



# Cross-sectional e-cigarette studies are unreliable without timing of exposure and disease diagnosis

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Dear Editor,

Over the past few years, many studies have used cross-sectional data from the National Health Interview Survey (NHIS) [1, 2], the Behavioral Risk Factor Surveillance Survey (BRFSS) [3–10]), and the Population Assessment of Tobacco and Health Survey (PATH) [8, 11] to claim that e-cigarette use is associated with asthma [3, 6, 7] chronic obstructive pulmonary disease (COPD) [3, 6–8], emphysema, chronic bronchitis [7], stroke [4, 5], congestive heart disease [4] myocardial infarction (MI) [1, 2, 4], pre-diabetes [9, 10] and hypertension [11]. Although study authors acknowledge that smoking is a factor for these illnesses, they generally contend that their results for e-cigarettes are adequately adjusted for smoking. However, the applicability of NHIS and BRFSS is also challenged by the fact that they do not contain any information about when participants started vaping or smoking, and when they were diagnosed with the diseases.

The PATH data have information about when smokers and vapers started, and when they were diagnosed with diseases, but it has been ignored in previous reports [8, 11, 12]. We used the first wave of the PATH survey to provide these respective age distributions for diagnoses of COPD, emphysema, MI and stroke, and compared them with the age ranges of e-cigarette and smoking initiation.

## Methods

We used data from the PATH Wave 1 Public-Use File (PUF), administered from September 2013 to December 2014. The PATH collected information from 32,320 civilian and non-institutionalized adults (ages 18 and older) in all 50 United States and the District of Columbia [13].

## Tobacco use

We classified participants as never smokers if they had not smoked 100 cigarettes in their lifetime. Current smokers had smoked 100+ cigarettes and smoked every day or some days at Wave 1; former smokers had smoked at least 100 cigarettes in their lifetime and did not smoke at Wave 1. Both current and former smokers were asked their age when they first started smoking cigarettes fairly regularly.

Ever e-cigarette users were respondents who had ever used an e-cigarette even one or two times. They were asked about their age when they first used an e-cigarette.

## Medical conditions

All participants were asked whether they had ever been diagnosed with multiple diseases. We chose four conditions that are strongly associated with smoking and for which claims have been made for e-cigarettes: COPD, emphysema, myocardial infarction and stroke. If participants answered affirmatively, a follow-up question asked them when they were first told about the diagnosis.

The PATH PUF provided the following respondents' age range for both tobacco use and medical conditions: (1) less than 18 years old, (2) 18–24, (3) 25–34, (4) 35–44, (5) 45–54, and (6) 55 years old or older.

Notably, PATH variable names and questions can be found in supplemental Table 1.

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**Table 1** Cross-tabulation between age (years) first time started using an e-cigarette (Panel A) and first time started smoking cigarettes regularly (Panel B) with age (years) first told COPD, emphysema, MI and stroke

		Panel A														
		Age first told COPD							Age first told emphysema							
		< 18	18-24	25-34	35-44	45-54	55+	Total	< 18	18-24	25-34	35-44	45-54	55+	Total	
Age when first used an <b>e-cigarette</b> , even one or two times	< 18	2		1	1			4	3						3	
	18-24	6	3	1	2			12	6	2	1	1			10	
	25-34		2	15	4			21		4	5	1			10	
	35-44			12	51	6	2	71		2	7	29	2	2	42	
	45-54	1	2	8	50	114	4	179			9	27	47	4	87	
	55+	4	2	5	12	57	181	261	3	1	2	12	30	85	133	
	Total	13	9	42	120	177	187	548	12	9	24	70	79	91	285	
			Age first told MI							Age first told stroke						
		< 18	18-24	25-34	35-44	45-54	55+	Total	< 18	18-24	25-34	35-44	45-54	55+	Total	
	< 18	2				1		3	1						1	
18-24	2	2			1		5	3	3					6		
25-34			4	2			6	4	6	8	1			19		
35-44		2	5	11	3	1	22	1	1	9	14	1	1	27		
45-54			5	18	31	4	58	3	2	8	15	27	3	58		
55+	1		2	12	29	62	106	5	0	3	9	23	48	88		
Total	5	4	16	43	65	67	200	17	12	28	39	51	52	199		
		Panel B														
		Age first told COPD							Age first told emphysema							
		< 18	18-24	25-34	35-44	45-54	55+	Total	< 18	18-24	25-34	35-44	45-54	55+	Total	
Age when first started <b>smoking cigarettes</b> fairly regularly	< 18	7	10	44	118	205	188	572	8	11	25	67	77	113	301	
	18-24	3	3	12	34	69	148	269	2	2	8	18	40	57	127	
	25-34	1		6	5	12	26	50			2	2	4	11	19	
	35-44	1			0	3	6	10					1	1	2	
	45-54				1	1	1	3								
	55+			1		1	2	4			1	1	1		3	
	Total	12	13	63	158	291	371	908	10	13	36	88	123	182	452	
			Age first told MI							Age first told stroke						
		< 18	18-24	25-34	35-44	45-54	55+	Total	< 18	18-24	25-34	35-44	45-54	55+	Total	
	< 18	2	8	27	51	87	98	273	10	9	21	44	58	74	216	
18-24	3	1	5	25	46	61	141	5	8	7	13	31	51	115		
25-34				5	7	10	22			2	2	6	5	15		
35-44	1				1		2					1	3	4		
45-54						1	1						1	1		
55+																
Total	6	9	32	81	141	170	439	15	17	30	59	96	134	351		

Panel A: Diseases after 1st e-cigarette exposure: COPD 3.8% (21/548), emphysema 3.9% (11/285), MI 6% (12/200), stroke 3% (6/199)

Panel B: Diseases after 1st cigarette smoking exposure: COPD 97% (881/908), emphysema 96% (435/452), MI 98% (432/439), stroke 93% (326/351)

### Cross-tabulation analysis

Two-dimensional tables cross-tabulates participants' age at first use of e-cigarettes and age at smoking cigarettes

regularly with age when they were told they had individual diseases were obtained. For participants reporting the same age (group) for e-cigarette initiation and diagnosis, a second

table cross-tabulating age of e-cigarette initiation with age of regular smoking was obtained

### Results

Table 1, Panel A shows the cross-tabulation of age at first e-cigarette use (rows) and at first disease diagnoses (columns). The unshaded cells in the lower left half of the individual tables represent disease cases that cannot be associated with e-cigarettes, because the disease occurred prior to first use. The bold diagonals represent the disease cases that occurred in the same age group as the first e-cigarette exposure. In the remaining shaded cells are the cases that definitely occurred after first exposure. They represent 3.8% of COPD (21/548), 3.9% of emphysema (11/285), 6% of MI (12/200) and 3% of stroke (6/199).

Table 1, Panel B also presents the cross-tabulation results for smoking fairly regularly. In contrast to the

findings for e-cigarettes, disease cases among smokers that definitely occurred after first exposure are 97% for COPD (881/908), 96% for emphysema (435/452), 98% for MI (432/439) and 93% for stroke (326/351).

In Panel A the largest numbers lie in the bold diagonals, in which participants' diagnoses with these diseases occurred in the same age group as they first used e-cigarettes.

We investigated further by cross-tabulating between age when first using e-cigarettes and age at first smoking regularly among participants in the Table 1 Panel A diagonals. The shaded areas of Table 2 show that large majorities of participants with COPD (97%), emphysema (96%), MI (99%) and stroke (89%) who reported the same age group for first e-cigarette use and first diagnosis were smoking cigarettes regularly prior to using e-cigarettes. In fact, in most cases, it was decades earlier. Diagnosed cases in Table 2 who never smoked were very rare, only six COPD, five emphysema, one MI and seven stroke.

**Table 2** Cross-tabulation between age first used an e-cigarette and age first started smoking cigarettes regularly among participants who reported the same ages for first used e-cigarettes and first told had diseases (i.e., diagonals in Table 1)

		COPD <sup>1</sup>								Emphysema <sup>2</sup>								
		Age first started smoking cigarettes regularly								Age first started smoking cigarettes regularly								
		< 18	18-24	25-34	35-44	45-54	55+	NS	Total	< 18	18-24	25-34	35-44	45-54	55+	NS	Total	
		< 18	18-24	25-34	35-44	45-54	55+	NS	Total	< 18	18-24	25-34	35-44	45-54	55+	NS	Total	
Age first used an e-cigarette, even one or two times	< 18	1							1	1							1	
	18-24	3							3	2							2	
	25-34	7	5						12	3	1						4	
	35-44	32	12	2					46	18	8	0					26	
	45-54	79	19	5	1			2	106	29	13	1	1			1	45	
	55+	84	59	10	5	1	2	4	165	50	20	5	1			4	80	
	Total	206	95	17	6	1	2	6	333	103	42	6	2			5	158	
			MI <sup>3</sup>								Stroke <sup>4</sup>							
			Age first started smoking cigarettes regularly								Age first started smoking cigarettes regularly							
			< 18	18-24	25-34	35-44	45-54	55+	NS	Total	< 18	18-24	25-34	35-44	45-54	55+	NS	Total
		< 18									1							1
		18-24	2							2	1	1					1	3
		25-34	4							4	5						1	6
		35-44	7	2	2					11	10	1					1	12
	45-54	20	7	2					29	17	4	2				2	25	
	55+	35	17	2		1		1	56	26	12	1			1	2	42	
	Total	68	26	6		1		1	102	60	18	3			1	7	89	

NS never smokers

<sup>1</sup>missing 33 out of 366 participants

<sup>2</sup>missing 13 out of 171

<sup>3</sup>missing 10 out of 112

<sup>4</sup>missing 12 out of 101

## Discussion

Our simple cross-tabulation tables have revealed crucial information relevant to previous studies. Only 4% of COPD and emphysema cases, 6% of MIs and 11% of stroke had occurred in PATH participants who had used e-cigarettes prior to the diagnoses. In contrast, over 94% of all cases occurred after smoking cigarettes fairly regularly.

For those participants who were the same age range when they first used an e-cigarette and were first diagnosed, large majorities had smoked cigarettes regularly prior to e-cigarette initiation and only a few never smokers used e-cigarettes. This evidence indicates a potential reverse association between e-cigarette use and these diseases. In other words, having a diagnosis for respiratory and cardiovascular diseases leads smokers to use e-cigarettes. Even when the age of e-cigarette initiation and the age of diagnosis is the same in Table 2, Panel B, smoking remains a dominant factor with these diseases.

Studies based on cross-sectional data with no information on age of e-cigarette initiation and age of diagnosis invariably overestimate associations by including cases that were diagnosed before e-cigarette exposure [12, 14]. Although the authors of those studies did not make causal claims in the reports, university media releases [15, 16] and subsequent media articles invariably misled the public to believe that e-cigarette use increases risk for diseases.

Using PATH restricted data, which contains actual ages instead of age groups, would enhance the details of the results presented here, but it would not negate them. However, presentations of the findings from restricted data might be compromised by restrictions on cell counts involving small numbers.

The ages of e-cigarette initiation and first diagnosis were not addressed in previous studies using PATH data [8, 11], but those omissions resulted in retraction of another study claiming that vaping causes heart attacks [12]. Furthermore, our findings clearly apply to studies using cross-sectional data such as NHIS and BRFSS, which do not contain any information on exposure initiation or diagnosis. In the absence of that information, those studies exaggerate the associations and are simply unreliable.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11739-022-03141-3>.

## Declarations

**Conflict of interest** This study was supported by the Kentucky Research Challenge Trust Fund and by unrestricted grants to the University of Louisville from tobacco manufacturers.

**Human and animal rights and informed consent** For this type of study human and animal rights and informed consent are not relevant.

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