Functionally important respiratory symptoms and continued cigarette use versus e-cigarette switching: population assessment of tobacco and health study waves 2-6

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Summary

Background Substitution of noncombustible tobacco products for cigarettes could improve respiratory symptoms. We hypothesized that complete cigarette-to-e-cigarette switching would improve respiratory symptoms compared to continued smoking.

Methods Longitudinal analysis of data from waves 2–6 (W2–W6; 2014–2021) of the Population Assessment of Tobacco and Health (PATH) Study, an observational cohort study that surveyed 5653 US adults ≥18 years without COPD/chronic bronchitis/emphysema. We compiled 14,947 two-wave (1–2 year) observations with persons who smoked cigarettes at baseline and compared the relation between functionally important respiratory symptoms and switching to exclusive e-cigarette use or quitting tobacco versus continued cigarette use (reference). A 9-point wheezing/nighttime cough index was dichotomized based on index scores of ≥2 or ≥3, previously associated with poorer functional health. Multivariable models assessed how changes in cigarette use predicted worsening/improvement of symptoms.

Findings Among those with an index score <2, 3.5% switched to e-cigarettes, and 11.1% quit all tobacco. Functionally important respiratory symptoms worsened (≥2 at follow-up) in 15.4%, 10.0% and 10.1% of those who continued cigarettes, switched to e-cigarettes, and quit, respectively. Adjusted relative risk (RR) for respiratory symptom worsening was 0.69 (95% confidence interval (CI), 0.52, 0.91) for e-cigarette switching and 0.73 (95% CI, 0.54, 0.97) for quitting. Of persons with index score ≥2, 2.8% switched to e-cigarettes, and 6.7% quit. Respiratory symptoms improved (<2 at follow-up) in 27.7%, 45.8% and 42.1% of those who continued cigarettes, switched to e-cigarettes, and quit, respectively. The RR for improving was 1.31 (95% CI, 1.05, 1.64) for e-cigarette switching and 1.36 (95% CI, 1.15, 1.62) for quitting. The RRs for exclusive e-cigarette use with a cutoff of ≥3 for respiratory symptom worsening and improvement were not significant (0.74 [0.53, 1.05] and 1.20 [0.95, 1.51] respectively) but were significant in an unweighted analysis that included partial data for individuals lost to follow-up (0.74 [0.57, 0.95] and 1.21 [1.06, 1.39] respectively).

Interpretation Switching completely from past 30-day use of cigarettes to e-cigarettes had short-term beneficial associations with functionally important respiratory symptoms similar to quitting tobacco completely.

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Keywords: Longitudinal study; Cigarette smoking; e-cigarette; e-cigarette switching; Respiratory symptoms; Wheezing

Research in context

Evidence before this study

Many observational studies have found an association between e-cigarette use and an increased risk for respiratory symptoms compared to no tobacco use (Glantz SA et al., 2024). Because many persons who use e-cigarettes also currently or previously smoked combusted cigarettes, it is difficult to disentangle respiratory effects of each product. Moreover, comparing risks with persons who have never used tobacco provides little information for the group most likely to benefit from e-cigarette use: persons who smoke cigarettes, the focus of our study. We compare change in functionally important respiratory wheezing/cough symptoms for those who continued cigarette use with those who switched completely to e-cigarettes, and those who quit tobacco completely.

Added value of this study

The findings suggest that switching completely from past 30-day use of cigarettes to e-cigarettes had short-term beneficial associations with functionally important respiratory symptoms similar to quitting tobacco completely.

Implications of all the available evidence

The findings demonstrate a short-term health benefit of improved respiratory symptoms for switching completely from cigarettes to e-cigarettes for adults who smoke. Further research can determine how switching to e-cigarettes affects long term respiratory outcomes.

Introduction

Cigarette smoking has long been associated with respiratory symptoms.[1] People who smoke with preserved pulmonary function experience respiratory symptom exacerbations, limitation of activity,[2] missed income from work,[3] and increased hospitalization risk.[4]

Respiratory symptoms were a key predictor of forced expiratory volume in 1 s and forced vital capacity decline among young adults in a large prospective study.[5] Quitting smoking is associated with diminution of symptoms[6]; however, many who smoke cigarettes are unwilling/unable to completely stop smoking.[7] For those individuals, it is important to know whether switching completely to a lower exposure tobacco product (i.e., without smoke constituents) would affect respiratory symptoms.[8]

Many studies have examined the association between e-cigarette use and respiratory outcomes, often showing increased risk for respiratory symptoms when compared to no tobacco use.[9] Longitudinal studies that considered cigarette smoking as a reference category are less common but have found that persons who used both cigarettes and e-cigarettes had similar risk for respiratory symptoms compared to persons who exclusively smoke cigarettes, but that exclusive e-cigarette use was associated with lower risk.[10,11] Moreover, a recent meta-analysis of studies of asthma and asthma symptoms found that the pooled relative risk for e-cigarette compared to cigarette use was 0.84 (0.75, 0.95), suggesting a possible harm reduction role for e-cigarettes in this condition.[12]

We analyzed longitudinal short term (two-wave) changes for persons who smoked cigarettes from Waves 2–6 (W2–W6; 2014–2021) of the Population Assessment of Tobacco and Health (PATH) Study to determine how complete cigarette-to-e-cigarette switching affected wheezing and cough symptoms previously shown to be associated with asthma and functional outcomes (functionally important respiratory symptoms),[13] compared to continued cigarette smoking or complete cessation of tobacco products. Our prespecified hypotheses apply to persons who smoke cigarettes regardless of other tobacco products used and include: 1a) among persons with low symptom burden, risk of worsening respiratory symptoms will be lower among those who transition to exclusive e-cigarette use compared to those who continue smoking; 1b) risk of worsening symptoms will be similar to those who quit smoking entirely; and 2) among persons with high symptom burden, risk of respiratory symptom improvement will be higher than for those who continue smoking.

Methods

Study design, setting, participants, and attrition

The PATH Study is a longitudinal study that collects data on tobacco use behaviors and tobacco-related health outcomes. It was created to inform FDA's regulatory activities under the Family Smoking Prevention and Tobacco Control Act. Recruitment for Wave 1 (W1, 2013–2014) of the PATH Study employed stratified address-based, area-probability sampling with oversampling of adults who use tobacco, young adults, and Black adults. Audio computer-assisted self-interviews collected data for tobacco use and health outcomes. This secondary data analysis utilized W1 – W6 of the adult

Restricted Use Files (https://doi.org/10.3886/ICPSR36231.v21). PATH Study design and methods are reported elsewhere.[14–16]

The survey sample included PATH respondents who completed all 6 survey waves, excluding adults who by W5 reported a diagnosis of COPD, chronic bronchitis, or emphysema. Respiratory symptoms were reported starting in Wave 2. We created an analytic dataset that included up to 4 two-wave observations for each individual: W2 → W3, W3 → W4, W4 → W5, and W5 → W6 (N = 14,947 total observations, Fig. 1). Individuals would be included in a two-wave observation if they used cigarettes (regardless of other tobacco products used) in the past 30 days at the baseline wave *for that observation period*; and either continued to use cigarettes, switched completely to e-cigarettes, or quit tobacco entirely *at the follow up wave* (items and response categories listed in eTable 1). Any other tobacco transition (e.g., from cigarette smoking to exclusive cigar use) was excluded. Also excluded were observations with missing data for covariates or respiratory outcomes (missing data rate = 21.7%). Missing data on sex, race, Hispanic ethnicity, and education were imputed as described in the PATH Study Restricted Use Files User Guide (http://doi.org/10.3886/Series606); these are suggested variables for use with weights and do not figure into our missingness calculations. Supplemental eFig. 1 is a flow diagram that shows the N's for missing data on respiratory outcomes and covariates. eTable 2 gives N's for respondents and observations for each of the two-wave observation periods.

The primary analysis applied the Wave 6 all-waves weights to derive US population estimates that account for the complex sample design and loss to follow-up; therefore, observations were not included for those who used cigarettes but did not participate in all six waves. The weighted response rates for W2–W6 adult interview were as follows: W2: 83.2%; W3: 78.4%; W4: 73.5%; W5: 69.4%; W6: 57.5%; a non-response bias analysis report was published online.[17]

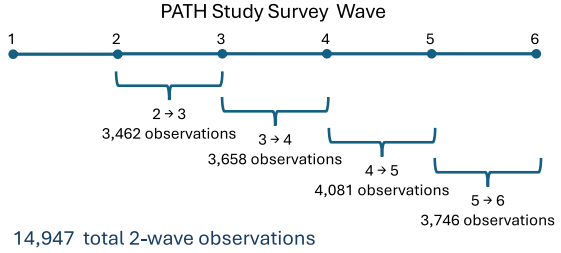

***Fig. 1:* Derivation of 2-wave observations for the study sample.** Individuals were included in a longitudinal 2-wave observation if they used cigarettes (regardless of other tobacco product use) in the past 30 days at the baseline wave *for that observation period;* and either continued to use cigarettes, switched completely to e-cigarettes, or quit tobacco entirely *at the follow up wave.*

Also shown in eTable 2 are number of observations that included transition to exclusive e-cigarette use, N = 551, or 4% of the 14,947 observations. We anticipated that transitions to exclusive e-cigarette use would be rare, so we also planned an unweighted sensitivity analysis that also included data from individuals who were lost to follow up. eTable 2 also gives N's for respondents, and observations for each of the two-wave observation periods for the unweighted sample. Adding these data increased the total number of observations to 22,376 and the number of transitions to exclusive e-cigarette use from 551 to 817 (eFig. 2 shows a flow diagram for the unweighted sample).

Participant-reported outcomes

Functionally important respiratory symptoms

The PATH Study utilized seven wheezing/cough questions from the International Study of Allergies and Asthma in Childhood; for example, "Have you had wheezing or whistling in the chest in the past 12 months?"[18] Responses were used to create a respiratory symptom index (range 0 [none] to 9 [worst]), previously validated in the PATH Study adult sample based on its internal consistency, test-retest reliability, and its association with self-reported physician diagnosis of asthma (see eTable 1 for all items).[13] We considered but chose not to focus on asthma diagnosis because our primary focus was respiratory symptoms, an outcome that may get better or worse from year-to-year in response to a change from cigarette smoking to exclusive e-cigarette use. In contrast, asthma is a chronic condition and generally does not resolve the year after. In addition, a previous study found no associations between tobacco use and prevalent or incident diagnosis of asthma in this dataset.[19]

Respondents with cut-off values of ≥2 had significantly higher risk for physical limitations, fatigue, and poorer perception of health assessed by items from the Patient Reported Outcomes Measurement Information System (PROMIS; physical question bank).[20] Primary analyses were performed for worsening (defined as the index score crossing the threshold from <2 to ≥2) and improvement (defined as the index score crossing the threshold from ≥2 to <2) of functionally important respiratory symptoms. A sensitivity analysis was run to assess our results with the higher symptom burden cut-off of 3.[11]

Exposures

Tobacco product use

Included in the baseline of each two-wave observation period were respondents who had used cigarettes in the past 30 days, regardless of other product(s) used. Previous research in the PATH Study has shown that the association between cigarette smoking and functionally important respiratory symptoms was independent of which other tobacco products were used in

combination with cigarettes.[11] Our research focus was on individuals who switched completely to past 30-day e-cigarette use at follow-up, comparing respiratory outcomes with those who continued cigarette use (regardless of other product(s) used) and those who quit all tobacco product use (no tobacco product use within the past 30 days).

Covariates

Covariates included variables associated with both tobacco exposure and functionally important respiratory symptoms. Sociodemographic variables included age, sex, race/ethnicity, education, and income, since low socioeconomic status is associated with tobacco use[21] and poorer lung function.[22] Medical conditions that can also cause respiratory symptoms include ever diagnosis of asthma, congestive heart failure, heart attack, diabetes, any cancer, overweight/obesity, and use of certain antihypertensives that may cause cough or bronchospasm (e.g., angiotensin receptor blockers and angio-converting enzyme (ACE) inhibitors) or bronchospasm (beta blockers). Other exposures measured at baseline included pack-years of cigarette smoking, second-hand smoke exposure (number of hours in the past 7 days exposed to others who were smoking), and past 30-day cannabis use. See eTable 1 for more details. Because of coronavirus infection risk, data collection for W6 began with telephone interviews only. As conditions improved in certain parts of the country, the PATH Study began in-person interviews with participants on May 7, 2021. All in-person contacts with participants were conducted in compliance with local and state restrictions for COVID-19 mitigation. Wave 6 data were collected with a mix of telephone and in-person interviews. Because W6 data were collected with a mix of telephone and in-person interviews, we included W6 data collection mode to account for differential reporting.

Statistical analysis

Missing data analysis

We used weights to address attrition from the sample. However, they did not address loss due to missing data on one or more survey items. To address that, we examined missingness percentage by sociodemographics, cigarette exposure, and functionally important respiratory symptoms, in order to determine if there were large differences that might limit the generalizability of our findings.

Analytical approach

All main analyses were weighted using the W6 longitudinal full-sample and replicate weights. Variances were estimated using the Balanced Repeated Replication method[23] with Fay's adjustment set to 0.3 to increase estimate stability.[24] For all covariates in the analysis, we entered the baseline value for each observation period excepting sex, race/ethnicity, education and income, for which we entered values from the first available wave. Pack-years of cigarette smoking and second-hand smoke exposure were Winsorized at the 95th and 99th percentiles, respectively, to address outliers.[25]

We reported the proportion with functionally important respiratory symptoms for Wave 2 of the W2 → W3 analytic sample. We then examined the associations between changes in cigarette use over any two-wave period to either continued cigarette use, switching to exclusive e-cigarette, or quitting tobacco altogether at follow-up and worsening or improvement of functionally important respiratory symptoms using longitudinal multivariable generalized estimating equations to produce population-averaged estimates. Generalized estimating equations analysis also allows for inclusion of multiple observations for an individual over time by considering interdependence among observations contributed by the same individuals, using an unstructured correlation matrix.[26–28] We used a Poisson model with a log link and an offset term for wave years to estimate risk ratios. Statistical analyses were performed using Stata survey data procedures (version 17) and statistical significance is based on a two-sided test with $p < 0.05$.

Sensitivity analyses

We re-ran a sensitivity analysis using a higher cut-off level (index score ≥ 3) for functionally important respiratory symptoms in which we 1) tested the robustness of the findings, and 2) conducted an unweighted analysis on all participants who contributed one or more observations (preplanned analyses). We conducted several additional sensitivity analyses on the primary data analysis (functionally important respiratory symptom index threshold of two) to support our findings: 3) We tested whether persons who used both cigarettes and e-cigarettes (dual product use) had similar risk as those who continued to smoke cigarettes; 4) We tested whether the results changed when we used those who continued stable cigarette use (individuals for whom daily cigarette use varied by ≤ 2 cigarettes per day across the two waves) as a reference category; 5) To address whether we over-adjusted for conditions (mediators) caused by cigarette smoking, we reran the primary analysis after excluding the following covariates: congestive heart failure, heart attack, diabetes, cancer; and regular use of beta blockers, angiotensin receptor blockers, and ACE inhibitors; 6) To address whether inclusion of follow-up values for time-varying covariates could affect respiratory symptoms, we re-ran the analysis with follow-up values for the following variables: past 30-day marijuana use, and past 7-day second-hand smoke exposure; ever diagnosis of heart attack, congestive heart failure, or cancer; and regular use of ACE inhibitors.

Ethics statement

All adult respondents provided informed consent. The study was conducted by Westat and approved by

the Westat Institutional Review Board and guided by the ethical principles regarding research involving human subjects as presented in the report by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, universally recognized as The Belmont Report—April 18, 1979.

Role of the funding source
Representatives from the National Institute on Drug Abuse, National Institutes of Health and the Center for Tobacco Products, U.S. Food and Drug Administration contributed to the design and conduct of the study; interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

Sample description and change in tobacco status

Table 1 reports the proportion at Wave 2 with high versus low symptom burden for functionally important respiratory symptoms and covariates for persons in the W2 → W3 observation period. Risk factors associated with higher symptom burden included age, race, education, obesity, asthma, cardiac disease, diabetes, cancer, use of ACE inhibitors, past 30-day cannabis use, higher cigarette pack-years and second-hand smoke exposure.

As shown in eTable 3, individuals with missing data were significantly older, had lower incomes, had more medical conditions (obesity, heart attack, and diabetes), were more likely to have used cannabis, and had much higher mean pack-years of cigarette smoking (11.9 versus 15.6 in the analytic compared to the nonanalytic sample) and higher rates for functionally important respiratory symptoms (26.9 versus 43.5 in the analytic and nonanalytic samples respectively).

Most observations (86.7%) resulted in continued cigarette smoking, 3.7% included switching completely to e-cigarettes, and 9.6% included quitting tobacco altogether at follow-up (N = 14,947 observations; eTable 2). More than half of those who switched completely to e-cigarettes used them daily; the 25th percentile of e-cigarette use was 18 of 30 days per month (data not shown in tables/figures).

Respiratory symptom worsening among persons with low symptom burden at baseline

Among 10,133 observations with low symptom burden (index score <2) at baseline, 85.3% continued cigarettes, 3.5% switched to e-cigarettes, and 11.1% quit tobacco. Functionally important respiratory symptoms worsened (index score ≥2) in 14.6% overall; shown in Fig. 2 Panel A, symptoms worsened in 15.4% (95% confidence interval [CI] 14.3, 16.5) of observations with continued cigarette use, compared to 10.0% (7.8, 12.8) for e-cigarette switching, and 10.1% (7.5, 13.5) for quitting tobacco entirely. Compared to continued cigarette smoking, adjusted relative risk (RR) for respiratory symptom worsening was 0.69 (0.52, 0.91) for e-cigarette switching and 0.73 (0.54, 0.97) for quitting tobacco (Table 2). eTable 4 shows results for all covariates in this model.

Respiratory symptom improvement among persons with high symptom burden at baseline

Among 4813 observations with high respiratory symptom burden (index score ≥2) at baseline, 90.4% continued cigarettes, 2.8% switched to e-cigarettes, and 6.7% quit tobacco. Functionally important respiratory symptoms improved (index score <2) in 29.2% overall; shown in Fig. 2 Panel B, symptoms improved in 27.7% (26.2, 29.2) of observations with continued cigarette use, compared to 45.8% (36.1, 55.9) for e-cigarette switching, and 42.1% (34.7, 49.9) for quitting tobacco entirely. Compared to continued cigarette smoking, RR for respiratory symptom improvement was 1.31 (1.05, 1.64) for e-cigarette switching and 1.36 (1.15, 1.62) for quitting tobacco (Table 2). eTable 4 shows results for all covariates in this model.

Sensitivity analyses

Panel 1 of Table 3 shows that the pattern of results did not change when the analysis was repeated at a higher functionally important respiratory symptom index score of 3. Compared to a threshold cut-off of 2, fewer (10.8% overall) had respiratory symptom worsening and more (40.2%) had symptom improvement. The RRs comparing exclusive e-cigarette use with continued cigarette use were 0.74 (0.53, 1.05) and 1.20 (0.95, 1.51) for respiratory symptom worsening and improvement, respectively, but were not statistically significant. Conducting an unweighted analysis (not nationally representative) did not change the pattern of results, and the relative risks for exclusive use of e-cigarettes were statistically significant: 0.74 (0.57, 0.95) and 1.21 (1.06, 1.39) for respiratory symptom worsening and improvement respectively (Panel 2, Table 3).

Whereas 3.3% (95% CI 3.0, 3.7) switched completely to e-cigarettes, a significantly larger percentage (4.5% [4.1, 5.0]) transitioned to dual product use (past 30 day use of cigarettes and e-cigarettes). When we selected those who transitioned to dual use as a third comparison category in the weighted sample, their RRs were not significantly different from those who continued smoking cigarettes (functionally important respiratory symptom worsening 1.14 [0.92, 1.41]; improvement 1.06 [0.88, 1.29] (see Panel 3a in eTable 5). When those who transitioned to dual use were treated as the reference category, people who completely switched to e-cigarettes had significantly better outcomes for respiratory symptom worsening (0.61 [0.43, 0.86]) but not for improvement (1.24 [0.93, 1.65]; Row 3b in eTable 5). When we restricted the comparison group to those

Covariate	Functionally important respiratory symptom burden at Wave 2[b]				
	Low (index <2)		High (index 2+)		p-value (chi-squared)
	N = 2504		N = 958		
	Weighted %	95% CI	Weighted %	95% CI	
Age					
18–24	77.9	75.1, 80.4	22.1	19.6, 24.9	0.003
25–39	72.4	69.7, 75.0	27.6	25.0, 30.3	
40–54	69.2	65.5, 72.7	30.8	27.3, 34.5	
55+	75.7	71.5, 79.4	24.3	20.6, 28.5	
Sex					
Female	71.9	69.4, 74.2	28.1	25.8, 30.6	0.152
Male	74.1	72.0, 76.2	25.9	23.8, 28.0	
Race/ethnicity					
Non-Hispanic White	69.5	67.5, 71.4	30.5	28.6, 32.5	<0.001
Non-Hispanic Black	79.6	75.5, 83.1	20.4	16.9, 24.5	
Non-Hispanic Other	75.5	67.2, 82.2	24.5	17.8, 32.8	
Hispanic	81.7	77.4, 85.4	18.3	14.6, 22.6	
Education					
<High School/GED	71.4	67.8, 74.7	28.6	25.3, 32.2	0.020
High School Graduate	73.4	70.1, 76.5	26.6	23.5, 29.9	
Some college/Associates degree	71.5	68.7, 74.1	28.5	25.9, 31.3	
Bachelor's degree	80.4	75.9, 84.3	19.6	15.7, 24.1	
Advanced degree	79.5	68.3, 87.4	20.5	12.6, 31.7	
Income					
<$25,000	70.9	68.7, 73.0	29.1	27.0, 31.3	0.066
$25,000–$74,999	73.6	70.1, 76.8	26.4	23.2, 29.9	
$75,000+	77.6	72.7, 81.9	22.4	18.1, 27.3	
Not reported	76.6	68.7, 83.1	23.4	16.9, 31.3	
Weight category					<0.001
Underweight	77.2	68.0, 84.4	22.8	15.6, 32.0	
Normal	78.4	75.7, 81.0	21.6	19.0, 24.3	
Overweight	74.0	71.0, 76.8	26.0	23.2, 29.0	
Class 1 obese	65.4	60.4, 70.1	34.6	29.9, 39.6	
Class 2+ obese	64.6	59.2, 69.6	35.4	30.4, 40.8	
Lifetime diagnosis of					
Asthma	41.3	35.1, 47.8	58.7	52.2, 64.9	<0.001
Congestive heart failure	44.1	25.7, 64.3	55.9	35.7, 74.3	0.001
Heart attack	48.6	33.3, 64.2	51.4	35.8, 66.7	0.001
Diabetes	61.4	55.5, 66.9	38.6	33.1, 44.5	<0.001
Cancer	62.2	53.0, 70.6	37.8	29.4, 47.0	0.007
Regular medication use, past 12 months					
Ace inhibitors	54.8	45.8, 63.6	45.2	36.4, 54.2	<0.001
Beta blockers	65.7	56.8, 73.6	34.3	26.4, 43.2	0.055
Angiotensin receptor blockers	66.2	49.3, 79.8	33.8	20.2, 50.7	0.329
Other exposures					
Past month cannabis use	66.9	63.9, 69.7	33.1	30.3, 36.1	<0.001
Cigarette pack years (mean)	10.2	9.6, 10.8	15.7	14.7, 16.6	<0.001
Past 7 days SHS exposure in hours (mean)	12.5	11.5, 13.4	19.7	17.9, 21.5	<0.001

CI, Confidence interval; GED, General Education Development; SHS, Secondhand smoke. [a]Percents are weighted using the PATH Study Wave 6 all-waves longitudinal weights for the Wave 1 Cohort (R06_A_A01WGT and 100 replicate weights). To be included in the analysis, respondents must have participated in all 6 waves. This table does not include respondents who entered the sample after W2, although those respondents were eligible for inclusion in subsequent analyses (see eTable 2). [b]Functionally-important respiratory symptoms assessment determined whether individuals had low or high symptom burden based on whether their index score was <2 or ≥2.

Table 1: **Selected sociodemographic, medical history, and tobacco exposure characteristics by persons who smoked cigarettes in the past 30 days and by functionally important respiratory symptom burden at Wave 2 (2014/15) of the PATH Study.[a]**

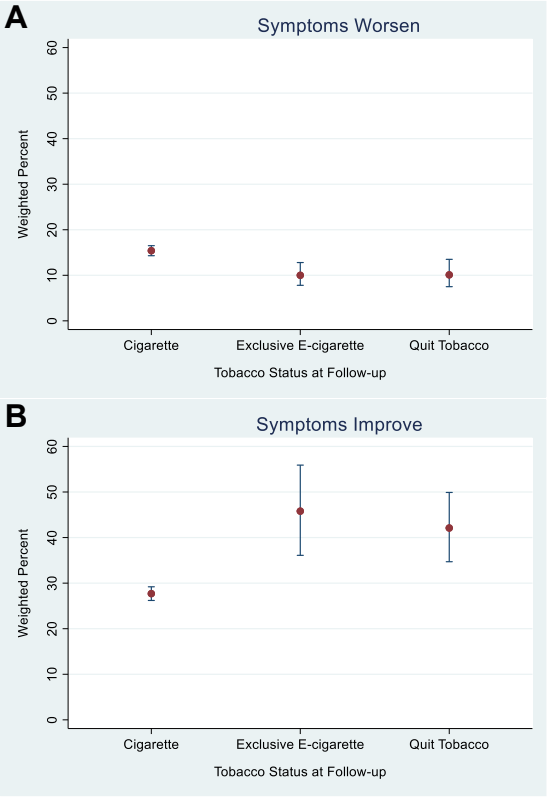

Fig. 2: **Longitudinal analysis showing weighted percent of observations from persons with low respiratory symptom burden at baseline whose symptoms worsened at follow-up (Panel A) and percent of observations from persons who smoked cigarettes with high respiratory symptom burden at baseline whose symptoms improved (Panel B), by tobacco use status at follow-up**. Error bars represent 95% confidence intervals. All persons smoked cigarettes at the beginning of each observation period. Panel A: All had low symptom burden (<2) at baseline (N = 10,134); figure illustrates the percent with high symptom burden (≥2) at follow-up, by follow-up tobacco status. Panel B: All had high symptom burden (≥2) at baseline (N = 4813); figure illustrates the percent with low symptom burden (<2) at follow-up, by follow-up tobacco status.

whose use of cigarettes was stable (within ±2 cigarettes/day) between baseline and follow-up, the estimate for e-cigarettes in the respiratory symptom worsening and improvement models changed little, from 0.69 to 0.76 (0.57, 1.01) and 1.31 to 1.28 (1.00, 1.62), respectively (Panel 4, eTable 5).

When we removed covariates that could be on the causal pathway from tobacco use to respiratory symptoms, the RRs for e-cigarettes changed little, RR = 0.66 (0.51, 0.87) and RR = 1.32 (1.06, 1.64) for the symptoms worsening and improvement models respectively (Panel 5, eTable 5). Finally, when we substituted follow-up status for time-varying covariates the estimates changed little, RR = 0.70 (0.51, 0.96) and RR = 1.31 (1.03, 1.67) for the symptoms worsening and improvement models respectively. However, in this set of models, the RR for quitting all tobacco in the analysis for persons with low symptom burden lost statistical significance (0.76 [0.56, 1.03]; Panel 6, eTable 5).

Discussion

In this sample of US adults who smoked cigarettes, switching to exclusive e-cigarette use reduced risk for worsening of functionally important respiratory symptoms and raised the chances that those with symptoms would improve over 1–2 years, compared to continuing to use cigarettes; risks were similar to those who quit tobacco completely. In contrast, persons who switched from cigarettes to dual use did not benefit and may be at added risk for asthma symptoms compared to those who only smoke cigarettes according to a recent meta-analysis.[12] The strength of the association for symptom worsening was attenuated by about 17% at a higher cut-off level for our criterion for functionally important respiratory symptoms, and the association for symptom improvement was attenuated by about one-third, raising questions about the robustness of these findings at even higher symptom thresholds. The findings withstood sensitivity checks, including choice of reference group and unweighted analysis that allowed for the inclusion of those with partial data who were lost to follow-up. Finally, the findings are consistent with a recently published meta-analysis which found lower risk for asthma/asthma symptoms in exclusive e-cigarette users compared to persons who smoke cigarettes.[12]

Most published studies of e-cigarette use and respiratory symptoms have compared e-cigarette use against never use of tobacco and have found e-cigarette use to be associated with a modest increased risk of respiratory symptoms.[8] Treating those who never used tobacco as the reference category provides information helpful for persons who do not use tobacco about possible risks associated with e-cigarettes, but not for persons who smoke cigarettes, who may benefit from switching to e-cigarettes. We could find few longitudinal population studies that addressed switching from cigarettes to exclusive e-cigarette use and asthma outcomes. Another longitudinal analysis of PATH Study data focused on incidence of wheeze or nighttime cough (two of the items in our functionally important respiratory symptoms index) also found that tobacco transition from dual use to exclusive use of e-cigarettes was associated with a decreased risk for both symptoms.[10] Our study used an index that included all of the PATH Study questions assessing wheezing and nighttime cough, validated by its association with asthma and functional limitations–walking limitations, fatigue, and poor perception of health,[19] – allowing us to examine symptom worsening and improvement across two respiratory symptom severity levels.

Change in cigarette use at follow-up	Change in functionally important respiratory symptoms									
	Symptoms worsen (10,134 observations) Index <2 at baseline → Index ≥2 at follow-up					Symptoms improve (N = 4813 observations) Index ≥2 at baseline → Index<2 at follow-up				
	Obs[b]	Worsen %[c]	Relative risk[d]	95% confidence interval	p-value	Obs[b]	Improve %[c]	Relative risk[d]	95% confidence interval	p-value
Continues using cigarettes	8610	15.4	Ref			4347	27.7	Ref		
Stopped smoking cigarettes[e] and										
Uses e-cigarettes only	398	10.0	0.69	0.52, 0.91	0.009	153	45.8	1.31	1.05, 1.64	0.016
Uses no tobacco product	1126	10.1	0.73	0.54, 0.97	0.029	313	42.1	1.36	1.15, 1.62	0.001

[a]Table 2 presents results only for the tobacco predictor. Please see eTable 4 for results for the covariates. [b]Number of observations from adult respondents without chronic obstructive pulmonary disease, chronic bronchitis, or emphysema, who smoked cigarettes in the past 30 days at the baseline wave and had Wave 6 (W6) longitudinal (all-wave) weights. Wave pairs for the longitudinal analysis include: W2–W3 (2014/15–2015/16), W3–W4 (2015/16–2016/17), W4–W5 (2016/17–2018/19), W5–W6 (2018/19–2021), with the first wave in the pair defined as the baseline wave and the second wave in the pair as follow-up. [c]Symptom worsening is defined by moving from a symptom score <2 to a score ≥ 2 (low symptom burden at baseline to high symptom burden at follow-up). Symptom improvement is defined by moving from a symptom score of ≥ 2 to <2 (high symptom burden at baseline to low symptom burden at follow-up). [d]All adjusted risk ratios include the variables in Table 2: age (continuous), sex, race/ethnicity, education, income, self-reports for asthma, body mass index, heart attack, congestive heart failure, diabetes, cancer, and regular use of beta blockers, angiotensin receptor blockers, or angiotensin converting enzyme inhibitors, second-hand smoke exposure, cigarette pack years, and past month cannabis use. Analyses also adjusted for W6 data collection protocol (in-person or telephone), as well as data collection wave. Model used is Poisson regression with a log link to estimate risk ratios. [e]Stopped smoking cigarettes is defined as not smoking cigarettes within the past 30 days at the follow-up wave.

Table 2: **Longitudinal change in functionally important respiratory symptoms (using an index threshold of 2) by tobacco use status at follow-up among persons who smoked cigarettes in the past 30 days at baseline, PATH Study Waves 2–6 (2014–2021).[a]**

The present study adds to the published literature by finding an association between switching from cigarettes to exclusive e-cigarette use and respiratory symptom improvement among individuals with high respiratory symptom burden at baseline, raising the question of whether e-cigarettes could be considered as an alternative option for individuals who persistently smoke cigarettes and have respiratory symptoms. While the limitations of this observational research preclude the recommendation of using e-cigarettes for harm

Change in cigarette use at F/U	Change in functionally important respiratory symptoms (threshold of 3)									p-value
	Symptoms worsen (11,746 observations for weighted & 17,553 for unweighted analysis) Index <3 at baseline → Index ≥3 at follow-up				p-value	Symptoms improve (3201 observations for weighted & 4823 for unweighted analysis) Index ≥3 at baseline → Index<3 at follow-up				
	Obs[a]	Worsen %[b]	Relative risk[c]	95% confidence interval		Obs[a]	Improve %[b]	Relative risk[c]	95% confidence interval	
1. Weighted analysis[d]										
Continues using cigarettes	10,049	11.4	Ref	Ref	Ref	2908	38.7	Ref	Ref	Ref
Stopped smoking cigarettes[e] and										
Uses e-cigarettes only	460	7.8	0.74	0.53, 1.05	0.089	91	56.7	1.20	0.95, 1.51	0.125
Uses no tobacco product	1237	6.6	0.66	0.48, 0.92	0.014	202	54.0	1.26	1.07, 1.48	0.007
2. Unweighted analysis[f]										
Continues using cigarettes	15,017	11.8	Ref	Ref	Ref	4399	40.3	Ref	Ref	Ref
Stopped smoking cigarettes and										
Uses e-cigarettes only	680	8.1	0.74	0.57, 0.95	0.018	137	60.6	1.21	1.06, 1.39	0.006
Uses no tobacco product	1856	6.3	0.61	0.51, 0.73	<0.001	287	57.5	1.28	1.16, 1.41	<0.001

[a]Number of observations from adult respondents without chronic obstructive pulmonary disease, chronic bronchitis, or emphysema, who smoked cigarettes in the past 30 days at the baseline wave and had Wave 6 longitudinal (all-wave) weights. Wave pairs include: W2–W3 (2014/15–2015/16), W3–W4 (2015/16–2016/17), W4–W5 (2016/17–2018/19), W5–W6 (2018/19–2021), with the first wave in the pair defined as the baseline wave and the second wave in the pair as follow-up. [b]Symptom worsening is defined by moving from a symptom score <3 to a score ≥ 3 (low symptom burden at baseline to high symptom burden at follow-up). Symptom improvement is defined by moving from a symptom score of ≥ 3 to <3 (high symptom burden at baseline to low symptom burden at follow-up). [c]All adjusted relative risks (RR) include the variables in Table 2: table, age (continuous), sex, race/ethnicity, education, income, self-reports for asthma, body mass index, heart attack, congestive heart failure, diabetes, cancer, and regular use of beta blockers, angiotensin receptor blockers, or angiotensin converting enzyme inhibitors, second-hand smoke exposure, cigarette pack years, and past month cannabis use. Analyses also adjusted for Wave 6 data collection protocol (in-person or telephone), as well as data collection wave. Model used is Poisson regression with a log link to estimate risk ratios. [d]The weighted analysis used the Wave 6 PATH Study longitudinal (all-waves) weights and includes only individuals who participated in Waves 2 through 6. [e]Stopped smoking cigarettes is defined as not smoking cigarettes within the past 30 days at the follow-up wave. [f]The unweighted sensitivity analysis includes data from all individuals who had valid baseline and follow-up data for at least one wave pair, regardless of whether they were successfully followed up to Wave 6.

Table 3: **Preplanned Sensitivity Analysis of longitudinal change in functionally important respiratory symptoms (using an index threshold of 3) by tobacco use status at follow-up, persons who smoked cigarettes in the past 30 days at baseline for the observation (obs) period, Population Assessment of Tobacco and Health (PATH) Study Waves 2–6 (2014–2021).**

reduction in people who smoke cigarettes, the present study provides evidence to support randomized controlled trials of e-cigarettes to confirm or refute the associations reported herein. Although it is not clear how long follow-up periods should be for these trials, our findings suggest that symptom resolution could be expected over the course of a year, consistent with a randomized trial of e-cigarettes (compared to nicotine replacement therapy) for smoking cessation that found decreases in phlegm, cough, wheezing, and shortness of breath at the end of one year.[29]

This study has many strengths, including its longitudinal design; use of an index of respiratory symptoms validated against functional outcomes; adjustment for smoking history, cannabis use, and several diseases and treatments known to be associated with respiratory symptoms; and multiple sensitivity tests confirming the robustness of the associations we reported in the context of symptom severity, choice of the reference category, and potential bias due to loss to follow-up.

There are also a number of limitations. Due to the differences between our analytic sample and the non-analytic sample, our results may be biased in two ways. First, we may be underestimating the impact of complete switching from cigarettes to e-cigarettes, since those with higher rates of functionally important respiratory symptoms and other medical conditions, who may have the greatest response to switching, are missing and not included in our models. On the other hand, their high disease burden may make it so that changes in smoking status would not have as appreciable impact on respiratory symptoms. Additional research should explore whether disease or smoking history modifies the impact of complete e-cigarette switching. Assessments allowed for wave-to-wave categorical changes in behavior and symptoms but could not speak to how smoking history might modify the response or dose response. This is a prospective study, so exposures likely preceded changes in respiratory status; however, we cannot be certain that changes in tobacco use preceded changes in respiratory symptoms. There is a possibility that symptom development in low symptom burden individuals prompted a change in tobacco use. We think it highly unlikely that a high symptom burden individual would be prompted to change their tobacco use upon resolution of their symptoms, so that switching to e-cigarette use predicts both symptom transitions provides reassurance.

We can speak to only short-term changes in cigarette smoking behavior; some will relapse to cigarette smoking, and only sustained quitting can confer disease prevention-level harm reduction. We offer no biological explanation for the findings; future studies could assess biological endpoints and mediators. As with any observational study, there may be unmeasured confounders of the associations we reported, unmeasured use of other tobacco products, omitted details of cigarette smoking history, and disease processes not accounted for. Randomized trials of e-cigarette switching for persons who smoke cigarettes would be the best way to address whether unmeasured confounding was an issue in this study.

E-cigarettes are a relatively new tobacco product class; their widespread distribution and use has had public health benefits and risks.[30,31] Whether e-cigarettes represent a net health benefit or harm depends on the population of focus. Its adoption of use by large numbers of adolescents remains a serious health concern, exposing millions of youth to the neurocognitive effects and addicting properties of nicotine.[32] For those who smoke cigarettes, especially those 40 years and older who are at highest risk of developing smoking related diseases, the public health utility of the e-cigarette relates to its ability to replace the cigarette. Unfortunately, the majority of persons who smoke cigarettes and begin using e-cigarettes continue to smoke,[11,33] which continues to negatively impact their health, and also suggests limitations in the ability of the e-cigarette to replace the cigarette for these individuals. The findings in the present study support e-cigarette switching by suggesting that persons able to switch completely from cigarettes to e-cigarettes have similar risk for respiratory symptom onset and resolution to those who quit tobacco altogether. Further research could determine whether the e-cigarette represents a lower harm option for individuals with respiratory symptoms who cannot quit smoking cigarettes.

Contributors

JS, KE, TM, MB, ST, LP, KN, AH, TM, MC, and HK were responsible for study conceptualization; all authors contributed to acquisition, analysis or interpretation of data; JS, KE, and KL drafted the manuscript; all authors contributed to critical revision of the manuscript for important intellectual content; KE and HK assessed and verified the data; JS, TM, KE, and KL conducted the statistical analysis; JS AH and HK obtained funding, and KE and HK provided study supervision.

Data sharing statement

The data used in this study are available at ICPSR's website: https://doi.org/10.3886/ICPSR36231.v21.

Declaration of interests

K. Michael Cummings provides expert testimony on the health effects of smoking and tobacco industry tactics in lawsuits filed against the tobacco industry.

Maciej Goniewicz has received a research grant from Pfizer and served as a member of scientific advisory board to Johnson & Johnson, pharmaceutical companies that manufacture smoking cessation medications.

Andrew Hyland reports consulting fees from UCSF and MD Anderson. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102951.

References

1 Higgins IT. Tobacco smoking, respiratory symptoms, and ventilatory capacity; studies in random samples of the population. *Br Med J*. 1959;1(5118):325–329. https://doi.org/10.1136/bmj.1.5118.325.
2 Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med*. 2016;374(19):1811–1821. https://doi.org/10.1056/NEJMoa1505971.
3 Tan W, Bourbeau J, Hernandez P, et al. Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. *Thorax*. 2014;69(8):709–717. https://doi.org/10.1136/thoraxjnl-2013-205048.
4 Çolak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Prognostic significance of respiratory symptoms in individuals with preserved pulmonary function without known airway disease. *Eur Respir J*. 2019;54(suppl 63):OA291. https://doi.org/10.1183/13993003.congress-2019.OA291.
5 Kalhan R, Dransfield MT, Colangelo LA, et al. Respiratory symptoms in young adults and future lung disease. The CARDIA Lung Study. *Am J Respir Crit Care Med*. 2018;197(12):1616–1624. https://doi.org/10.1164/rccm.201710-2108OC.
6 Gratziou C. Respiratory, cardiovascular and other physiological consequences of smoking cessation. *Curr Med Res Opin*. 2009;25(2):535–545. https://doi.org/10.1185/03007990802707642.
7 Klemperer EM, Streck JM, Lindson N, et al. A systematic review and meta-analysis of interventions to induce attempts to quit tobacco among adults not ready to quit. *Exp Clin Psychopharmacol*. 2023;31(2):541. https://doi.org/10.1037/pha0000583.
8 National Academies of Sciences Engineering and Medicine. *Public health consequences of E-cigarettes*. Washington DC: The National Academies Press; 2018. https://doi.org/10.17226/24952.
9 Wills TA, Soneji SS, Choi K, Jaspers I, Tam EK. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. *Eur Respir J*. 2021;57(1). https://doi.org/10.1183/13993003.01815-2019.
10 Berlowitz JB, Xie W, Harlow AF, et al. Cigarette–E-cigarette transitions and respiratory symptom development. *Am J Prev Med*. 2023;64(4):556–560. https://doi.org/10.1016/j.amepre.2022.10.006.
11 Sargent JD, Halenar MJ, Edwards KC, et al. Tobacco use and respiratory symptoms among adults: findings from the longitudinal population assessment of tobacco and health (PATH) study 2014–2016. *Nicotine Tob Res*. 2022;24(10):1607–1618. https://doi.org/10.1093/ntr/ntac080.
12 Glantz SA, Nguyen N, Oliveira da Silva AL. Population-based disease odds for e-cigarettes and dual use versus cigarettes. *NEJM Evid*. 2024;3(3):EVIDoa2300229. https://doi.org/10.1056/EVIDoa2300229.
13 Halenar MJ, Sargent JD, Edwards KC, et al. Validation of an index for functionally important respiratory symptoms among adults in the nationally representative population assessment of tobacco and health study, 2014-2016. *Int J Environ Res Public Health*. 2021;18(18). https://doi.org/10.3390/ijerph18189688.
14 Hyland A, Ambrose BK, Conway KP, et al. Design and methods of the population assessment of tobacco and health (PATH) study. *Tob Control*. 2017;26(4):371–378. https://doi.org/10.1136/tobaccocontrol-2016-052934.
15 Piesse A, Opsomer J, Dohrmann S, et al. Longitudinal uses of the population assessment of tobacco and health study. *Tob Regul Sci*. 2021;7(1):3–16. https://doi.org/10.18001/trs.7.1.1.
16 National Addiction & HIV Data Archive Program. Population assessment of tobacco and health (PATH) study series. University of Michigan. https://www.icpsr.umich.edu/icpsrweb/NAHDAP/series/606. Accessed November 18, 2019.
17 Center for Tobacco Products. Data collection nonresponse bias analysis for wave 6 population assessment of tobacco and health (PATH) study restricted-use Files. Inter-university Consortium for Political and Social Research [distributor]. Available at: https://doi.org/10.3886/ICPSR36231.v39. Accessed August 8, 2024.
18 Asher MI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8(3):483–491. https://doi.org/10.1183/09031936.95.08030483.
19 Brunette MF, Halenar MJ, Edwards KC, et al. Association between tobacco product use and asthma among US adults from the Population Assessment of Tobacco and Health (PATH) Study waves 2–4. *BMJ Open Respir Res*. 2023;10(1):e001187. https://doi.org/10.1136/bmjresp-2021-001187.
20 Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. 2010;63(11):1179–1194. https://doi.org/10.1016/j.jclinepi.2010.04.011.
21 Drope J, Liber AC, Cahn Z, et al. Who's still smoking? Disparities in adult cigarette smoking prevalence in the United States. *CA Cancer J Clin*. 2018;68(2):106–115. https://doi.org/10.3322/caac.21444.
22 Hegewald MJ, Crapo RO. Socioeconomic status and lung function. *Chest*. 2007;132(5):1608–1614. https://doi.org/10.1378/chest.07-1405.
23 McCarthy PJ. Pseudo-replication: half samples. *Rev Inst Int Stat*. 1969:239–264.
24 Judkins DR. Fay's method for variance estimation. *J Off Stat*. 1990;6(3):223–239. Available at https://www.proquest.com/docview/1266811483?sourcetype=Scholarly%20Journals. Accessed December 10, 2024.
25 Rivest L-P. Statistical properties of Winsorized means for skewed distributions. *Biometrika*. 1994;81(2):373–383. https://doi.org/10.1093/biomet/81.2.373.
26 Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73(1):13–22. https://doi.org/10.1093/biomet/73.1.13.
27 Hilbe JM, Hardin JW. Generalized estimating equations for longitudinal panel analysis. *Handb longitudinal res*. 2008;1:467–474.
28 Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology*. 2010:467–474. https://doi.org/10.1097/EDE.0b013e3181caeb90.
29 Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380(7):629–637. https://doi.org/10.1056/NEJMoa1808779.
30 Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms of e-cigarette use in the United States. *PLoS One*. 2018;13(3):e0193328. https://doi.org/10.1371/journal.pone.0193328.
31 Warner KE, Mendez D. E-Cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine Tob Res*. 2019;21(1):41–47. https://doi.org/10.1093/ntr/nty062.
32 *Youth E-cigarette use remains serious public health concern amid COVID-19 pandemic*; 2021. https://www.fda.gov/news-events/press-announcements/youth-e-cigarette-use-remains-serious-public-health-concern-amid-covid-19-pandemic. Accessed June 15, 2023.
33 Hedman L, Backman H, Stridsman C, et al. Association of electronic cigarette use with smoking habits, demographic factors, and respiratory symptoms. *JAMA Netw Open*. 2018;1(3):e180789. https://doi.org/10.1001/jamanetworkopen.2018.0789.