher's exact tests were used to test for statistically significant differences between groups. Lifetables were then used to describe the distribution of the incident hypertension outcomes at follow-up (Wave 2-Wave 5). The hazard estimates reflect the weighted conditional probability for self-reported hypertension for respondents in the risk set at each discrete time interval.[38]

We used discrete time survival models to analyze the incidence of self-reported hypertension across Wave 2-Wave 5 of follow-up (approximately 5 years). Discrete time survival models are appropriate when the exact timing until an event is not known.[38] The data was fit to an unbalanced person-period data set where each individual contributed a number of rows equal to the time period until they were diagnosed with hypertension or were right

censored.[39] As such, all 17,539 respondents in the self-reported hypertension sample had a separate row of data for each period, with a maximum of four rows per respondent, resulting in a person-period data set with 59,367 observations. The structure of the reorganized person-period dataset allowed for an examination of the conditional probability of self-reported and medicated incident hypertension at each discrete time interval. All discrete-time survival models were estimated using a complimentary log-log (cloglog) link function on the person-period dataset. Data were weighted using Wave 1 (W1) weights, including full-sample and 100 replicate weights, to ensure that our respondents were representative of the non-institutionalized adult population in the United States at baseline.

Several sensitivity analyses were included as robustness checks. First, to assess the impact of attrition, we compared baseline characteristics for censored and non-censored respondents (Table S2). Because the censored respondents had a slightly different sociodemographic profile than the non-censored respondents, as a sensitivity analysis, we estimated the discrete time models using the 'all waves weights,'which account for this type of attrition[31] and restricts the analysis to a longitudinal cohort of respondents who participated in all waves of the PATH study (Table S3). Third, to better approximate clinical hypertension and minimize potential false positive errors in self-reported hypertension, we also included a measure of medicated hypertension as a sensitivity analysis. Respondents who self-reported hypertension and responded 'yes' when asked, "*In the past 12 months, did you take heart or blood pressure medication regularly,"* were considered to have medicated hypertension (Table S4). Fourth, to examine whether more frequent cigarette/ENDS use was associated with incident hypertension, we included a more frequent cigarette/ENDS use exposure (measured as 10+ days in the past 30 days) as a sensitivity analysis (Table S5). Fifth, to more clearly distinguish between adults who

never smoked cigarettes from former smokers, we created a revised exposure with adults who reported 'never established smoking' as the reference group, with the following use categories: (1) former cigarette, no ENDS; (2) current cigarette, no ENDS; (3) former cigarette, current ENDS; (4) current cigarette and ENDS; (5) exclusive ENDS (see Table S6). Finally, we restricted our analysis to adults who reported they had never smoked 100 cigarettes in their lifetime at baseline and examined the association between ENDS use and hypertension among respondents who had never smoked (Table S7). For all analyses, variances were computed using the balanced repeated replication methods with Fay's adjustment set to 0.3 as recommended by the PATH study.[33,40] All analyses were conducted using Stata 16.1.[41]

Results

The weighted baseline sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for the self-reported hypertension (n=17,539) analytic sample are outlined in Table 1. At baseline, respondents had a mean age of 39 years (SD=15.4) and were predominately female (53.9%), NH White (63.0%), and reported a household income of less than $50,000 (56.0%). Most respondents were not current cigarette or ENDS users at baseline (n=11,063; 79.2%) while a similar percentage of respondents were exclusive ENDS users (n=336; 1.1%) or dual users (n=570; 1.7%). Current cigarette use was the most common tobacco use status at baseline (n=5,570; 18.0%). 13.4% of respondents were former established smokers at baseline, among current or former established smokers, the average cigarette pack-years was 13.9 (SD=20.0). In terms of baseline hypertensive risk factors, approximately one quarter of respondents reported a family history of heart attack (27.7%) and obesity (24.6%), while diabetes mellitus (4.7%) and regular binge drinking (4.5%) were reported less frequently.

Table 2 presents the sample characteristics stratified by our tobacco exposure variable at baseline. Compared to all other groups, respondents who exclusively smoked cigarettes were the most likely to be NH Black (12.6%), most likely to report household incomes under $50,000 (74.3%). Compared to exclusive cigarette users, exclusive ENDS users at baseline were younger (33.2 (SD=16.7) vs. 37.1 (SD=17.7) years), reported higher household incomes (33.2% vs. 23.8%), and were more likely to report a family history of heart attack (31.7% vs. 29.4%) and obesity (33.2% vs. 23.8%). Importantly, nearly two thirds of exclusive ENDS users were former established smokers at baseline (63.7%). The average pack-years value for exclusive ENDS users who were former established smokers (17.9, SD=23.6) was higher than for current exclusive cigarette users (14.1, SD=22.4) at baseline. Dual users shared similar sociodemographic characteristics with exclusive ENDS users, except dual users were more likely to be NH White (76.7%-vs. 69.3%), to have diabetes mellitus (5.1% vs 3.2%) and reported more regular binge drinking (12.1% vs. 10.5%-10.3%). The average pack-years values for dual users (11.1, SD=16.9), on the other hand, was lower than exclusive cigarette users (14.1, SD=22.4), and for former smokers who were non-current users (13.9, SD=15.3) or exclusive ENDS users (17.9, SD=23.61) at baseline.

Table 1. Weighted sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for adult respondents (18+) at baseline, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	N	%^	95% CI
Age (mean, sd)	17,539	38.97 (15.42)	
Sex			
Female	9,073	53.9	53.2-54.6
Male	8,466	46.1	45.4-46.8
Race/Ethnicity			
NH White	10,250	63	62.2-63.8
Hispanic	3,446	17.6	17.0-18.2
NH Black	2,422	11	10.5-11.5
NH Asian	526	5.8	5.3-6.3
NH Other	895	2.6	2.4-2.9
Household Income			
<$50,000	11,481	56	54.6-57.3
>$50,000	5,699	41.8	40.4-43.1
missing	359	2.2	1.9-2.7
Cigarette/ecigarette baseline exposure			
Non user	11,063	79.2	78.5-79.9
Cigarette only	5,570	18	17.3-18.7
E-cigarette only	336	1.1	.92-1.2
Dual user	570	1.7	1.6-2.0
Family history of heart attack			
No	12,852	72.3	71.2-73.3
Yes	4,687	27.7	26.7-28.8
Obesity (BMI >30)			
No	13,318	75.4	74.3-76.5
Yes	4,221	24.6	23.5-25.7
Diabetes diagnosis at baseline			
No	16,848	95.3	94.8-95.8
Yes	691	4.7	4.2-5.2
Regular Binge drinking			
No	16,297	95.5	95.1-95.8
Yes	1,242	4.5	4.2-4.9
Former established smoker at baseline			
No	15,618	86.6	85.8-87.5
Yes	1,921	13.4	12.5-14.2
Pack-years among current/former smokers (mean, sd)^^	8,061	13.9 (20.0)	

ENDS = electronic nicotine delivery systems

^ Percentages were calcuated using W1 weights

^^mean pack years value for ever established (both current and former) smokers.

Table 2. Sample characteristics by baseline cigarette/ENDS use, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	Non-user	Exclusive Cigarette user	Exclusive ENDS user	Dual User
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Age (mean, sd)	39.6 (14.2)	37.1 (17.7)	33.2 (16.7)	34.2 (16.6)
Sex				
Female	55.9 (55.1-56.8)	45.9 (44.5-47.3)	45.9 (39.9-52.1)	47.5 (43.4-51.6)
Male	44.1 (43.2-44.9)	54.1 (52.7-55.5)	54.1 (47.9-60.1)	52.5 (48.4-56.6)
Race/Ethnicity				
NH White	61.2 (60.1-62.4)	68.9 (67.3-70.5)	69.3 (63.0-75.0)	76.7 (72.7-80.4)
Hispanic	19 (18.2-19.7)	12.6 (11.7-13.6)	12.3 (9.1-16.5)	[illegible] (7.5-13.0)
NH Black	10.8 (10.2-11.4)	12.6 (11.5-13.7)	8.5 (5.6-12.5)	5.8 (3.8-8.7)
NH Asian	6.6 (6.1-7.3)	2.4 (1.8-3.2)	5.7 (2.7-11.5)	2.3 (1.0-4.9)
NH Other	2.4 (2.1-2.7)	3.5 (3.1-3.9)	4.2 (2.4-7.1)	5.3 (3.8-7.2)
Household Income				
<$50,000	51.4 (49.9-52.9)	74.3 (72.7-75.9)	65.2 (59.3-70.7)	66.2 (61.0-70.9)
>$50,000	46.2 (44.7-47.7)	23.8 (22.3-25.3)	33.2 (27.4-39.5)	32.1 (27.5-37.3)
missing	2.4 (2.0-2.9)	1.9 (1.5-2.3)	1.6 (.65-3.7)	1.6 (.80-3.2)
Family history of heart attack				
No	72.8 (71.6-74.0)	70.6 (69.2-72.0)	68.3 (63.3-73.0)	65.8 (61.0-70.3)
Yes	27.2 (26.0-28.4)	29.4 (28.0-30.8)	31.7 (27.0-36.7)	34.2 (29.7-39.0)
Obesity (BMI >30)				
No	75.5 (74.1-76.8)	75.3 (73.8-76.7)	72 (65.7-77.5)	76.2 (72.2-79.8)
Yes	24.5 (23.2-25.9)	24.7 (23.3-26.2)	28 (22.5-34.3)	23.8 (20.2-27.8)
Diabetes diagnosis at baseline				
No	95.3 (94.6-95.8)	95.5 (94.9-96.0)	96.8 (94.3-98.2)	94.9 (92.3-96.6)
Yes	4.7 (4.2-5.4)	4.5 (4.0-5.1)	3.2 (1.8-5.7)	5.1 (3.4-7.7)
Regular Binge drinking				
No	97.2 (96.8-97.5)	89 (88.0-89.9)	89.5 (85.1-92.7)	87.9 (84.6-90.6)

Yes	2.8 (2.5-3.2)	11 (10.1-12.0)	10.5 (7.3-14.9)	12.1 (9.4-15.4)
Former established smoker at baseline				
No	84 (82.9-85.0)	100	36.3 (30.3-42.9)	100
Yes	16 (15.0-17.1)	0	63.7 (57.1-69.7)	0
Pack-years smoking at baseline (mean, sd)^	13.9 (15.3)	14.1 (22.4)	17.9 (23.6)	11.1 (16.9)

ENDS = electronic nicotine delivery systems

^mean pack years value for ever established (both current and former) smokers.

Lifetables describing the conditional probability for self-reported incident hypertension are displayed in Table 3. Hypertension was self-reported by 1930 respondents in the analytic sample, with an annual incidence hazard of 3.7% (range 2.9% to 4.6% between W2 and W5). The hazard estimates were similar across all discrete time intervals, with slight increases between Wave 4-Wave 5, reflecting a two-year time interval between waves.

Table 3. Life tables describing the incidence of self-reported hypertension among adults (18+), Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

Interval	Total	Diagnosis	Censored	Hazard Estimate^
Period 1 (W1-W2)	17539	652	1230	0.039
Period 2 (W2-W3)	15660	464	1137	0.033
Period 3 (W3-W4)	14067	334	1632	0.029
Period 4 (W4-W5)	12101	480	11612	0.046

^ hazard estimates were calculated using W1 weights

Table 4 presents discrete time hazard models examining the risk of self-reported incident hypertension. In the unadjusted model, respondents who exclusively smoked cigarettes had a significantly higher risk of self-reported incident hypertension compared to those who did not currently use cigarettes or ENDS products (hazard ratio [HR] 1.28, 95% CI:1.15-1.42). The risk did not statistically differ for respondents who used ENDS, either exclusively (HR 0.84, 95% CI: 0.68-1.47) or with cigarettes (HR 1.00, 95% CI: 0.77-1.30), from respondents who did not use either product. After adjusting for sociodemographic risk factors, baseline risk factors, and smoking history variables, the results were very similar as exclusive cigarette use was associated with a 21 percent higher risk of self-reported incident hypertension (95% CI: 1.06-1.38), while exclusive ENDS use (adjusted hazard ratio [aHR] 1.0, 95% CI: 0.68-1.47) and dual use (aHR 1.15, 95% CI:0.87-1.52) were not. Other hypertensive risk factors associated with an increased

risk of self-reported hypertension included being older age, male sex, NH Black (vs. NH White) race/ethnicity, lower (vs. higher) household income, family history of heart attack, obesity, diabetes diagnosis and regular binge drinking at baseline in adjusted (multivariable) models.

Sensitivity Analyses

As sensitivity analyses, discrete-time models were estimated using the longitudinal cohort who participated in all waves of follow-up (Table S3); with a medicated hypertension outcome (Table S4); and with cigarette/ENDS use measured as 10+ days in the past 30 days rather than every day or someday use (Table S5). Across these sensitivity analyses, the substantive results remained robust as exclusive cigarette use was associated with an increased risk of incident hypertension compared to non-use in both unadjusted and fully adjusted models. In contrast, compared to non-use, exclusive ENDS and dual use were not associated with increased hypertension risk in unadjusted or fully adjusted models in any of these analyses. Discrete-time models were also estimated with an expanded cigarette/ENDS exposure incorporating never and former smoking as a sensitivity analysis (Table S6). Compared to never smoking, current cigarette smoking and non-ENDS use (aHR 1.20, 95% CI 1.04, 1.38) was associated with an increased risk of incident hypertension while current ENDS use among respondents who had formerly smoked (aHR 1.01, 95% CI 0.64, 1.60) and dual ENDS and cigarette smoking (aHR 1.13, 95% CI 0.84, 1.52) were not associated with increased hypertension risk. Finally, respondents with established cigarette use patterns were removed from the analytic sample, and the association between ENDS use and hypertension was examined among respondents who never smoked as an additional sensitivity analysis (Table S7). Time-varying ENDS use was not associated with an increased risk of incident hypertension compared to non-ENDS use in either unadjusted (HR = 0.56, 95% CI 0.28, 1.13) or adjusted models (aHR=0.75, 95% CI 0.37, 1.52).

Table 4. Discrete time survival analysis predicting incidence of self-reported hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.28	1.15-1.42	1.21	1.06-1.38
Exclusive ENDS use	0.84	.58-1.21	1	.68-1.47
Dual use	1	.77-1.30	1.15	.87-1.52
Sociodemographic Risk factors				
Age (mean)^	1.03	1.03-1.04	1.03	1.03-1.04
Sex (Male=1)	1.28	1.11-1.48	1.33	1.16-1.53
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	0.83	.71-.98	0.99	.84-1.17
NH Black	1.44	1.24-1.68	1.62	1.38-1.90
NH Asian	0.38	.23-.64	0.55	.33-.94
NH Other	1.03	.73-1.44	1.06	.76-1.49
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	0.8	.70-.92	0.83	.72-.96
missing	0.67	.32-1.39	0.58	.27-1.22
Baseline Risk Factors				
Family History of heart attack	1.43	1.24-1.66	1.27	1.08-1.49
Obesity (BMI>30)	1.89	1.66-2.15	1.71	1.50-1.96
Diabetes diagnosis	2.48	2.0-3.06	1.74	1.37-2.21
Binge Drinking	1.22	.99-1.50	1.25	1.01-1.56
Smoking History Variables				
Former Established smoker	1.42	1.18-1.72	1.03	.83-1.27
Pack years (intervals of 10)^	1.17	1.13-1.21	1.03	.98-1.08

Notes: Person N=17,539 ; Risk Period N=59,367
^for interpretation, pack-years were rescaled to intervals of 10 packyears

Discussion

This study examined the time-varying association between cigarette smoking and ENDS use on the incidence of self-reported hypertension among a nationally representative sample of US adults. We found that exclusive cigarette use was associated with an increased risk of incident hypertension in both unadjusted and fully adjusted models. While the association between chronic cigarette use and hypertension is complex,[42] and the causal link is still debated,[42,43] this finding aligns with previous research indicating a modest association between current cigarette smoking and the risk of incident hypertension.[5,8,10,44,45] Moreover, this finding is consistent with hypertension risk prediction models that include current cigarette smoking as a covariate,[7] and with the findings from the 2014 Surgeon General's report, which concluded that cigarette smoking is directly associated with coronary heart disease, including hypertension.[9] In contrast, studies examining the effects of ENDS use on hypertension have only recently been published,[22] and in a longitudinal follow-up of approximately five years, we found no evidence that short term and time-varying ENDS use was associated with an increased risk of incident hypertension.

Dual use of cigarettes and ENDS was not associated with the incidence of hypertension, although the direction of the hazard estimates was positive in fully adjusted models for both self-reported and medicated hypertension outcomes. However, it is important to note that dual users were different from exclusive cigarette smokers, and the non-significant association between dual use and incident hypertension may be partially explained by residual confounding by sociodemographic characteristics and tobacco use histories of dual users. In our study, dual users were younger, more likely to be NH White, and reported higher household incomes than exclusive cigarette smokers. These characteristics are all correlated with lower risk for hypertension.[8,46,47] In addition, dual users had lower pack-years values than exclusive cigarette

users, with pack-years values very similar to exclusive ENDS users. The different smoking histories between exclusive cigarette and dual users is consistent with other research finding that dual use is associated with reduced cigarette consumption,[48-50] and may represent part of a transitional state as smokers move away from smoking cigarettes.[50,51] It is possible that dual users may have a different risk profile than exclusive cigarette users, which may then translate into a lower risk of disease relative to exclusive cigarette users. Studies with a larger number of ENDS users are needed to better understand the risk of incident hypertension among dual users.

Taken together, the results from this study do not support an association between ENDS use and self-reported incident hypertension. By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.[27] This is the most likely reason why our findings differ from a recent cross-sectional examination of the lifetime prevalence of hypertension using PATH data,[23] where the authors did not account for the relative timing of the ENDS exposure and hypertension. In addition, we also controlled for the potential confounding of past cigarettes smoking history, measured as pack-years, which is important given that 64% of exclusive adult ENDS users at baseline were former established cigarette smokers. The substantial history of cigarette use among the majority of exclusive ENDS users further highlights the importance of controlling for their past cigarette smoking history when trying to estimate the independent effect of ENDS use on hypertension and other health outcomes.

Limitations

Our study has several important limitations that need to be considered. First, the results from this study are based on observational data from a prospective longitudinal study, and the results should be interpreted with the same level of caution required in all self-reported studies. Our non-randomized data means that our results could be affected by unmeasured confounding, and while we included a measure of medicated hypertension as a sensitivity analysis, both our hypertensive outcomes are self-reported. Since systolic and diastolic blood pressure measures are not available in the PATH study, the reported incidence may underestimate the true incidence of hypertension,[35,36] particularly for some sociodemographic groups.[35] Future research would benefit from including measured hypertension instead of self-reported hypertension where possible. Second, while the PATH study was representative of the US population at baseline, the loss to follow-up was significant and respondent attrition may not have been random. While we examined differences between censored and uncensored cases and conducted a sensitivity analysis with weights meant to adjust for attrition, this problem cannot be fully eliminated, as is true of most longitudinal studies. The discrete-time survival approach, which allows us to include all available information from respondents at each time interval, is a way to maximize information on the longitudinal sample. Third, while PATH has the biggest representative sample of longitudinal tobacco use and health in the US, ENDS use was only reported by a relatively small number of participants, limiting the power to detect statistical associations between ENDS use and incident hypertension. Fourth, if some respondents used ENDS to quit smoking cigarettes, it is possible that these respondents also made other lifestyle changes that may have concomitantly reduced the impact of ENDS use on incident hypertension. Similarly, some might have decided to switch in response to symptoms or health issues. Future research is

needed to better understand the characteristics of respondents who transition from cigarettes to ENDS use, their reasons for doing so, and the future health outcomes of these transitions. Finally, ENDS products have only been widely available in the US for little more than a decade.[52] The findings from our study are based on approximately five years of longitudinal follow-up, and longer exposure to ENDS products may be required to more fully understand the role of ENDS use on the risk of hypertension. Moreover, ENDS products continue to evolve, and more recent generations of ENDS products have more efficient nicotine delivery. This study did not adjust for cumulative exposure to ENDS or for nicotine level by product type. Future studies should seek to develop valid methods for better understanding exposure to ENDS products, and this analysis will need to be updated as more longitudinal data on long-termer term ENDS use becomes available.

Conclusions

Using nationally representative prospective longitudinal data among US adults, we found that time-varying cigarette smoking increased the risk of self-reported incident hypertension, but time-varying ENDS use did not. These results highlight the importance of using prospective longitudinal data to disentangle the temporal ordering between cigarette and ENDS use and the need to control for the potential confounding effect of cigarette smoking histories among ENDS users. This type of longitudinal analysis can be extended in future research examining the cardiovascular health effects of ENDS use, as longer-term data becomes available.

Contributorship statement: SC conducted the data analysis and drafted and revised the manuscript. JH and NF initiated the research project in collaboration with RM and DL. IB and RM provided statistical consultation, and GB and DA provided medical expertise and helped interpret the findings. EM, AP, and JJ created the measures used in the analysis. All co-authors revised the draft of the paper, and NF revised the final draft prior to submission.

Ethics statement: This study used de-identified data an no personal identifying information is included in the manuscript. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

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Data sharing statement: Data may be obtained from a third party and are not publicly available. Data are derived from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available de-identified data set. However, this analysis used the Restricted Use Files to use variables such as continuous age, and cigarette pack-years. These variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21.

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Supplemental Material

Figure S1. Flowchart of Sample Selection for Analytic Sample, Self-Reported Hypertension Outcome

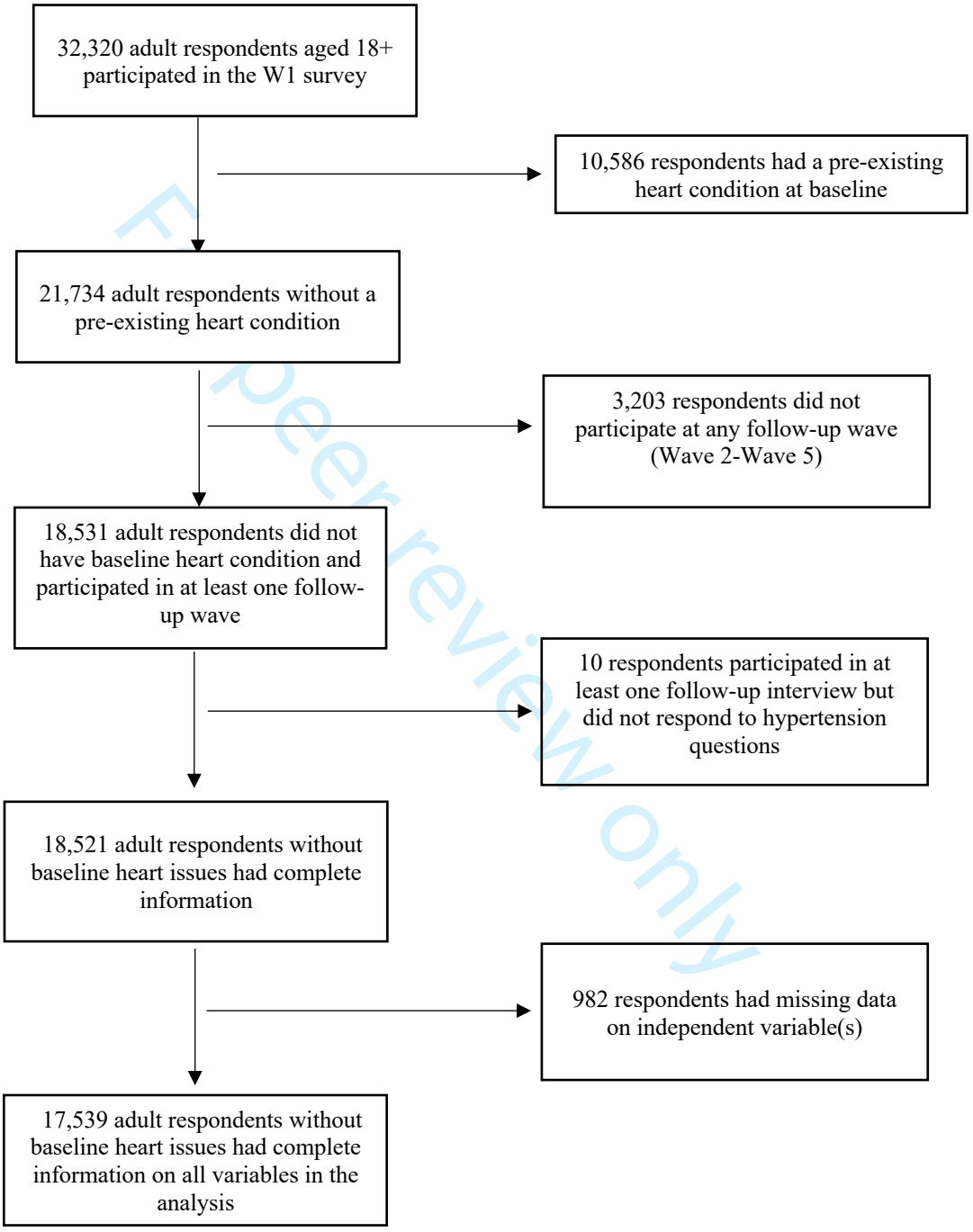

Table S1. Descriptive Statistics for Time-Varying Cigarette/ENDS Use, Established Adult Cigarette Smokers, Population Assessment of Tobacco & Health Study

	Follow-Up Interview*							
	Wave 1		Wave 2		Wave 3		Wave 4	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Time varying cigarettes/ENDS use								
Non use	79.2	78.5-79.9	78.6	77.9-79.4	79	78.2-79.7	79.9	79.0-80.6
Exclusive cigarette use	18	17.3-18.7	17.8	17.1-18.5	17.5	16.9-18.3	16.9	16.2-17.7
Exclusive ENDS use	1.1	0.92-1.96	1.3	1.2-1.5	1.4	1.3-1.6	1.5	1.3-1.7
Dual use	1.7	1.6-2.0	2.2	2.0-2.5	2.1	1.8-2.3	1.8	1.6-2.0

*time-varying covariates were lagged by one wave to limit issues with reverse causation

Table S2. Analysis of Censored Cases, Self-reported hypertension

	Non-censored	Censored	P
Age (mean)	39.2	38	**
Sex			***
Female	55.5%	47.9%	
Male	44.5%	52.1%	
Baseline cigarettes/ENDS exposure			***
Non use	80.1%	75.7%	
Exclusive cigarette use	17.2%	20.9%	
Exclusive ENDS use	1.1%	1.1%	
Dual use	1.6%	2.3%	
Race/Ethnicity			**
NH White	62.7%	63.9%	
Hispanic	17.8%	16.9%	
NH Black	1150.0%	9.2%	
NH Asian	530.0%	7.4%	
NH Other	260.0%	2.6%	
Household Income			***
<$50,000	56.5%	54.1%	
>$50,000	42.3%	39.9%	
missing	1.2%	6.0%	
Family history of heart attack			NS
No	71.7%	74.2%	
Yes	28.3%	25.8%	
Obesity (BMI >30)			**
No	74.5%	78.7%	
Yes	25.5%	21.3%	
Diabetes diagnosis at baseline			NS
No	95.2%	95.6%	
Yes	4.8%	4.4%	
Binge drinking			***
No	95.6%	94.9%	
Yes	4.4%	5.1%	
Former established smoker at baseline			NS
No	86.4%	87.7%	
Yes	13.6%	12.3%	
Pack-years at baseline (10 PY intervals)	0.453	0.458	NS

*p<0.05, **p<0.01, ***p<0.001

Table S3. Discrete time survival analysis predicting incidence of hypertension among adults using longitudinal cohort 'all waves weights', Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.35***	1.18-1.55	1.26**	1.07-1.49
Exclusive ENDS use	0.95	.63-1.41	1.07	.70-1.63
Dual use	1.11	.81-1.51	1.25	.89-1.75
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.03	1.03***	1.02-1.03
Sex (Male=1)	1.36***	1.16-1.59	1.45***	1.23-1.70
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.78*	.65-.94	0.92	.76-1.10
NH Black	1.53***	1.31-1.79	1.65***	1.39-1.96
NH Asian	.34***	.21-.53	.49**	.30-.81
NH Other	1	.69-1.47	1.07	.72-1.59
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.82*	.70-.97	0.85	.72-1.01
missing	1	.36-2.82	0.79	.26-2.38
Baseline Risk Factors				
Family History of heart attack	1.45***	1.22-1.71	1.29**	1.07-1.56
Obesity (BMI>30)	2.05***	1.77-2.36	1.81***	1.54-2.13
Diabetes diagnosis	2.61***	2.05-3.32	1.98***	1.54-2.55
Binge Drinking	1.19	.93-1.54	1.19	.91-1.55
Smoking History Variables				
Former Established smoker	1.48**	1.19-1.83	1.09	.86-1.38
Pack years (intervals of 10)^	1.17***	1.12-1.21	1.04	.99-1.09

Person N=11,437 ; Risk Period N =45,250

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S4. Discrete time survival analysis predicting incidence of medicated hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Medicated Hypertension			
	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.29**	1.10-1.51	1.25*	1.02-1.53
Exclusive ENDS use	0.62	.36-1.08	0.88	.51-1.50
Dual use	0.85	.61-1.18	1.07	.73-1.57
Sociodemographic Risk factors				
Age (mean)^	1.04***	1.04-1.05	1.04***	1.04-1.05
Sex (Male=1)	1.23*	1.04-1.47	1.23*	1.04-1.46
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.81*	.66-.99	1.03	.83-1.28
NH Black	1.41***	1.17-1.70	1.71***	1.39-2.10
NH Asian	.32*	.13-.77	0.52	.21-2.10
NH Other	0.71	.44-1.15	0.81	.52-1.26
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.78**	.66-.92	0.85	.72-1.03
missing	0.78	.29-2.08	0.57	.21-1.54
Baseline Risk Fators				
Family History of heart attack	1.34**	1.10-1.62	1.12	.91-1.38
Obesity (BMI>30)	1.86***	1.59-2.18	1.68***	1.41-2.00
Diabetes diagnosis	3.21***	2.51-4.11	2.12***	1.62-2.78
Binge Drinking	1.11	.84-1.47	1.27	.95-1.68
Smoking History Variables				
Former Established smoker	1.42**	1.14-1.77	0.88	.68-1.13
Pack years (intervals of 10)^	1.20***	1.15-1.24	1.06*	1.00-1.12

Person N=14,868 ; Risk Period N =52,818

*p<0.05, **p<0.01, ***p<0.001

^tested for nonlinearity but the quadratic term was not significant

Table S5. Discrete time survival analysis predicting incidence of self-reported hypertension among adults with 'regular' cigarette/ENDS use (10+ days), Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.28***	1.15-1.42	1.18**	1.05, 1.33
Exclusive ENDS use	0.84	.58-1.21	0.95	0.67, 1.35
Dual use	1	.77-1.30	1.14	0.80, 1.64
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.04	1.03***	1.03, 1.04
Sex (Male=1)	1.28**	1.11-1.48	1.33***	1.16,1 .54
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.83*	.71-.98	0.99	0.84, 1.17
NH Black	1.44***	1.24-1.68	1.62***	1.39, 1.90
NH Asian	.38***	.23-.64	0.55*	0.33, 0.93
NH Other	1.03	.73-1.44	1.06	0.76, 1.49
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.80**	.70-.92	0.83*	0.72, 0.96
missing	0.67	.32-1.39	0.58	0.27, 1.23
Baseline Risk Factors				
Family History of heart attack	1.43***	1.24-1.66	1.27**	1.08, 1.49
Obesity (BMI>30)	1.89***	1.66-2.15	1.71***	1.50, 1.96
Diabetes diagnosis	2.48***	2.0-3.06	1.74***	1.37, 2.20
Binge Drinking	1.22	.99-1.50	1.26*	1.02, 1.57
Smoking History Variables				
Former Established smoker	1.42***	1.18-1.72	1.02	0.83, 1.27
Pack years (intervals of 10)^	1.17***	1.13-1.21	1.04	0.99, 1.09

Notes: Person N=17,539 ; Risk Period N=59,367

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S6. Discrete time survival analysis predicting incidence of self-reported hypertension with revised cigarette/ENDS exposure, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Never established use	REF	REF	REF	REF
Former cigarettes, no ENDS	1.43**	1.17, 1.75	0.97	0.78, 1.21
Current cigarettes, no ENDS	1.38***	1.22, 1.56	1.20*	1.04, 1.38
Former cigarettes, current ENDS	1	0.64, 1.55	1.01	0.64. 1.60
Current cigarettes and ENDS	1.07	0.80, 1.41	1.13	0.84, 1.52
Exclusive ENDS	0.64	0.31, 1.32	0.86	0.41, 1.82
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.04	1.03***	1.03, 1.04
Sex (Male=1)	1.28**	1.11-1.48	1.33***	1.15, 1.53
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.83*	.71-.98	1	0.85, 1.17
NH Black	1.44***	1.24-1.68	1.61***	1.37, 1.89
NH Asian	.38***	.23-.64	0.56*	0.33, 0.94
NH Other	1.03	.73-1.44	1.05	0.75, 1.47
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.80**	.70-.92	0.83*	0.72, 0.96
missing	0.67	.32-1.39	0.58	0.27, 1.24
Baseline Risk Factors				
Family History of heart attack	1.43***	1.24-1.66	1.28**	1.09, 1.49
Obesity (BMI>30)	1.89***	1.66-2.15	1.72***	1.50, 1.98
Diabetes diagnosis	2.48***	2.0-3.06	1.76***	1.39, 2.22
Binge Drinking	1.22	.99-1.50	1.26*	1.01, 1.57
Smoking History Variables				
Pack years (intervals of 10)^	1.17***	1.13-1.21	1.04	0.99, 1.09

Notes: Person N=17,539 ; Risk Period N=59,367

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S7. Discrete time survival analysis predicting incidence of self-reported hypertension among never established cigarette smokers, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying ENDS use	0.56	0.28, 1.13	0.75	0.37, 1.52
Sociodemographic Risk factors				
Age (mean)^	1.04***	1.03, 1.04	1.04***	1.03, 1.04
Sex (Male=1)	1.25*	1.03, 1.52	1.31**	1.07, 1.60
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	0.84	0.67, 1.05	0.89	0.69, 1.14
NH Black	1.42**	1.17, 1.72	1.56***	1.25, 1.93
NH Asian	0.40**	0.21, 0.77	0.54	0.28, 1.05
NH Other	1.25	0.80, 1.97	1.34	0.81, 2.19
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	0.75**	0.62, 0.90	0.74**	0.60, 0.90
missing	0.71	0.27, 1.87	0.53	0.19, 1.43
Baseline Risk Factors				
Family History of heart attack	1.41**	1.16, 1.71	1.23	0.99, 1.52
Obesity (BMI>30)	2.09***	1.72, 2.53	1.80***	1.47, 2.20
Diabetes diagnosis	2.59***	1.95, 3.45	1.71**	1.23, 2.36
Binge Drinking	1.09	0.71, 168	1.4	0.89, 2.18

Notes: Person N=9478 ; Risk Period N=32,579

*p<0.05, **p<0.01, ***p<0.001

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	(a)-1 (b)-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	Fig A1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	(a)-9-10 (c, d, e) -10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Fig A1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study

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Running Head: ENDS AND HYPERTENSION AMONG US ADULTS

The time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study

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Abstract

Objectives: Electronic Nicotine Delivery Systems (ENDS) products have emerged as the most popular alternative to combustible cigarettes. However, ENDS products contain potentially dangerous toxicants and chemical compounds, and little is known about their health effects. The aim of the present study was to examine the prospective association between cigarette and ENDS use on self-reported incident hypertension.

Design: Longitudinal cohort study**.**

Setting: Nationally representative sample of the civilian, non-institutionalized population in the United States.

Participants: 17,539 adults aged 18 or older who participated at follow-up and had no self-reported heart condition or previous diagnosis of hypertension or high cholesterol at baseline.

Measures: We constructed a time-varying tobacco exposure, lagged by one wave, defined as no use, exclusive established use (daily or some days) of ENDS or cigarettes, and dual use. We controlled for demographics (age, sex, race/ethnicity, household income), clinical risk factors (family history of heart attack, obesity, diabetes, binge drinking) and smoking history (cigarette pack-years).

Outcomes: Self-reported incident hypertension diagnosis.

Results: The self-reported incidence of hypertension was 3.7% between Waves 2-5. At baseline, 18.0% (n=5,570) of respondents exclusively smoked cigarettes, 1.1% (n=336) exclusively used ENDS, and 1.7% (n=570) were dual users. In adjusted models, exclusive cigarette use was associated with an increased risk for self-reported incident hypertension compared to non-use (aHR=1.21, 95% CI: 1.06-1.38), while exclusive ENDS use (aHR=1.00, 95% CI: 0.68-1.47) and dual use (aHR=1.15, 95% CI: 0.87-1.52) were not.

Conclusions: We found that smoking increased the risk of self-reported hypertension but ENDS use did not. These results highlight the importance of using prospective longitudinal data to examine the health effects of ENDS use.

Keywords: ENDS, cigarettes, hypertension, cardiovascular disease

Strengths and limitations of this study

- In this study, we examine the time-varying association between cigarette smoking and ENDS use on the incidence of hypertension among a nationally representative sample of US adults.
- By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.
- We also controlled for the potential confounding of past smoking history, measured as cigarette pack-years, which important because most adults who use ENDS are either currently smoking cigarettes or have smoked cigarettes in the past.
- Our study was limited by relying on self-reported hypertension, as systolic and diastolic blood pressure measures were not available.
- Our non-randomized data means that our results could be affected by unmeasured confounding, and the results should be interpreted with the same level of caution required in all prospective longitudinal studies.

Introduction

Cigarette smoking is the leading cause of premature mortality in the US,[1,2] and a significant proportion of smoking-attributable deaths are related to cardiovascular disease.[3,4] Smoking is known to cause an acute rise in blood pressure,[5] contribute to arterial stiffness,[6] and has been associated with an increased risk of developing hypertension.[5,7-10] Hypertension, in turn, is an important risk factor for most downstream cardiovascular diseases.[11-13] The health hazards of smoking on cardiovascular disease underscore the importance of further reducing smoking prevalence in the general population, and the continued need to promote smoking cessation among adults who smoke.

Electronic Nicotine Delivery Systems (ENDS) products became widely available around 2010, and they refer to a broad range of devices that produce an aerosol from heating an e-liquid. ENDS products quickly emerged as the most popular alternative to combustible cigarettes in the US, as their prevalence doubled among young adults between 2014-2018,[14] and more than 5.6 million U.S. adults reported ENDS use in 2018-2019.[15] Some adults use ENDS products as a way to help them quit smoking,[15,16] and because they are generally believed to be less harmful than combustible cigarettes,[17,18] and it has been argued that their use should be encouraged as part of a harm minimization strategy.[17] However, non-smoking youth are also using ENDS products,[19] raising concerns about tobacco use renormalization. Furthermore, ENDS contain toxicants and chemical compounds that are potentially dangerous, including aldehydes, carbonyl, nicotine, and flavoring additives.[20,21] Very little is known about the health consequences of ENDS product use,[21] and we need reliable and rigorous estimates of their health effects.

One potential consequence of ENDS product use may be an increased risk of hypertension. Evidence of a short-term elevation in both systolic blood pressure and diastolic

blood pressure from ENDS product use have been found in experimental studies,[22] and a recent epidemiological study found evidence of a cross-sectional association between ENDS product use and self-reported hypertension among adults.[23] However, cross-sectional research on the cardiovascular risks of ENDS use has resulted in a contentious debate,[24-28] largely centered around the issue of reverse causation.[27] Without information on the timing of both the ENDS use and the disease outcome, it is simply not possible to know whether ENDS use came before or after the disease outcome. The latter is likely common given the use of ENDS by some smokers trying to quit after being diagnosed with a cardiovascular disease.[29] Therefore, the results from these cross-sectional studies need to be interpreted with caution. Researchers have highlighted the need for prospective longitudinal data to better understand the temporal ordering between ENDS use and cardiovascular disease endpoints.[22,28]

In this study, we use data from a nationally representative prospective cohort study to examine the time-varying association between cigarette and ENDS use on the incidence of self-reported hypertension, which limits potential concerns with reverse causation. In addition, we developed a composite exposure variable combining current cigarette and ENDS use to examine the relative contribution of exclusive cigarette use, exclusive ENDS use, and dual cigarette/ENDS use, compared to no use. We also adjust for past cigarette smoking history.

Methods

Data

We used data on adults from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available data set. However, this analysis used the Restricted Use Files[30] in order to use variables such as continuous age, and cigarette pack-years. These

variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

The PATH study is an ongoing, nationally representative cohort study of the civilian, non-institutionalized population in the United States. A stratified area probability design was used to sample geographical segments from 156 geographical primary sampling units. An address-based sampling frame was then used to randomly select households based on residential addresses derived from the United States Postal Service. Once households were identified, an introductory letter and brochure were mailed to sampled addresses followed by an in-person field interview within two weeks. A two-phase sampling procedure was used to select adults within sampled households for the in-person interview.[31]African-Americans and tobacco users were oversampled related to population proportions, and weighting procedures adjusted for oversampling and non-response based on US Census Bureau Data. Data were collected from September, 2013 to December, 2014 for Wave 1(response rate among screened households, 74.0%); October, 2014 to October, 2015 for Wave 2 (response rate, 83.2%); October, 2015 to October, 2016 for Wave 3 (response rate, 78.4%); December, 2016 to January, 2018 for Wave 4 (response rate, 73.5%); and December, 2018 to November 2019 for Wave 5 (response rate, 69.4%). All PATH survey interviews were completed in-person, using Audio-Assisted Self-Interviewing (ACASI) administrations, available in English or Spanish. Data collection protocols were used to ensure that follow-up interviews were close to the anniversary of their participation in the previous wave.[32] Further details about the design and methods of the PATH Study have been published elsewhere.[31-34]

The analytic sample for the current study was restricted to adult respondents (18+) (Wave 1, n=32,320) with no self-reported heart condition (e.g., congestive heart failure, heart attack, stroke) or previous diagnosis of hypertension or high cholesterol at baseline (n=21,734). A total of 3203 respondents were excluded as they did not participate at any follow-up interview, and respondents who did not report a hypertension diagnosis were right censored at their last observation point. Respondents with missing variable information (n=992; 5.3%) were excluded from the analysis using listwise deletion. The final analytic sample consisted of 17,539 respondents. A flowchart summarizing the analytic sample is provided in the appendix (Figure S1).

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Self-Reported Hypertension

We examined the incidence of self-reported hypertension at follow-up among respondents who reported they had never been diagnosed with hypertension at baseline. The reliability and concurrent validity of self-reported hypertension has been established in a previous study using PATH Study data.[32] In Wave 2 and Wave 3, *all* respondents were asked, *"In the past 12 months, has a doctor, nurse or other health professional told you that you had high blood pressure?"* Due to a change in the skip pattern in Wave 4 and Wave 5, this question was *only* asked to respondents who reported they saw a *"medical doctor, nurse, or other health professional"* during the past 12 months. We adopted an inclusive measurement strategy because self-reported hypertension is known to have low sensitivity (i.e., it is underestimated) in epidemiological studies,[35] especially among females[36] and Non-Hispanic Black adults.[37] To minimize this bias,

we classified respondents who answered 'yes' to the blood pressure question as having self-reported hypertension regardless of whether they reported seeing a doctor during the past year. In Wave 4 and 5, we classified respondents who did not report seeing a doctor during the past year as not having self-reported hypertension.

Cigarette/ENDS Exposure Variable

Our exposure variable was based on answers to questions about established cigarette (100 or more cigarettes smoked in lifetime) and ENDS (ever fairly regularly used ENDS) use, as well as every day or someday use of cigarettes and ENDS (current use). Based on these variables, we developed a four-category exposure variable: non-current user (of either product, which included people who never used either product), exclusive cigarette smoker, exclusive ENDS user, and dual user of cigarettes and ENDS. This variable was constructed at each wave and was included as a time-varying exposure. To minimize missing values for a given wave, we imputed missing tobacco exposure data borrowing information from a previous wave. To ensure that the tobacco product use exposure preceded the hypertension diagnosis, we lagged our time-varying exposure by one wave. The descriptive statistics of the time-varying tobacco use exposure can be found in the appendix (Table S1).

Covariates

We included age (continuous ages 18-90) sex (0=female, 1=male), race/ethnicity (Hispanic, Non-Hispanic [NH] White, NH Black, NH Asian, NH Other), and household income (less than $49,999, more than $50,000, missing) as baseline sociodemographic variables. Missing values for baseline sociodemographic variables were updated with data from other waves when available to reduce item non-response. We also included baseline risk factors to

control for potential confounding, including familial history of heart attack/bypass surgery, obesity (BMI >30), diabetes mellitus, and regular binge drinking (five or more drinks in one sitting on at least five separate days during the past month).

To account for the potential confounding effect of lifetime cigarette smoking, two additional covariates were included. First, we included a dichotomous predictor for former established smokers (smoked at least 100 cigarettes in lifetime but reports no current use at baseline). Second, we included cigarette pack-years as a measure of lifetime cigarette smoking at baseline. Pack-years were calculated by multiplying the duration of cigarette smoking by the average number of packs of cigarettes smoked per day while individuals smoked. Respondents who reported smoking more than 200 cigarettes per day (10 packs per day) were considered implausible and were set to missing (n=99).

Statistical Analysis

Descriptive statistics were first calculated for sociodemographic characteristics, cigarette/ENDS use, and hypertension risk factors at baseline. The sample characteristics were then calculated according to respondent's cigarette/ENDS use at baseline. Chi-square tests or Fisher's exact tests were used to test for statistically significant differences between groups. Lifetables were then used to describe the distribution of the incident hypertension outcomes at follow-up (Wave 2-Wave 5). The hazard estimates reflect the weighted conditional probability for self-reported hypertension for respondents in the risk set at each discrete time interval.[38]

We used discrete time survival models to analyze the incidence of self-reported hypertension across Wave 2-Wave 5 of follow-up (approximately 5 years). Discrete time survival models are appropriate when the exact timing until an event is not known.[38] The data was fit to an unbalanced person-period data set where each individual contributed a number of

rows equal to the time period until they were diagnosed with hypertension or were right censored.[39] As such, all 17,539 respondents in the self-reported hypertension sample had a separate row of data for each period, with a maximum of four rows per respondent, resulting in a person-period data set with 59,367 observations. The structure of the reorganized person-period dataset allowed for an examination of the conditional probability of self-reported and medicated incident hypertension at each discrete time interval. All discrete-time survival models were estimated using a complimentary log-log (cloglog) link function on the person-period dataset. Data were weighted using Wave 1 (W1) weights, including full-sample and 100 replicate weights, to ensure that our respondents were representative of the non-institutionalized adult population in the United States at baseline.

Several sensitivity analyses were included as robustness checks. First, to assess the impact of attrition, we compared baseline characteristics for censored and non-censored respondents (Table S2). Because the censored respondents had a slightly different sociodemographic profile than the non-censored respondents, as a sensitivity analysis, we estimated the discrete time models using the 'all waves weights,'which account for this type of attrition[31] and restricts the analysis to a longitudinal cohort of respondents who participated in all waves of the PATH study (Table S3). Third, to better approximate clinical hypertension and minimize potential false positive errors in self-reported hypertension, we also included a measure of medicated hypertension as a sensitivity analysis. Respondents who self-reported hypertension and responded 'yes' when asked, "*In the past 12 months, did you take heart or blood pressure medication regularly,"* were considered to have medicated hypertension (Table S4). Fourth, to examine whether more frequent cigarette/ENDS use was associated with incident hypertension, we included a more frequent cigarette/ENDS use exposure (measured as 10+ days in the past 30

days) as a sensitivity analysis (Table S5). Fifth, to more clearly distinguish between adults who never smoked cigarettes from former smokers, we created a revised exposure with adults who reported 'never established smoking' as the reference group, with the following use categories: (1) former cigarette, no ENDS; (2) current cigarette, no ENDS; (3) former cigarette, current ENDS; (4) current cigarette and ENDS; (5) exclusive ENDS (see Table S6). Finally, we restricted our analysis to adults who reported they had never smoked 100 cigarettes in their lifetime at baseline and examined the association between ENDS use and hypertension among respondents who had never smoked (Table S7). For all analyses, variances were computed using the balanced repeated replication methods with Fay's adjustment set to 0.3 as recommended by the PATH study.[33,40] All analyses were conducted using Stata 16.1.[41]

Results

The weighted baseline sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for the self-reported hypertension (n=17,539) analytic sample are outlined in Table 1. At baseline, respondents had a mean age of 39 years (SD=15.4) and were predominately female (53.9%), NH White (63.0%), and reported a household income of less than $50,000 (56.0%). Most respondents were not current cigarette or ENDS users at baseline (n=11,063; 79.2%) while a similar percentage of respondents were exclusive ENDS users (n=336; 1.1%) or dual users (n=570; 1.7%). Current cigarette use was the most common tobacco use status at baseline (n=5,570; 18.0%). 13.4% of respondents were former established smokers at baseline, among current or former established smokers, the average cigarette pack-years was 13.9 (SD=20.0). In terms of baseline hypertensive risk factors, approximately one quarter of respondents reported a

family history of heart attack (27.7%) and obesity (24.6%), while diabetes mellitus (4.7%) and regular binge drinking (4.5%) were reported less frequently.

Table 2 presents the sample characteristics stratified by our tobacco exposure variable at baseline. Compared to all other groups, respondents who exclusively smoked cigarettes were the most likely to be NH Black (12.6%), most likely to report household incomes under $50,000 (74.3%). Compared to exclusive cigarette users, exclusive ENDS users at baseline were younger (33.2 (SD=16.7) vs. 37.1 (SD=17.7) years), reported higher household incomes (33.2% vs. 23.8%), and were more likely to report a family history of heart attack (31.7% vs. 29.4%) and obesity (33.2% vs. 23.8%). Importantly, nearly two thirds of exclusive ENDS users were former established smokers at baseline (63.7%). The average pack-years value for exclusive ENDS users who were former established smokers (17.9, SD=23.6) was higher than for current exclusive cigarette users (14.1, SD=22.4) at baseline. Dual users shared similar sociodemographic characteristics with exclusive ENDS users, except dual users were more likely to be NH White (76.7%-vs. 69.3%), to have diabetes mellitus (5.1% vs 3.2%) and reported more regular binge drinking (12.1% vs. 10.5%-10.3%). The average pack-years values for dual users (11.1, SD=16.9), on the other hand, was lower than exclusive cigarette users (14.1, SD=22.4), and for former smokers who were non-current users (13.9, SD=15.3) or exclusive ENDS users (17.9, SD=23.61) at baseline.

Table 1. Weighted sociodemographic characteristics, smoking behaviors, and hypertensive risk factors for adult respondents (18+) at baseline, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	N	%^	95% CI
Age (mean, sd)	17,539	38.97 (15.42)	
Sex			
Female	9,073	53.9	53.2-54.6
Male	8,466	46.1	45.4-46.8
Race/Ethnicity			
NH White	10,250	63	62.2-63.8
Hispanic	3,446	17.6	17.0-18.2
NH Black	2,422	11	10.5-11.5
NH Asian	526	5.8	5.3-6.3
NH Other	895	2.6	2.4-2.9
Household Income			
<$50,000	11,481	56	54.6-57.3
>$50,000	5,699	41.8	40.4-43.1
missing	359	2.2	1.9-2.7
Cigarette/ecigarette baseline exposure			
Non user	11,063	79.2	78.5-79.9
Cigarette only	5,570	18	17.3-18.7
E-cigarette only	336	1.1	.92-1.2
Dual user	570	1.7	1.6-2.0
Family history of heart attack			
No	12,852	72.3	71.2-73.3
Yes	4,687	27.7	26.7-28.8
Obesity (BMI >30)			
No	13,318	75.4	74.3-76.5
Yes	4,221	24.6	23.5-25.7
Diabetes diagnosis at baseline			
No	16,848	95.3	94.8-95.8
Yes	691	4.7	4.2-5.2
Regular Binge drinking			
No	16,297	95.5	95.1-95.8
Yes	1,242	4.5	4.2-4.9
Former established smoker at baseline			
No	15,618	86.6	85.8-87.5
Yes	1,921	13.4	12.5-14.2
Pack-years among current/former smokers (mean, sd)^^	8,061	13.9 (20.0)	

ENDS = electronic nicotine delivery systems

^ Percentages were calcuated using W1 weights

^^mean pack years value for ever established (both current and former) smokers.

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Table 2. Sample characteristics by baseline cigarette/ENDS use, Population Assessment of Tobacco & Health Study (Wave 1, 2013-2014)

	Non-user	Exclusive Cigarette user	Exclusive ENDS user	Dual User
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Age (mean, sd)	39.6 (14.2)	37.1 (17.7)	33.2 (16.7)	32.2 (16.6)
Sex				
Female	55.9 (55.1-56.8)	45.9 (44.5-47.3)	45.9 (39.9-52.1)	47.5 (43.4-51.6)
Male	44.1 (43.2-44.9)	54.1 (52.7-55.5)	54.1 (47.9-60.1)	52.5 (48.4-56.6)
Race/Ethnicity				
NH White	61.2 (60.1-62.4)	68.9 (67.3-70.5)	69.3 (63.0-75.0)	76.6 (72.7-80.4)
Hispanic	19 (18.2-19.7)	12.6 (11.7-13.6)	12.3 (9.1-16.5)	10.2 (7.5-13.0)
NH Black	10.8 (10.2-11.4)	12.6 (11.5-13.7)	8.5 (5.6-12.5)	6.1 (3.8-8.7)
NH Asian	6.6 (6.1-7.3)	2.4 (1.8-3.2)	5.7 (2.7-11.5)	2.7 (1.0-4.9)
NH Other	2.4 (2.1-2.7)	3.5 (3.1-3.9)	4.2 (2.4-7.1)	5.3 (3.8-7.2)
Household Income				
<$50,000	51.4 (49.9-52.9)	74.3 (72.7-75.9)	65.2 (59.3-70.7)	66.2 (61.0-70.9)
>$50,000	46.2 (44.7-47.7)	23.8 (22.3-25.3)	33.2 (27.4-39.5)	32.5 (27.5-37.3)
missing	2.4 (2.0-2.9)	1.9 (1.5-2.3)	1.6 (.65-3.7)	1.3 (.80-3.2)
Family history of heart attack				
No	72.8 (71.6-74.0)	70.6 (69.2-72.0)	68.3 (63.3-73.0)	65.7 (61.0-70.3)
Yes	27.2 (26.0-28.4)	29.4 (28.0-30.8)	31.7 (27.0-36.7)	34.3 (29.7-39.0)
Obesity (BMI >30)				
No	75.5 (74.1-76.8)	75.3 (73.8-76.7)	72 (65.7-77.5)	76.2 (72.2-79.8)
Yes	24.5 (23.2-25.9)	24.7 (23.3-26.2)	28 (22.5-34.3)	23.8 (20.2-27.8)
Diabetes diagnosis at baseline				
No	95.3 (94.6-95.8)	95.5 (94.9-96.0)	96.8 (94.3-98.2)	94.8 (92.3-96.6)
Yes	4.7 (4.2-5.4)	4.5 (4.0-5.1)	3.2 (1.8-5.7)	5.2 (3.4-7.7)
Regular Binge drinking				
No	97.2 (96.8-97.5)	89 (88.0-89.9)	89.5 (85.1-92.7)	87.8 (84.6-90.6)

Yes	2.8 (2.5-3.2)	11 (10.1-12.0)	10.5 (7.3-14.9)	12 (9.4-15.4)
Former established smoker at baseline				
No	84 (82.9-85.0)	100	36.3 (30.3-42.9)	100
Yes	16 (15.0-17.1)	0	63.7 (57.1-69.7)	0
Pack-years smoking at baseline (mean, sd)^	13.9 (15.3)	14.1 (22.4)	17.9 (23.6)	11 (16.9)

ENDS = electronic nicotine delivery systems

^mean pack years value for ever established (both current and former) smokers.

Lifetables describing the conditional probability for self-reported incident hypertension are displayed in Table 3. Hypertension was self-reported by 1930 respondents in the analytic sample, with an annual incidence hazard of 3.7% (range 2.9% to 4.6% between W2 and W5). The hazard estimates were similar across all discrete time intervals, with slight increases between Wave 4-Wave 5, reflecting a two-year time interval between waves.

Table 3. Life tables describing the incidence of self-reported hypertension among adults (18+), Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

Interval	Total	Diagnosis	Censored	Hazard Estimate^
Period 1 (W1-W2)	17539	652	1230	0.039
Period 2 (W2-W3)	15660	464	1137	0.033
Period 3 (W3-W4)	14067	334	1632	0.029
Period 4 (W4-W5)	12101	480	11612	0.046

^ hazard estimates were calculated using W1 weights

Table 4 presents discrete time hazard models examining the risk of self-reported incident hypertension. In the unadjusted model, respondents who exclusively smoked cigarettes had a significantly higher risk of self-reported incident hypertension compared to those who did not currently use cigarettes or ENDS products (hazard ratio [HR] 1.28, 95% CI:1.15-1.42). The risk did not statistically differ for respondents who used ENDS, either exclusively (HR 0.84, 95% CI: 0.68-1.47) or with cigarettes (HR 1.00, 95% CI: 0.77-1.30), from respondents who did not use either product. After adjusting for sociodemographic risk factors, baseline risk factors, and smoking history variables, the results were very similar as exclusive cigarette use was associated with a 21 percent higher risk of self-reported incident hypertension (95% CI: 1.06-1.38), while exclusive ENDS use (adjusted hazard ratio [aHR] 1.0, 95% CI: 0.68-1.47) and dual use (aHR 1.15, 95% CI:0.87-1.52) were not. Other hypertensive risk factors associated with an increased

risk of self-reported hypertension included being older age, male sex, NH Black (vs. NH White) race/ethnicity, lower (vs. higher) household income, family history of heart attack, obesity, diabetes diagnosis and regular binge drinking at baseline in adjusted (multivariable) models.

Sensitivity Analyses

As sensitivity analyses, discrete-time models were estimated using the longitudinal cohort who participated in all waves of follow-up (Table S3); with a medicated hypertension outcome (Table S4); and with cigarette/ENDS use measured as 10+ days in the past 30 days rather than every day or someday use (Table S5). Across these sensitivity analyses, the substantive results remained robust as exclusive cigarette use was associated with an increased risk of incident hypertension compared to non-use in both unadjusted and fully adjusted models. In contrast, compared to non-use, exclusive ENDS and dual use were not associated with increased hypertension risk in unadjusted or fully adjusted models in any of these analyses. Discrete-time models were also estimated with an expanded cigarette/ENDS exposure incorporating never and former smoking as a sensitivity analysis (Table S6). Compared to never smoking, current cigarette smoking and non-ENDS use (aHR 1.20, 95% CI 1.04, 1.38) was associated with an increased risk of incident hypertension while current ENDS use among respondents who had formerly smoked (aHR 1.01, 95% CI 0.64, 1.60) and dual ENDS and cigarette smoking (aHR 1.13, 95% CI 0.84, 1.52) were not associated with increased hypertension risk. Finally, respondents with established cigarette use patterns were removed from the analytic sample, and the association between ENDS use and hypertension was examined among respondents who never smoked as an additional sensitivity analysis (Table S7). Time-varying ENDS use was not associated with an increased risk of incident hypertension compared to non-ENDS use in either unadjusted (HR = 0.56, 95% CI 0.28, 1.13) or adjusted models (aHR=0.75, 95% CI 0.37, 1.52).

Table 4. Discrete time survival analysis predicting incidence of self-reported hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.28	1.15-1.42	1.21	1.06-1.38
Exclusive ENDS use	0.84	.58-1.21	1	.68-1.47
Dual use	1	.77-1.30	1.15	.87-1.52
Sociodemographic Risk factors				
Age (mean)^	1.03	1.03-1.04	1.03	1.03-1.04
Sex (Male=1)	1.28	1.11-1.48	1.33	1.16-1.53
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	0.83	.71-.98	0.99	.84-1.17
NH Black	1.44	1.24-1.68	1.62	1.38-1.90
NH Asian	0.38	.23-.64	0.55	.33-.94
NH Other	1.03	.73-1.44	1.06	.76-1.49
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	0.8	.70-.92	0.83	.72-.96
missing	0.67	.32-1.39	0.58	.27-1.22
Baseline Risk Factors				
Family History of heart attack	1.43	1.24-1.66	1.27	1.08-1.49
Obesity (BMI>30)	1.89	1.66-2.15	1.71	1.50-1.96
Diabetes diagnosis	2.48	2.0-3.06	1.74	1.37-2.21
Binge Drinking	1.22	.99-1.50	1.25	1.01-1.56
Smoking History Variables				
Former Established smoker	1.42	1.18-1.72	1.03	.83-1.27
Pack years (intervals of 10)^	1.17	1.13-1.21	1.03	.98-1.08

Notes: Person N=17,539 ; Risk Period N=59,367
^for interpretation, pack-years were rescaled to intervals of 10 packyears

Discussion

This study examined the time-varying association between cigarette smoking and ENDS use on the incidence of self-reported hypertension among a nationally representative sample of US adults. We found that exclusive cigarette use was associated with an increased risk of incident hypertension in both unadjusted and fully adjusted models. While the association between chronic cigarette use and hypertension is complex,[42] and the causal link is still debated,[42,43] this finding aligns with previous research indicating a modest association between current cigarette smoking and the risk of incident hypertension.[5,8,10,44,45] Moreover, this finding is consistent with hypertension risk prediction models that include current cigarette smoking as a covariate,[7] and with the findings from the 2014 Surgeon General's report, which concluded that cigarette smoking is directly associated with coronary heart disease, including hypertension.[9] In contrast, studies examining the effects of ENDS use on hypertension have only recently been published,[22] and in a longitudinal follow-up of approximately five years, we found no evidence that short term and time-varying ENDS use was associated with an increased risk of incident hypertension.

Dual use of cigarettes and ENDS was not associated with the incidence of hypertension, although the direction of the hazard estimates was positive in fully adjusted models for both self-reported and medicated hypertension outcomes. However, it is important to note that dual users were different from exclusive cigarette smokers, and the non-significant association between dual use and incident hypertension may be partially explained by residual confounding by sociodemographic characteristics and tobacco use histories of dual users. In our study, dual users were younger, more likely to be NH White, and reported higher household incomes than exclusive cigarette smokers. These characteristics are all correlated with lower risk for hypertension.[8,46,47] In addition, dual users had lower pack-years values than exclusive cigarette

users, with pack-years values very similar to exclusive ENDS users. The different smoking histories between exclusive cigarette and dual users is consistent with other research finding that dual use is associated with reduced cigarette consumption,[48-50] and may represent part of a transitional state as smokers move away from smoking cigarettes.[50,51] It is possible that dual users may have a different risk profile than exclusive cigarette users, which may then translate into a lower risk of disease relative to exclusive cigarette users. Studies with a larger number of ENDS users are needed to better understand the risk of incident hypertension among dual users.

Taken together, the results from this study do not support an association between ENDS use and self-reported incident hypertension. By examining the prospective incident cases of hypertension and using a lagged time-varying cigarette/ENDS exposure variable, our study does not have the same concerns with reverse causation that have been identified in cross-sectional studies.[27] This is the most likely reason why our findings differ from a recent cross-sectional examination of the lifetime prevalence of hypertension using PATH data,[23] where the authors did not account for the relative timing of the ENDS exposure and hypertension. In addition, we also controlled for the potential confounding of past cigarettes smoking history, measured as pack-years, which is important given that 64% of exclusive adult ENDS users at baseline were former established cigarette smokers. The substantial history of cigarette use among the majority of exclusive ENDS users further highlights the importance of controlling for their past cigarette smoking history when trying to estimate the independent effect of ENDS use on hypertension and other health outcomes.

Limitations

Our study has several important limitations that need to be considered. First, the results from this study are based on observational data from a prospective longitudinal study, and the results should be interpreted with the same level of caution required in all self-reported studies. Our non-randomized data means that our results could be affected by unmeasured confounding, and while we included a measure of medicated hypertension as a sensitivity analysis, both our hypertensive outcomes are self-reported. Since systolic and diastolic blood pressure measures are not available in the PATH study, the reported incidence may underestimate the true incidence of hypertension,[35,36] particularly for some sociodemographic groups.[35] Future research would benefit from including measured hypertension instead of self-reported hypertension where possible. Second, while the PATH study was representative of the US population at baseline, the loss to follow-up was significant and respondent attrition may not have been random. While we examined differences between censored and uncensored cases and conducted a sensitivity analysis with weights meant to adjust for attrition, this problem cannot be fully eliminated, as is true of most longitudinal studies. The discrete-time survival approach, which allows us to include all available information from respondents at each time interval, is a way to maximize information on the longitudinal sample. Third, while PATH has the biggest representative sample of longitudinal tobacco use and health in the US, ENDS use was only reported by a relatively small number of participants, limiting the power to detect statistical associations between ENDS use and incident hypertension. Fourth, if some respondents used ENDS to quit smoking cigarettes, it is possible that these respondents also made other lifestyle changes that may have concomitantly reduced the impact of ENDS use on incident hypertension. Similarly, some might have decided to switch in response to symptoms or health issues. Future research is

needed to better understand the characteristics of respondents who transition from cigarettes to ENDS use, their reasons for doing so, and the future health outcomes of these transitions. Finally, ENDS products have only been widely available in the US for little more than a decade.[52] The findings from our study are based on approximately five years of longitudinal follow-up, and longer exposure to ENDS products may be required to more fully understand the role of ENDS use on the risk of hypertension. Moreover, ENDS products continue to evolve, and more recent generations of ENDS products have more efficient nicotine delivery. This study did not adjust for cumulative exposure to ENDS or for nicotine level by product type. Future studies should seek to develop valid methods for better understanding exposure to ENDS products, and this analysis will need to be updated as more longitudinal data on long-termer term ENDS use becomes available.

Conclusions

Using nationally representative prospective longitudinal data among US adults, we found that time-varying cigarette smoking increased the risk of self-reported incident hypertension, but time-varying ENDS use did not. These results highlight the importance of using prospective longitudinal data to disentangle the temporal ordering between cigarette and ENDS use and the need to control for the potential confounding effect of cigarette smoking histories among ENDS users. This type of longitudinal analysis can be extended in future research examining the cardiovascular health effects of ENDS use, as longer-term data becomes available.

Contributorship statement: SC conducted the data analysis and drafted and revised the manuscript. JH and NF initiated the research project in collaboration with RM and DL. IB and RM provided statistical consultation, and GB and DA provided medical expertise and helped interpret the findings. EM, AP, and JJ created the measures used in the analysis. All co-authors revised the draft of the paper, and NF revised the final draft prior to submission.

Ethics statement: This study used de-identified data an no personal identifying information is included in the manuscript. This study was approved by the Ethics Committed at the University of Michigan (HUM00153979).

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Data sharing statement: Data may be obtained from a third party and are not publicly available. Data are derived from Waves 1-5 (2013-2019) of the Population Assessment of Tobacco Health (PATH) Study, a publicly available de-identified data set. However, this analysis used the Restricted Use Files to use variables such as continuous age, and cigarette pack-years. These variables are not available in the Public Use Files. Further details on how to access the restricted use data are described in the PATH Study Restricted Use Files User Guide. Available at Guide available at https://doi.org/10.3886/ Series606.21.

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Supplemental Material

Figure S1. Flowchart of Sample Selection for Analytic Sample, Self-Reported Hypertension Outcome

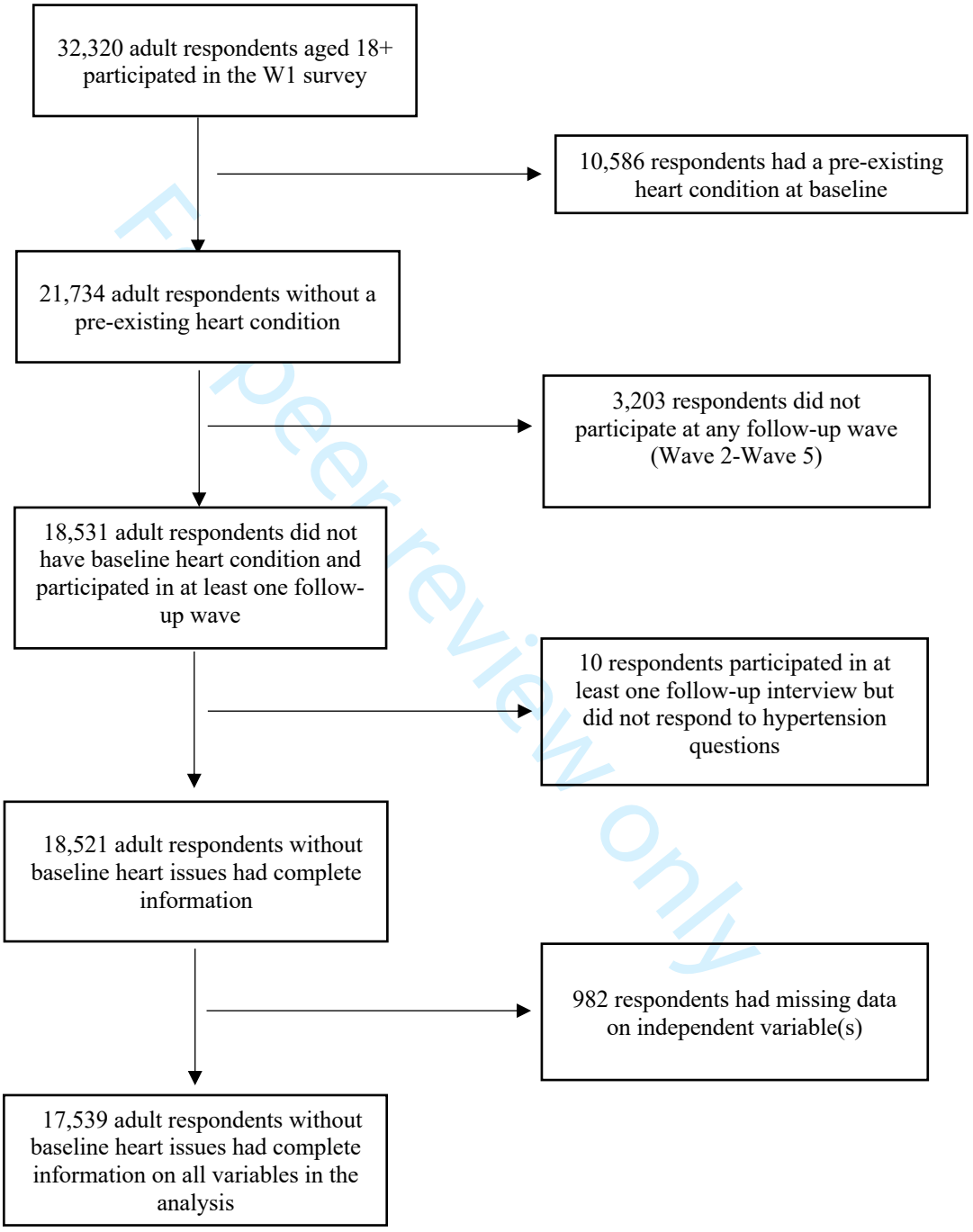

Table S1. Descriptive Statistics for Time-Varying Cigarette/ENDS Use, Established Adult Cigarette Smokers, Population Assessment of Tobacco & Health Study

	Follow-Up Interview*							
	Wave 1		Wave 2		Wave 3		Wave 4	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Time varying cigarettes/ENDS use								
Non use	79.2	78.5-79.9	78.6	77.9-79.4	79	78.2-79.7	79.9	79.0-80.6
Exclusive cigarette use	18	17.3-18.7	17.8	17.1-18.5	17.5	16.9-18.3	16.9	16.2-17.7
Exclusive ENDS use	1.1	0.92-1.96	1.3	1.2-1.5	1.4	1.3-1.6	1.5	1.3-1.7
Dual use	1.7	1.6-2.0	2.2	2.0-2.5	2.1	1.8-2.3	1.8	1.6-2.0

*time-varying covariates were lagged by one wave to limit issues with reverse causation

Table S2. Analysis of Censored Cases, Self-reported hypertension

	Non-censored	Censored	P
Age (mean)	39.2	38	**
Sex			***
Female	55.5%	47.9%	
Male	44.5%	52.1%	
Baseline cigarettes/ENDS exposure			***
Non use	80.1%	75.7%	
Exclusive cigarette use	17.2%	20.9%	
Exclusive ENDS use	1.1%	1.1%	
Dual use	1.6%	2.3%	
Race/Ethnicity			**
NH White	62.7%	63.9%	
Hispanic	17.8%	16.9%	
NH Black	1150.0%	9.2%	
NH Asian	530.0%	7.4%	
NH Other	260.0%	2.6%	
Household Income			***
<$50,000	56.5%	54.1%	
>$50,000	42.3%	39.9%	
missing	1.2%	6.0%	
Family history of heart attack			NS
No	71.7%	74.2%	
Yes	28.3%	25.8%	
Obesity (BMI >30)			**
No	74.5%	78.7%	
Yes	25.5%	21.3%	
Diabetes diagnosis at baseline			NS
No	95.2%	95.6%	
Yes	4.8%	4.4%	
Binge drinking			***
No	95.6%	94.9%	
Yes	4.4%	5.1%	
Former established smoker at baseline			NS
No	86.4%	87.7%	
Yes	13.6%	12.3%	
Pack-years at baseline (10 PY intervals)	0.453	0.458	NS

*p<0.05, **p<0.01, ***p<0.001

Table S3. Discrete time survival analysis predicting incidence of hypertension among adults using longitudinal cohort 'all waves weights', Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.35***	1.18-1.55	1.26**	1.07-1.49
Exclusive ENDS use	0.95	.63-1.41	1.07	.70-1.63
Dual use	1.11	.81-1.51	1.25	.89-1.75
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.03	1.03***	1.02-1.03
Sex (Male=1)	1.36***	1.16-1.59	1.45***	1.23-1.70
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.78*	.65-.94	0.92	.76-1.10
NH Black	1.53***	1.31-1.79	1.65***	1.39-1.96
NH Asian	.34***	.21-.53	.49**	.30-.81
NH Other	1	.69-1.47	1.07	.72-1.59
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.82*	.70-.97	0.85	.72-1.01
missing	1	.36-2.82	0.79	.26-2.38
Baseline Risk Factors				
Family History of heart attack	1.45***	1.22-1.71	1.29**	1.07-1.56
Obesity (BMI>30)	2.05***	1.77-2.36	1.81***	1.54-2.13
Diabetes diagnosis	2.61***	2.05-3.32	1.98***	1.54-2.55
Binge Drinking	1.19	.93-1.54	1.19	.91-1.55
Smoking History Variables				
Former Established smoker	1.48**	1.19-1.83	1.09	.86-1.38
Pack years (intervals of 10)^	1.17***	1.12-1.21	1.04	.99-1.09

Person N=11,437 ; Risk Period N =45,250

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S4. Discrete time survival analysis predicting incidence of medicated hypertension among adults, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Medicated Hypertension			
	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.29**	1.10-1.51	1.25*	1.02-1.53
Exclusive ENDS use	0.62	.36-1.08	0.88	.51-1.50
Dual use	0.85	.61-1.18	1.07	.73-1.57
Sociodemographic Risk factors				
Age (mean)^	1.04***	1.04-1.05	1.04***	1.04-1.05
Sex (Male=1)	1.23*	1.04-1.47	1.23*	1.04-1.46
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.81*	.66-.99	1.03	.83-1.28
NH Black	1.41***	1.17-1.70	1.71***	1.39-2.10
NH Asian	.32*	.13-.77	0.52	.21-2.10
NH Other	0.71	.44-1.15	0.81	.52-1.26
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.78**	.66-.92	0.85	.72-1.03
missing	0.78	.29-2.08	0.57	.21-1.54
Baseline Risk Fators				
Family History of heart attack	1.34**	1.10-1.62	1.12	.91-1.38
Obesity (BMI>30)	1.86***	1.59-2.18	1.68***	1.41-2.00
Diabetes diagnosis	3.21***	2.51-4.11	2.12***	1.62-2.78
Binge Drinking	1.11	.84-1.47	1.27	.95-1.68
Smoking History Variables				
Former Established smoker	1.42**	1.14-1.77	0.88	.68-1.13
Pack years (intervals of 10)^	1.20***	1.15-1.24	1.06*	1.00-1.12

Person N=14,868 ; Risk Period N =52,818

*p<0.05, **p<0.01, ***p<0.001

^tested for nonlinearity but the quadratic term was not significant

Table S5. Discrete time survival analysis predicting incidence of self-reported hypertension among adults with 'regular' cigarette/ENDS use (10+ days), Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Non use	REF	REF	REF	REF
Exclusive cigarette use	1.28***	1.15-1.42	1.18**	1.05, 1.33
Exclusive ENDS use	0.84	.58-1.21	0.95	0.67, 1.35
Dual use	1	.77-1.30	1.14	0.80, 1.64
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.04	1.03***	1.03, 1.04
Sex (Male=1)	1.28**	1.11-1.48	1.33***	1.16,1 .54
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.83*	.71-.98	0.99	0.84, 1.17
NH Black	1.44***	1.24-1.68	1.62***	1.39, 1.90
NH Asian	.38***	.23-.64	0.55*	0.33, 0.93
NH Other	1.03	.73-1.44	1.06	0.76, 1.49
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.80**	.70-.92	0.83*	0.72, 0.96
missing	0.67	.32-1.39	0.58	0.27, 1.23
Baseline Risk Factors				
Family History of heart attack	1.43***	1.24-1.66	1.27**	1.08, 1.49
Obesity (BMI>30)	1.89***	1.66-2.15	1.71***	1.50, 1.96
Diabetes diagnosis	2.48***	2.0-3.06	1.74***	1.37, 2.20
Binge Drinking	1.22	.99-1.50	1.26*	1.02, 1.57
Smoking History Variables				
Former Established smoker	1.42***	1.18-1.72	1.02	0.83, 1.27
Pack years (intervals of 10)^	1.17***	1.13-1.21	1.04	0.99, 1.09

Notes: Person N=17,539 ; Risk Period N=59,367

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S6. Discrete time survival analysis predicting incidence of self-reported hypertension with revised cigarette/ENDS exposure, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying cigarettes/ENDS use				
Never established use	REF	REF	REF	REF
Former cigarettes, no ENDS	1.43**	1.17, 1.75	0.97	0.78, 1.21
Current cigarettes, no ENDS	1.38***	1.22, 1.56	1.20*	1.04, 1.38
Former cigarettes, current ENDS	1	0.64, 1.55	1.01	0.64. 1.60
Current cigarettes and ENDS	1.07	0.80, 1.41	1.13	0.84, 1.52
Exclusive ENDS	0.64	0.31, 1.32	0.86	0.41, 1.82
Sociodemographic Risk factors				
Age (mean)^	1.03***	1.03-1.04	1.03***	1.03, 1.04
Sex (Male=1)	1.28**	1.11-1.48	1.33***	1.15, 1.53
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	.83*	.71-.98	1	0.85, 1.17
NH Black	1.44***	1.24-1.68	1.61***	1.37, 1.89
NH Asian	.38***	.23-.64	0.56*	0.33, 0.94
NH Other	1.03	.73-1.44	1.05	0.75, 1.47
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	.80**	.70-.92	0.83*	0.72, 0.96
missing	0.67	.32-1.39	0.58	0.27, 1.24
Baseline Risk Factors				
Family History of heart attack	1.43***	1.24-1.66	1.28**	1.09, 1.49
Obesity (BMI>30)	1.89***	1.66-2.15	1.72***	1.50, 1.98
Diabetes diagnosis	2.48***	2.0-3.06	1.76***	1.39, 2.22
Binge Drinking	1.22	.99-1.50	1.26*	1.01, 1.57
Smoking History Variables				
Pack years (intervals of 10)^	1.17***	1.13-1.21	1.04	0.99, 1.09

Notes: Person N=17,539 ; Risk Period N=59,367

*p<0.05, **p<0.01, ***p<0.001

^cigarette pack-years were rescaled to intervals of 10 packyears

Table S7. Discrete time survival analysis predicting incidence of self-reported hypertension among never established cigarette smokers, Population Assessment of Tobacco and Health Study (Waves 1-5, 2013-2019)

	Unadjusted		Adjusted	
	Hazard	95% CI	Hazard	95% CI
Time varying ENDS use	0.56	0.28, 1.13	0.75	0.37, 1.52
Sociodemographic Risk factors				
Age (mean)^	1.04***	1.03, 1.04	1.04***	1.03, 1.04
Sex (Male=1)	1.25*	1.03, 1.52	1.31**	1.07, 1.60
Race/Ethnicity				
NH White	REF	REF	REF	REF
Hispanic	0.84	0.67, 1.05	0.89	0.69, 1.14
NH Black	1.42**	1.17, 1.72	1.56***	1.25, 1.93
NH Asian	0.40**	0.21, 0.77	0.54	0.28, 1.05
NH Other	1.25	0.80, 1.97	1.34	0.81, 2.19
Household Income				
<$50,000	REF	REF	REF	REF
>$50,000	0.75**	0.62, 0.90	0.74**	0.60, 0.90
missing	0.71	0.27, 1.87	0.53	0.19, 1.43
Baseline Risk Factors				
Family History of heart attack	1.41**	1.16, 1.71	1.23	0.99, 1.52
Obesity (BMI>30)	2.09***	1.72, 2.53	1.80***	1.47, 2.20
Diabetes diagnosis	2.59***	1.95, 3.45	1.71**	1.23, 2.36
Binge Drinking	1.09	0.71, 168	1.4	0.89, 2.18

Notes: Person N=9478 ; Risk Period N=32,579

*p<0.05, **p<0.01, ***p<0.001

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	(a)-1 (b)-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	Fig A1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	(a)-9-10 (c, d, e) -10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Fig A1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.