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Brief Report

E-cigarette Use and Incident Cardiometabolic Conditions in the All of Us Research Program

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Abstract

Introduction: Although several potential respiratory and cardiovascular health effects of e-cigarettes have been reported, their association with incident cardiometabolic conditions remains unclear.

Aims and Methods: We used longitudinal data from the All of Us research program to investigate the association between current exclusive e-cigarette use (EE), exclusive combustible cigarette use (ECC), and dual use (DU) with incident cardiometabolic conditions, including hypertension, type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD), heart failure (HF), and atherosclerotic cardiovascular disease (ASCVD), using Cox regression analyses adjusted for age, sex, race and ethnicity, and body mass index. ECC use was used as a positive control to validate our methodology and findings.

Results: Among 249 190 individuals (67.2% female, 52.0% non-Hispanic White, 21.5% non-Hispanic Black) followed for 3.7–3.9 years, EE, compared with nonuse, was not significantly associated with hypertension (1.01 [95% CI 0.83 to 1.23]), T2DM (0.88 [0.66–1.16]), ASCVD (1.05 [0.59–1.86]), or HF (0.82 [0.47–1.41]), but was significantly associated with COPD (2.29 [1.42-3.71]). Among individuals aged 30–70 years, EE was significantly associated with hypertension (1.39 [1.09–1.77]). ECC and DU were strongly associated with all outcomes, with DU having higher point estimates but overlapping confidence intervals compared to ECC for all outcomes except ASCVD (2.18 [1.82 to 2.62]) where risk with DU appeared higher.

Conclusion: We demonstrated a significant longitudinal association between exclusive e-cigarette use and COPD, and hypertension only among individuals aged 30–70 years. ECC and DU were strongly associated with all conditions, with DU potentially associated with higher ASCVD risk. These findings highlight some potential risks of e-cigarette use and provide context to inform advisories and regulatory policies on novel products on their health risks.

Implications: These findings help to clarify the potential risks associated with e-cigarette use. Understanding these risks can aid the Food and Drug Administration in developing regulatory frameworks for tobacco products.

Introduction

Since their introduction to the United States (US) market in 2003, e-cigarettes have become the second most prevalent form of tobacco use after combustible cigarettes, and the most common among young adults and adolescents.[1–3] Because e-cigarettes generate much lower levels of combustion-derived products, they have been marketed as a safer alternative to smoking.[4,5] While most studies show that combustible cigarettes contain higher levels of toxicants, some studies indicate that e-cigarette aerosols may contain significant levels of volatile organic compounds and higher levels of nicotine, which is addictive and harmful.[6,7] Hence, comprehensive studies are needed to evaluate their safety for the general population.

Combustible cigarettes significantly increase the risk of cardiometabolic diseases, contributing to cardiovascular morbidity, mortality, and other adverse conditions.[8] While some studies link e-cigarettes to adverse cardiometabolic conditions, most such studies are cross-sectional and limited in scope. For example, one cross-sectional study found an increased risk of cerebrovascular accidents and asthma,[9,10] and a longitudinal study indicated a higher risk of new respiratory diseases.[11] Additional longitudinal research on the health effects of e-cigarettes is crucial, given their high prevalence and controversial role as smoking cessation aids.[1,11]

We investigated the associations between e-cigarette use and incident cardiometabolic conditions using data from the All of Us research program, which represents the largest

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cohort of individuals using e-cigarettes to date with linked health data in the United States. We hypothesized that e-cigarette use is associated with an increased risk of developing all cardiometabolic conditions.

Methods

The All of Us Research Program is a nationwide, longitudinal cohort study funded by the National Institutes of Health, including participants from diverse backgrounds. We included 184 772 individuals who reported never using e-cigarettes or combustible cigarettes (nonuse), exclusively using e-cigarettes, exclusively using combustible cigarettes, or using both e-cigarettes and combustible cigarettes (dual use [DU]). We excluded individuals without linked electronic health records data, as well as all individuals who formerly used e-cigarettes or combustible cigarettes from all tobacco use categories including never use, exclusive e-cigarette use, exclusive combustible cigarette use, and DU. This was done to ensure clearer distinctions between exposure groups and minimize potential misclassification bias.

Comprehensive details on the methodology and participant recruitment have been previously published.[12] Tobacco use patterns were defined based on responses from a baseline lifestyle survey regarding current (within the past 30 days), former, or never use of e-cigarettes and combustible cigarettes.

We examined five cardiometabolic conditions using standardized medical terms (SNOMED) in the linked electronic health records: hypertension, type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD), heart failure (HF), and ASCVD (atherosclerotic cardiovascular disease, which includes myocardial infarction and cerebrovascular accidents).

Johns Hopkins University exempted our study from institutional review board review and informed consent because it used deidentified, publicly available data. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[13]

Statistical Analyses

We summarized participant characteristics by e-cigarette and combustible cigarette use patterns. We then used Cox proportional hazard regression models, adjusted for age, sex, race and ethnicity, and body mass index, to examine the associations of exclusive e-cigarette use, combustible cigarette use, and DU with incident cardiometabolic conditions. To improve age comparability across all tobacco use groups, we conducted a sub-analysis that restricted the age range to 30–70 years. The reference group was nonuse.

We included combustible cigarette use in a parallel analysis as a positive control to validate our methods and ensure reliability. Given their well-documented association with adverse health conditions, such as cardiovascular, pulmonary, and metabolic disorders, combustible cigarettes provided a benchmark for replicating established risks. This approach confirmed that our dataset, study design, and analytical procedures were capable of detecting known relationships, thereby supporting the validity of our findings on e-cigarette use.

Survival analysis was conducted in parallel for each outcome, excluding prevalent cases at the start of each specific analysis. All analyses were performed with R programming within the All of Us Workspace using Jupyter notebooks.[14] A two-sided alpha of < 0.05 determined statistical significance.

Results

The study included 249 190 individuals with a mean age (SD) of 51.0 (16.5) years, mostly female (63.8%) and diverse, with 52.0% non-Hispanic White and 21.5% non-Hispanic Black. About 81.8% never used e-cigarettes or combustible cigarettes, 1.3% used e-cigarettes exclusively, 13.6% used combustible cigarettes exclusively, and 3.3% used both e-cigarettes and combustible cigarettes (Table 1).

During a median follow-up interval of 3.7–3.9 years, there were 23,745 new cases of hypertension, 13,179 of T2DM, 7,925 of COPD, 9,801 of HF, and 6,139 of ASCVD, with incidence rates ranging from 5.2 to 32.2 per 1000 person-years (Supplementary Table 1). In the multivariable-adjusted Cox regression analyses, exclusive e-cigarette use was not significantly associated with hypertension (aHR 1.01 [0.83–1.23]), T2DM (0.88 [0.66–1.16]), HF (0.82 [0.47–1.41]), or ASCVD (1.05 [0.59–1.86]) but was significantly associated with COPD (2.29 [1.42–3.71]) (Table 2).

Exclusive combustible cigarette use significantly increased risks for hypertension (1.20 [1.15–1.26]), T2DM (1.18 [1.11–1.26]), COPD (6.75 [6.26–7.28]), HF (1.50 [1.40–1.62]), and ASCVD (1.66 [1.51–1.81]).

DU showed results relatively similar to exclusive combustible cigarette use, with higher point estimates but overlapping confidence intervals for most outcomes, including hypertension (1.21 [1.10–1.34]), COPD (7.91 [6.91–9.06]), and HF (1.76 [1.49–2.07]). However, there was a non-significant finding for T2DM and higher point estimates for ASCVD, with non-overlapping confidence intervals (2.18 [1.82–2.62]) (Table 2).

In an age-restricted analysis of individuals aged 30–70 years, exclusive e-cigarette use was significantly associated with hypertension (1.39 [1.09–1.77]), but not with other conditions. For all other outcomes across tobacco use, the results were relatively similar to findings in the total population. (Supplementary Table 2).

Discussion

In the largest longitudinal study of e-cigarettes and health outcomes to date, we observed that while the use of e-cigarettes was significantly associated with an increased risk of developing COPD, associations with other cardiometabolic outcomes examined were not statistically significant. This finding differs from the broader robustly significant associations observed with exclusive combustible cigarettes and DU across all health outcomes examined.

Our findings showing an association between the use of e-cigarettes and the increased risk of COPD support the conclusions of a 2024 systematic review, which pooled data primarily from cross-sectional and some longitudinal studies, indicating a 1.41-fold increase in COPD risk associated with e-cigarette use when compared with nonuse.[15] Our analysis demonstrated a numerically stronger association for COPD risk, perhaps due to its longitudinal design and careful exclusion of preexisting conditions. Also, directionally similar to our results, the 2024 systematic review noted a threefold increased risk of COPD associated with the DU of combustible cigarettes and e-cigarettes. However, this was lower than

Table 1. Participant Characteristics by Tobacco Use Patterns

Characteristics	Total population	Never	Exclusive e-cigarette use	Exclusive combustible cigarette use	Dual use
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
	249,190	203 932 (81.8%)	3164 (1.3%)	33 778 (13.6%)	8316 (3.3%)
Age, mean (SD)	51.0 (16.5)	51.6 (16.9)	29.2 (11.5)	51.4 (12.7)	41.5 (13.0)
Sex					
Male	89 374 (36.2%)	66 417 (32.8%)	1134 (36.0%)	17 921 (54.0%)	3902 (47.5%)
Female	157 516 (63.8%)	135 907 (67.2%)	2014 (64.0%)	15 287 (46.0%)	4309 (52.5%)
Race and Ethnicity					
Non-Hispanic White	126 017 (52.0%)	110 143 (55.3%)	1236 (39.9%)	10 115 (31.3%)	4 523 (56.9%)
Non-Hispanic Black	52 230 (21.5%)	33 509 (16.8%)	703 (22.7%)	16 195 (50.1%)	1823 (22.9%)
Non-Hispanic Asian	10 338 (4.3%)	9625 (4.8%)	197 (6.4%)	348 (1.1%)	168 (2.1%)
Hispanic	48 154 (19.9%)	41 286 (20.7%)	846 (27.3%)	4876 (15.1%)	1146 (14.4%)
Other	5754 (2.4%)	4578 (2.3%)	115 (3.7%)	765 (2.4%)	296 (3.7%)
BMI categories, Kg/m^2					
< 18.5	3168 (1.4%)	2131 (1.1%)	80 (2.8%)	776 (2.4%)	181 (2.4%)
18.5–24.9	62 442 (26.7%)	49 365 (25.9%)	977 (33.7%)	9760 (30.2%)	2340 (30.5%)
25.0–29.9	70 535 (30.2%)	58 147 (30.5%)	751 (25.9%)	9457 (29.3%)	2180 (28.4%)
30.0–34.9	48 189 (20.6%)	39 974 (21.0%)	506 (17.5%)	6270 (19.4%)	1439 (18.8%)
35.0–39.9	26 098 (11.2%)	21 734 (11.4%)	283 (9.8%)	3268 (10.1%)	813 (10.6%)
≥ 40	23 175 (9.9%)	19 394 (10.2%)	298 (10.3%)	2765 (8.6%)	718 (9.4%)
Cardiometabolic conditions					
Hypertension					
No	165 881 (66.6%)	135 085 (66.2%)	2789 (88.1%)	21 745 (64.4%)	6262 (75.3%)
Yes	83 309 (33.4%)	68 847 (33.8%)	375 (11.9%)	12 033 (35.6%)	2054 (24.7%)
Heart failure					
No	237 105 (95.2%)	194 085 (95.2%)	3120 (98.6%)	31 858 (94.3%)	8042 (96.7%)
Yes	12 085 (4.8%)	9847 (4.8%)	44 (1.4%)	1920 (5.7%)	274 (3.3%)
ASCVD					
No	241 184 (96.8%)	197 806 (97.0%)	3134 (99.1%)	32 174 (95.3%)	8070 (97.0%)
Yes	8006 (3.2%)	6126 (3.0%)	30 (0.9%)	1604 (4.7%)	246 (3.0%)
COPD					
No	238 536 (95.7%)	198 396 (97.3%)	3123 (98.7%)	29 482 (87.3%)	7535 (90.6%)
Yes	10 654 (4.3%)	5536 (2.7%)	41 (1.3%)	4296 (12.7%)	781 (9.4%)
T2DM					
No	211 863 (85.0%)	173 151 (84.9%)	3001 (94.8%)	28 296 (83.8%)	7415 (89.2%)
Yes	37 327 (15.0%)	30 781 (15.1%)	163 (5.2%)	4346 (15.7%)	901 (10.8%)

Numbers in parentheses represent proportions. SD, standard deviation; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; T2DM, type 2 diabetes mellitus.

Table 2. Association Between Tobacco Use Patterns and Incident Cardiometabolic Conditions

Cardiometabolic conditions	Nonuse	Exclusive e-cigarette Use	Exclusive combustible cigarette use	Dual use
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Hypertension	Reference	1.01 (0.83–1.23)	1.20 (1.15–1.26)	1.21 (1.10–1.34)
T2DM	Reference	0.88 (0.66–1.16)	1.18 (1.11–1.26)	1.12 (0.97–1.28)
COPD	Reference	2.29 (1.42–3.71)	6.75 (6.26–7.28)	7.91 (6.91–9.06)
Heart failure	Reference	0.82 (0.47–1.41)	1.50 (1.40–1.62)	1.76 (1.49–2.07)
ASCVD	Reference	1.05 (0.59–1.86)	1.66 (1.51–1.81)	2.18 (1.82–2.62)

Hazard ratios were adjusted for age, sex, race and ethnicity, and body mass index. CI, confidence interval; aHR, adjusted hazard ratio; T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; ASCVD, atherosclerotic cardiovascular disease.

our estimates of a six- to sevenfold increase in combustible smoking-related risk.[15]

In addition to COPD, we observed that among middle-aged to older adults (ages 30–70 years), exclusive e-cigarette use was significantly associated with incident hypertension. This finding is similar, albeit with lower estimates, to a cross-sectional study in 2022 using National Health and Nutrition Examination Survey (NHANES) data, which showed that exclusive e-cigarette use (not including former use) is associated with a twofold increase in the odds of high blood pressure.[16] This finding suggests that e-cigarettes may contain components, beyond nicotine, that elevate the risk of adverse cardiovascular effects such as hypertension, with potentially greater impacts in middle-aged and older individuals.[16,17]

Additionally, exclusive combustible cigarette use, with or without e-cigarette use, was associated with a higher risk of developing COPD as well as other cardiometabolic conditions compared with exclusive e-cigarette use. The risk profiles for DU and exclusive smoking were relatively similar for these conditions, with slightly higher point estimates for DU but overlapping confidence intervals. Consequently, any direct comparisons of these groups should be interpreted with caution, as the overlapping confidence intervals limit the ability to draw definitive conclusions about the relative risks between DU and exclusive combustible cigarette use. However, for ASCVD, DU had a higher point estimate than exclusive combustible cigarette use, with non-overlapping confidence intervals, which may suggest higher toxicant exposure in DU compared to exclusive smoking, thus exposing individuals to potentially greater harm.[17] However, this result should be interpreted with caution given the potential for residual confounding.

Similar to our findings, a 2022 study using Population Assessment of Tobacco and Health (PATH) data reported increased risks of cardiovascular diseases (myocardial infarction, heart failure, and stroke) among individuals who exclusively use combustible cigarettes, with or without e-cigarettes, compared to nonuse.[18] Consistent with the findings of a 2024 longitudinal study and a 2023 cross-sectional study using NHANES data, we observed no association between DU of e-cigarettes and combustible cigarettes and the incidence of type 2 diabetes.[15,19] The exact reason for this lack of association is unclear; however, it might be linked to the lack of association between e-cigarette use and insulin resistance. As demonstrated in a 2019 study using data from the NHANES and animal models, there was no significant difference in insulin resistance, measured by the homeostatic model assessment of insulin resistance and glucose tolerance tests, when comparing e-cigarette use to nonuse.[20]

In contrast to findings in exclusive combustible cigarette use and DU, there were no significant associations between exclusive e-cigarette use and most cardiometabolic conditions including T2DM, hypertension, HF, and ASCVD when compared to nonuse, indicating a relatively lower risk profile compared to exclusive combustible cigarette use. However, our estimates of risk associated with e-cigarette use were associated with moderately wide confidence intervals, raising the possibility that, with longer follow-up and further accrual of cases, the accuracy of these estimates may improve. This could allow for the detection of lower levels of risk than was possible in this study.

Nevertheless, the lack of large associations between e-cigarette use and some cardiometabolic outcomes such as stroke, heart disease, and T2DM is consistent with findings from a 2022 PATH study,[21] which showed that the levels of inflammatory and oxidative stress biomarkers for individuals who exclusively use e-cigarettes were like those observed with nonuse and relatively lower than those found in combustible cigarette use. This is further supported by a 2024 study using the Cross-Cohort Collaboration that harmonized data from six longitudinal cohorts, which showed that exclusive electronic cigarette use was associated with significantly lower high-sensitivity C-reactive protein levels compared to exclusive combustible cigarette use.[22]

Taken together, these findings support the notion that in comparison with combustible cigarettes, the use of e-cigarettes may pose a lower risk of inflammation and oxidative stress, which are underlying factors associated with adverse cardiometabolic conditions. Nonetheless, even though e-cigarettes may expose individuals to fewer harmful chemicals than combustible cigarettes,[4,5] the direct and prolonged exposure to aerosolized toxicants may contribute to early lung injury. Additionally, our study suggests that e-cigarettes may increase the risk of hypertension in individuals aged 30 years and older, who are more susceptible to this condition due to age. Therefore, avoiding e-cigarettes could potentially reduce this risk. Furthermore, it is generally established that exclusive use of e-cigarettes may serve as a gateway to other harmful substances, including combustible cigarettes, thus potentially increasing overall harm.[23,24]

Our findings provide new data critical for assessing the relative risk of e-cigarettes along the tobacco risk continuum. Although our results indicate that e-cigarettes may be associated with significantly lower health risks than combustible cigarettes or DU, any harm reduction benefit appears confined to complete switching in select individuals, as DU offers no appreciable cardiometabolic benefit and may even be linked to increased risk (eg, with ASCVD). These differential cardiovascular and pulmonary effects could inform regulatory policies on the modified risk tobacco product status of e-cigarettes and their appropriate public health role.

Limitations

Our study has several limitations. The relatively short follow-up period (3.7–3.9 years) may not have allowed us to comprehensively capture the long-term effects of e-cigarette use. Additionally, the lack of longitudinal data on cessation or product switching could have influenced our findings. Furthermore, some point estimates for the association of exclusive e-cigarette use with cardiometabolic conditions, such as ASCVD and hypertension, were similar to those for combustible smoking but with wide confidence intervals and therefore not reaching statistical significance. This may reflect insufficient statistical power due to the small sample size of individuals who reported exclusive e-cigarette use; therefore, while very large effects can likely be ruled out, smaller effect sizes remain possible and potentially undetectable in our study. Also, we could not account for tobacco dependence, which could drive individuals to use both e-cigarettes and combustible cigarettes to satisfy nicotine cravings, potentially affecting the observed health outcomes.

Despite the limitations, we believe that the consistency of our methodology, combined with extensive longitudinal data, the racially, and ethnically diverse cohort with participants from around the US enhances the reliability and

generalizability of our conclusions compared to prior smaller or cross-sectional studies.

Conclusion

Our study finds that compared to nonuse, exclusive e-cigarette use significantly increases the risk of developing COPD. DU of e-cigarettes and combustible cigarettes is associated with a higher risk of most examined cardiometabolic conditions compared to nonuse but with significant overlap in confidence intervals compared to exclusive combustible cigarette use, except for ASCVD where the risk appears potentially higher. These findings provide additional evidence on the risk profile of e-cigarette use and could inform the Food and Drug Administration's regulatory framework for these products, with implications for novel tobacco products.

Supplementary Material

Supplementary material is available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this article.

Author Contributions

John Erhabor (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Methodology [lead], Writing—original draft [lead], Writing—review & editing [lead]), Zhiqi Yao (Data curation [equal], Formal analysis [lead], Methodology [equal], Writing—review & editing [equal]), Erfan Tasdighi (Formal analysis [supporting], Methodology [equal], Writing—review & editing [equal]), Emelia Benjamin (Methodology [equal], Supervision [equal], Writing—review & editing [equal]), Aruni Bhatnagar (Methodology [equal], Supervision [equal], Writing—review & editing [equal]), and Michael Blaha (Conceptualization [lead], Data curation [equal], Formal analysis [equal], Funding acquisition [lead], Methodology [equal], Supervision [lead], Writing—review & editing [equal])

Data Availability

Access to the All of Us Research Program data is granted upon approval by the All of Us Research Program's Data and Research Center. For more information on how to request access, please visit https://www.researchallofus.org.

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