



The association between dual use of electronic nicotine products and illicit drugs with adverse cardiovascular and respiratory outcomes in a longitudinal analysis using the Population Assessment of Tobacco and Health (PATH) survey

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HIGHLIGHTS

- ENDS users are more likely to have respiratory conditions compared to non-users.
- Drug users are more likely to have respiratory conditions compared to non-users.
- Dual users have the largest OR of having respiratory problems compared to non-users.
- Exclusive drug users have higher odds of CVD compared to non-users.
- ENDS use among drug users does not result in significantly increased odds of CVD.

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ABSTRACT

Background: Drug use and electronic nicotine delivery systems (ENDS) are independently associated with increased risk of cardiovascular and respiratory outcomes. Literature on the association between the dual use of these key substances and potential health outcomes is limited.

Methods: We examined the association between dual use of ENDS and drugs (including heroin, methamphetamine, cocaine, painkillers, and misused stimulant medications) with adverse cardiovascular and respiratory outcomes in a longitudinal analysis using waves 1–5 from the Population Assessment of Tobacco and Health survey (2014–2018). Multivariable logistic regression with Generalized Estimating Equations was utilized.

Results: About 0.9% ($n = 368$) of respondents at wave 2 used both ENDS and drugs, 5.1% ($n = 1,985$) exclusively used ENDS, and 5.9% ($n = 1,318$) used drugs. Compared with people who do not use drugs, both those who used only ENDS (Adjusted Odds Ratio (AOR) 1.11 [95% CI 0.99–1.23], $P = 0.07758$) and those who used only drugs (AOR 1.36 [95% CI 1.15–1.60], $P = 0.00027$) were more likely to experience adverse respiratory conditions. Individuals who used drugs and ENDS compared to people who did not use drugs or ENDS had the largest odds of respiratory problems among all drug use category comparisons (AOR 1.52 [95% CI 1.20–1.93], $P = 0.00054$). Individuals who only used drugs had elevated odds of cardiovascular ailments compared to people who did not use drugs or ENDS (AOR 1.24 [95% CI 1.08–1.42], $P = 0.00214$) and compared to people who only used ENDS (AOR 1.22 [95% CI 1.04–1.42], $P = 0.0117$).

Conclusions: Inhaling electronic nicotine delivery systems and other substances may negatively affect the users' respiratory health.

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1. Introduction

Since 1990, the drug epidemic has caused a continuous rise in fatalities worldwide, with nearly half a million deaths occurring in 2019 alone (WDR, 2021). The U.S. drug epidemic caused 932,000 deaths from 1999 through 2020 (CDC, 2022). Despite government policy actions, over 70,000 Americans died from drug overdoses in 2019 (Farberman, 2020). Illicit drugs can affect nearly every organ in the body, including the respiratory and cardiovascular systems (Devlin et al., 2008; Khod-neva et al., 2016). Nonmedical drug use directly affects the pulmonary system (e.g., pulmonary edema) (Radke et al., 2014; Tseng et al., 2013). Evidence suggests drugs, including opioids, increase asthma prevalence above the national average (Naik et al., 2018; Lee et al., 2019). Drugs also affect the cardiovascular system, with studies showing a link between long-term use of opioids, cocaine, and certain amphetamines with cardiac structural changes such as myocardial fibrosis (Aquaro et al., 2011; Kevil et al., 2019; Seltenhammer et al., 2013). Accordingly, opioids, cocaine, and amphetamines are associated with cardiac-related mortality (Ray et al., 2016; Gislason et al., 2009; Dominic et al., 2022)

In 2007 electronic nicotine delivery systems (ENDS) were introduced into the consumer markets. In 2018, 14.9% of U.S. adults reported ever using an e-cigarette, and 3.2% of adults (equivalent to 8.1 million Americans) reported using e-cigarettes (Creamer et al., 2019; Villarreal et al., 2020). ENDS aerosols emit lower levels of toxic chemicals than tobacco smoke and are considered a safer alternative to combustible cigarettes (Dinakar and O'Connor, 2016; Rigotti, 2018).

ENDS are not risk-free and have been associated with adverse effects, such as pulmonary ailments, asthma exacerbation, and cardiovascular harm (Bayly et al., 2019; Buchanan et al., 2020; U.S. Department of Health and Human Services, 2016; Li et al., 2020; Sargent et al., 2022). Additionally, ENDS use is associated with elevated heart rate and blood pressure (Qasim et al., 2017; Skotsimara et al., 2019), increased risk of thrombosis and atherosclerosis (Kavousi et al., 2020), greater likelihood of myocardial infarction (Alzahrani et al., 2018), and other markers of cardiovascular disease pathogenesis (Qasim et al., 2017). While some studies suggest a potential association between ENDS usage and risk of cardiovascular disease, others suggest a null relationship (Berlowitz et al., 2022). Given the recent emergence of ENDS, data from clinical trials and long-term cohort studies is currently lacking (Kavousi et al., 2020).

Polysubstance use may have complex additive or synergistic effects on short- and long-term health outcomes. Illicit drug use is common among people who smoke tobacco (Lai et al., 2000; Rajabi et al., 2019; Skurtveit et al., 2010), and high rates of nicotine consumption are observed in populations with SUDs (Baldassarri et al., 2019; Stein et al., 2015; Gubner et al., 2016; Yoon et al., 2015; Li et al., 2010; Guydish et al., 2011, 2019; Pajusco et al., 2012; Weinberger et al., 2009; Zirakzadeh et al., 2013). Among young adults, e-cigarette use has been associated with the use of cocaine, amphetamines, inhalants, hallucinogens, misused prescription drugs, and other opioids (Dunbar et al., 2017; Grant et al., 2020; McCabe et al., 2017; Temple et al., 2017). Currently, 19.3 million Americans (7.8% of the U.S. population) use both opioids and e-cigarettes (SAMHSA, 2019). Research examining health outcomes tends to focus on illicit drugs and ENDS use individually, but this perspective overlooks data indicating that many Americans who use drugs and alcohol also use other substances.

Limited research suggests that dual use of drugs and ENDS affect similar biological pathways that impact the risk of certain health conditions. For example, cocaine, amphetamines, and nicotine all act on the adrenergic system, which has been linked to increased risk of myocardial infarction (MI) (Lu et al., 2015; Kim et al., 2019; Benowitz et al., 2016; Primatesta et al., 2001). Overlapping biologic targets of illicit drugs and ENDS warrants further investigation into adverse clinical outcomes from dual use of these substances.

As ENDS use increases amidst the drug crisis, it is crucial to understand the health implications of dual use. However, there is limited

research on the dual use of ENDS and illicit drugs with health outcomes. This study uses the Population Assessment of Tobacco and Health (PATH) to compare adverse respiratory and cardiovascular outcomes among a nationally representative sample of U.S. adults who use drugs (illicit and prescription misuse) and ENDS versus those who use only one or neither. PATH is a longitudinal study that allows for examining the association of ENDS and drug use with respiratory and cardiovascular conditions over time.

2. Methods

2.1. Data source

The current study used PATH data (Hyland et al., 2017). PATH is a nationally representative, longitudinal survey of tobacco use and health outcomes among the civilian household population in all 50 states and the District of Columbia. As a joint research effort between the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), the PATH study collects self-reported data on tobacco and other drug use patterns, attitudes toward tobacco, and health behaviors and outcomes. The survey collects data on other tobacco products (including cigarettes and e-cigarettes), demographic information, medicine use, and physical and mental health indicators.

The approximately 49,000 Americans who participate in the PATH Study (Hyland et al., 2017) are representative of the noninstitutionalized civilian U.S. population aged 12 and older. The first cohort (Wave 1 cohort) was sampled in 2013–2014 with complex sampling design. PATH used multistage cluster sampling with counties or contiguous counties serving as the primary sampling units (PSUs). PATH also employed stratified sampling based on age, race, and tobacco use status, and computed survey weights to account for complex design. Follow-up interviews occur every year or every other year, with data released through 2017–2018 (Wave 5). Data were collected through in-person CAPI or ACASI methods.

2.2. Sample

We followed the original Wave 1 cohort of 32,320 adults aged 18 and older through four-time points (waves 2, 3, 4, 5) from 2014 to 2018. Participants were only included in the analysis if they responded to all five waves; thus, we removed those lost to follow-up, leaving us with 18,893 respondents. We chose to follow participants through Wave 2 – Wave 5 due to discrepancies between these waves and Wave 1 in the cardiovascular and respiratory outcome survey items. Wave 1 participants self-reported whether they had ever been diagnosed with a respiratory or cardiovascular condition (yes/no), whereas in subsequent waves, participants self-reported whether they had been diagnosed in the past 12 months for the same conditions.

2.3. Measures

2.3.1. Dependent variables

We modeled two binary dependent variables and examined the presence or absence of adverse cardiovascular or respiratory conditions. Namely, a 'yes' for *having adverse cardiovascular conditions* corresponded to participants self-reporting having been diagnosed in the past 12 months with one or more of the following possible survey response options: high blood pressure, high blood cholesterol, heart attack (i.e., myocardial infarction), stroke, congestive heart failure, or some other heart condition. A 'yes' for *adverse respiratory conditions* corresponded to participants self-reporting having been diagnosed in the past 12 months with one or more of the following survey response options: chronic obstructive pulmonary disease (COPD), chronic bronchitis, asthma, emphysema, or another lung/respiratory condition. Given the heterogeneity in these conditions, we performed additional sensitivity analyses analyzing each cardiovascular or respiratory condition as separate

outcomes.

The wording of the questions asked regarding having been diagnosed with health conditions in Waves 4 and 5 were the same as the wordings in Waves 2 and 3. PATH changed the *questionnaire skip pattern* in wave 4. Respondents in Waves 2 and 3 were asked these questions *regardless* of whether they had seen a doctor in the past 12 months. In Waves 4 and 5, respondents were only asked these questions if they had also reported seeing a doctor in the last 12 months. We standardized Waves 4 and 5 by making those who were not asked about their health conditions to have "no" as their answer, rather than "inapplicable". Respondents in Waves 2 and 3 who had not seen a doctor in the last 12 months should also have responded "no" to the health complication questions, as a doctor could not have told them they had any conditions, without having seen a doctor.

2.3.2. Independent variables

The main independent variable tested was structured into four categories: (1) ENDS only, (2) illicit drug use or prescription drug misuse only, (3) dual use, and (4) neither. ENDS use was defined as using an electronic nicotine product daily or some days. In Wave 1, respondents were only asked about e-cigarette usage, whereas in later waves, they were asked about any electronic nicotine product usage (e-cigarettes, e-cigars, e-pipes, and e-hookahs). We defined the 'illicit drug or prescription drug misuse only' based on the five items available in PATH that measured illicit drug use and prescription drug misuse. Respondents were grouped into 'illicit drug use or prescription drug misuse only' if they had used any or multiple drugs from the following categories in the past 30 days: (1) heroin, inhalants, solvents, or hallucinogens, (2) stimulants like methamphetamine or speed, (3) cocaine or crack, (4) misuse of prescription drugs such as painkillers, sedatives, or tranquilizers, and/or (5) misuse of Ritalin (methylphenidate) or Adderall (amphetamine/dextroamphetamine).

We adjusted for the following demographic attributes: age, gender, race/ethnicity, region of residence, marital status, education, income, employment status, and availability of health insurance. To reduce missingness, demographic data (except health insurance) for respondents were extracted from Wave 1 or the next earliest wave with available data and were fixed throughout the longitudinal analysis. Age was measured as a seven-level categorical variable in PATH which we recoded it into a continuous variable by assigning participants the midpoint of their respective category.

2.3.3. Confounding risk factors

We also controlled for possible confounding risk factors, cigarette smoking and its duration, other tobacco use, heavy alcohol consumption, weight status, cannabis use, physical activity, and diabetes (i.e., a diagnosis in the past 12 months). Cigarette use was classified as current use (i.e., smoke every day or some days), former established use (i.e., have smoked more than 100 cigarettes in lifetime), and everyone else was classified as experimental/no-use. Data on the duration of "fairly regular" cigarette smoking was only available for people who currently and formerly smoked as a continuous variable in years and months. Thus, people who did not smoke or experimented with cigarettes were assumed to have smoked for zero months and years. Cigarette smoking status was determined for individuals each wave, but due to significant missingness in smoking duration data from Waves 2–5, smoking durations were extracted from Wave 1 and applied to all subsequent waves. Similarly, people with any other tobacco use (e.g. hookah, chew tobacco) were also classified as current use, former established use, and experimental/no-use. Heavy alcohol consumption was defined as, on average, consuming more than 4 alcoholic drinks per day for men (or more than 3 alcoholic drinks per day for women) on days in which alcohol had been consumed in the past 30 days. Weight status was defined by body mass index (BMI) using guidelines from the Centers for Disease Control and Prevention as underweight (BMI <18.5 kg/m²), healthy (18.5–24.9), overweight (25.0–29.9), and obese (≥ 30.0).

Cannabis use was binary indicated if someone had used in the past 30 days. Physical activity was measured by the number of days the respondent did any physical activity or exercise of at least moderate intensity in a typical week. Physical activity was not tracked in Wave 1, so Wave 2 data were used for both Wave 1 and Wave 2.

Since Wave 1 items for cardiovascular and respiratory outcomes assessed *lifetime prevalence* (rather than *incident* occurrences in Waves 2, 3, 4 & 5) of whether a doctor had ever told respondents that they had any of the included respiratory or cardiovascular conditions, Wave 1 responses were used as a baseline control variables and were adjusted for.

2.4. Statistical analyses

Descriptive statistics were calculated to summarize the respondent sample, with means and standard deviation used for continuous variables and column percentage used for categorical variables, with *p*-values calculated using chi-squared tests. Logistic regression with Generalized Estimating Equations (GEE) was used to analyze the association of dual ENDS and drug use with adverse respiratory or cardiovascular outcomes while controlling for demographic characteristics, potentially confounding risk factors, and repeated measurements (Liang and Zeger, 1986). All analyses were weighted to account for the complex survey design. Fay's method (Fay coefficient=0.3) of balanced repeated replication (BRR) was used for variance estimation. The PATH team provided 100 replicate weights with the public use files, and these provided replicate weights were used for variance estimation ("PATH Public-Use Files User Guide", 2020). All statistical tests are two-sided with a significance level of 5%, and all analyses were conducted using SAS 9.4 (Cary, North Carolina, USA).

3. Results

3.1. Sample characteristics

The final analytic sample had 18,893 respondents in each wave (Table 1A). The respondent sample consisted of 54.4% females and 45.7% males. Most respondents were non-Hispanic (NH) White (65.6%). Roughly one-fifth were current smoked cigarettes, and one-quarter formerly smoked (Table 2A). Among people who currently smoke or formerly smoked, the duration of smoking ranged from 1 month to 78 years (median=15.95 years; IQR=22.09 years). Approximately 0.9% of Wave 2 respondents used both ENDS and drugs, 5.1% exclusively used ENDS and 5.9% solely used drugs (Table 2A). By wave 5, dual use dropped to around 0.5% ($p < 0.8918$), ENDS-only use dropped to 4.3% ($p < 0.0001$), and drug-only use dropped to 1.5% ($p = 0.0074$). At baseline, 16.5% had ever been diagnosed with at least one adverse respiratory condition, with asthma being the most common condition (11.3%; Table 1B). At baseline, 40.2% of respondents had ever been diagnosed with at least one adverse cardiovascular condition, most commonly high blood pressure (27.2%), followed by high cholesterol (23.4%; Table 1B). In waves 2–5, between 10.9% and 12.1% of respondents were diagnosed with respiratory conditions, and between 30.3% and 33.1% were diagnosed with cardiovascular conditions (Table 2B).

3.2. Dual ends and drug use and respiratory outcomes

Compared with people who do not use drugs, both those who used only ENDS (AOR 1.11 [95% CI 0.99–1.23], $P = 0.07758$) and those who used only drugs (AOR 1.36 [95% CI 1.15–1.60], $P = 0.00027$) were more likely to experience adverse respiratory conditions (Table 3). Those who used only drugs were 23% more likely to experience respiratory ailments compared to those who only used ENDS (AOR 1.23 [1.03–1.47], $P = 0.02488$). The additional consumption of ENDS among people who used drugs was associated with a 12% higher likelihood of

Table 1A
Baseline (i.e., data from wave 1) demographic characteristics of participants by ENDS and Drug Use.

Characteristic	Electronic nicotine product ⁶ and/or illicit drug use ⁷				Total n ¹ (% ²)	p-value ⁵
	Both n ¹ (% ²)	ENDS Only n ¹ (% ²)	Drug Only n ¹ (% ²)	Neither n ¹ (% ²)		
Total ³	136 (0.3)	763 (1.9)	1340 (5.5)	16,654 (92.3)	18,893 (100)	
Gender						0.3993
Male	66 (49.1)	362 (49.4)	605 (44.3)	7903 (45.7)	8936 (45.7)	
Female	70 (50.9)	401 (51.6)	735 (55.8)	8751 (54.3)	9957 (54.4)	
Race/Ethnicity						<0.0001
Non-Hispanic White	96 (73.8)	533 (73.7)	795 (63.3)	9857 (65.5)	11,281 (65.6)	
Non-Hispanic Black	13 (10.1)	64 (8.6)	219 (15.8)	2632 (12.0)	2928 (12.1)	
Non-Hispanic Other/Multiracial	14 (8.7)	68 (7.6)	100 (5.6)	1192 (7.3)	1374 (7.3)	
Hispanic	13 (7.4)	98 (10.2)	226 (15.4)	2973 (15.2)	3310 (15.1)	
Education						<0.0001
Did not graduate from high school	22 (16.4)	73 (8.6)	205 (13.4)	2095 (10.5)	2395 (10.6)	
High school graduate/GED	33 (23.7)	260 (35.1)	394 (31.6)	477,327.3)	5460 (27.7)	
Associate's degree/Some college	66 (51.1)	321 (40.0)	522 (35.5)	5758 (30.9)	6667 (31.4)	
Bachelor's or advanced degree	13 (8.9)	107 (16.3)	217 (19.5)	3953 (31.3)	4290 (30.3)	
Employment status						<0.0001
Full-time (≥ 35 h/week)	53 (40.3)	331 (45.3)	502 (38.5)	7585 (47.7)	8471 (47.2)	
Part-time < 35 h/week	36 (24.9)	169 (21.8)	247 (15.5)	3237 (16.5)	3689 (16.6)	
Unemployed	47 (34.9)	262 (33.0)	591 (46.0)	5824 (35.7)	6724 (36.2)	
Total household income						<0.0001
Less than \$10,000	38 (25.2)	146 (17.1)	326 (20.2)	3083 (12.9)	3593 (13.4)	
\$10,000 to \$24,999	29 (21.6)	208 (26.0)	367 (25.8)	3655 (19.5)	4259 (20.0)	
\$25,000 to \$49,999	26 (19.3)	184 (25.5)	281 (22.9)	3694 (22.6)	4185 (22.7)	
\$50,000 to \$99,999	25 (21.3)	161 (22.9)	214 (17.7)	3526 (26.1)	3926 (25.5)	
\$100,000 or more	17 (12.5)	54 (8.6)	133 (13.4)	2231 (19.0)	2435 (18.5)	
Marital status						<0.0001
Married	35 (26.6)	285 (38.5)	443 (41.7)	7217 (56.0)	7980 (54.8)	
Divorced/Separated/Widowed	38 (29.9)	165 (23.4)	360 (29.8)	3142 (20.4)	3705 (21.0)	
Never married	63 (43.5)	313 (38.0)	536 (28.5)	6287 (23.7)	7199 (24.3)	
Region of residence						0.0064
Northeast	10 (8.0)	73 (10.6)	205 (18.0)	2532 (17.6)	2820 (17.5)	
Midwest	35 (23.9)	208 (24.9)	290 (19.9)	4173 (22.2)	4706 (22.1)	
South	44 (34.9)	298 (40.9)	516 (37.7)	6175 (36.6)	7033 (36.7)	
West	47 (33.2)	184 (23.7)	329 (24.4)	3774 (23.6)	4334 (23.7)	
BMI						0.0003
Underweight	3 (2.1)	21 (2.3)	43 (2.3)	427 (2.1)	494 (2.1)	
Normal	50 (35.5)	277 (37.4)	437 (29.5)	5508 (31.7)	6272 (31.7)	
Overweight	29 (22.2)	206 (28.2)	388 (30.3)	5184 (34.2)	5807 (33.8)	
Obese	52 (40.2)	242 (32.1)	449 (37.9)	5049 (32.0)	5792 (32.3)	
Exercise ⁴ [median±IQR]	2.0 [4.0]	2.3 [3.6]	2.2 [3.8]	2.4 [3.5]	2.4 [3.5]	0.171
Age [median±IQR]	29.6 [17.4]	30.8 [21.8]	42.5 [25.1]	41.3 [27.5]	41.1 [27.3]	<0.0001

¹ Unweighted frequency.

² Weighted percentage, except for the total column.

³ Total sample size of respondents with non-missing data.

⁴ The average number of days per week respondents exercise with at least moderate intensity.

⁵ P-values compare the demographic variables against the primary exposure in wave 1 (ENDS/Drug Use).

⁶ Currently use every day or some days.

⁷ In the past 30 days, any use of heroin, inhalants, solvents, or hallucinogens or use of non-prescribed prescription drugs such as painkillers, sedatives, or tranquilizers.

respiratory ailments compared to people who only used drugs, but this relationship was not significant (AOR 1.12 [95% CI 0.85–1.47]; $P = 0.43088$). Individuals who used both drugs and ENDS compared to people who do not use drugs or ENDS, had the largest odds of having respiratory problems among all drug use category comparisons (AOR 1.52 [95% CI 1.20–1.93], $P = 0.00054$).

When stratifying by sex of the individual, compared to females do not use drugs or ENDS, females who use both have 63% higher odds of an adverse respiratory condition (AOR 1.63 [95% CI 1.20–2.22], $P = 0.00172$) (Table 4). This same relationship for males is only on the boundary of significance, with males who use both having 39% higher odds of a respiratory condition compared to males who use neither (AOR 1.39 [95% CI 0.99–1.97], $P = 0.06001$).

Looking at individual respiratory outcomes, dual use of drugs and ENDS has the greatest odds of emphysema (AOR 1.96 [95% CI 1.17–3.27], $P = 0.01012$; Supplemental Table 4.3) and COPD (AOR 1.52 [95% CI 1.03–2.26], $P = 0.03688$; Supplemental Table 4.1) compared to people who do not use drugs or ENDS.

Looking at individual categories of drug use, dual use of cocaine/crack and ENDS (AOR 2.16 [95% CI 1.40–3.34], $P = 0.00051$) and dual use of painkillers and ENDS (AOR 1.57 [95% CI 1.16–2.13], $P = 0.00336$) have the greatest odds of developing adverse respiratory conditions compared to individuals who did not use either.

3.3. Dual ends and drug use and cardiovascular outcomes

Similarly, people who only used drugs had elevated odds of cardiovascular ailments compared to people who did not use drugs or ENDS (AOR 1.24 [95% CI 1.08–1.42], $P = 0.00214$) and compared to people who only used ENDS (AOR 1.22 [95% CI 1.04–1.42], $P = 0.0117$; Table 3). Those who used both drugs and ENDS, compared to people who do not use drugs or ENDS, carried 23% higher odds of having adverse cardiovascular outcomes (AOR 1.23 [95% CI 0.99–1.52], $P = 0.05717$; Table 3). People who only used ENDS did not have elevated odds of cardiovascular ailments compared to people who did not use drugs or ENDS (AOR 1.02 [0.90–1.15]; $P = 0.78548$). Dual consumption

Table 1B

Baseline (i.e., data from wave 1) summary statistics of adverse respiratory and cardiovascular conditions among participants by ENDS and Drug Use.

Characteristic	Electronic nicotine product ⁶ and/or illicit drug use ⁷					p-value ⁵
	Both n ¹ (% ²)	ENDS Only n ¹ (% ²)	Drug Only n ¹ (% ²)	Neither n ¹ (% ²)	Total n ¹ (% ²)	
Respiratory ³						<0.0001
Yes	43 (4.5)	188 (22.7)	369 (23.9)	2931 (15.8)	3531 (16.5)	
No	93 (71.0)	575 (77.3)	968 (76.1)	13,665 (84.2)	15,301 (83.5)	
Asthma						0.0008
Yes	28 (18.9)	119 (13.9)	226 (13.7)	2106 (11.1)	2479 (11.3)	
No	108 (81.1)	644 (86.2)	1111 (86.3)	14,490 (88.9)	16,353 (88.7)	
Chronic bronchitis						<0.0001
Yes	13 (8.4)	53 (6.3)	91 (6.3)	532 (2.8)	689 (3.0)	
No	123 (91.6)	710 (93.7)	1246 (93.7)	16,064 (97.3)	18,143 (97.0)	
COPD						<0.0001
Yes	6 (4.2)	47 (5.8)	79 (5.9)	471 (2.6)	603 (2.8)	
No	130 (95.8)	716 (94.2)	1258 (94.1)	16,125 (97.5)	18,229 (97.2)	
Emphysema						<0.0001
Yes	3 (1.7)	24 (2.6)	53 (3.1)	202 (1.1)	282 (1.2)	
No	133 (98.3)	739 (97.4)	1284 (97.0)	16,394 (99.0)	18,550 (98.8)	
Other lung or respiratory condition						<0.0001
Yes	12 (8.5)	25 (2.8)	64 (4.8)	321 (2.0)	422 (2.2)	
No	124 (91.5)	738 (97.2)	1273 (95.2)	16,275 (98.0)	18,410 (97.8)	
Cardiovascular ⁴						<0.0001
Yes	39 (26.5)	249 (32.1)	576 (48.6)	5441 (40.0)	6305 (40.2)	
No	97 (73.5)	513 (67.9)	758 (51.4)	11,158 (60.1)	12,526 (59.8)	
High blood pressure						<0.0001
Yes	28 (19.3)	165 (21.6)	419 (34.1)	3658 (26.9)	4270 (27.2)	
No	108 (80.7)	597 (78.4)	915 (65.9)	12,941 (73.1)	14,561 (72.8)	
High cholesterol						<0.0001
Yes	21 (15.4)	116 (15.1)	287 (26.8)	3005 (23.5)	3429 (23.4)	
No	115 (84.6)	646 (84.9)	1047 (73.2)	13,594 (76.5)	15,402 (76.6)	
Heart attack						0.1952
Yes	4 (2.9)	14 (1.6)	36 (2.7)	261 (1.9)	315 (1.9)	
No	132 (97.1)	748 (98.4)	1298 (97.3)	16,338 (98.1)	18,516 (98.1)	
Congestive heart failure						0.0575
Yes	5 (3.5)	11 (1.3)	24 (1.9)	188 (1.2)	228 (1.2)	
No	131 (96.6)	751 (98.8)	1310 (98.1)	16,411 (98.8)	18,603 (98.8)	
Stroke						0.0002
Yes	1 (0.8)	18 (2.1)	37 (3.8)	262 (1.7)	318 (1.8)	
No	135 (99.2)	744 (97.9)	1297 (96.2)	16,337 (98.3)	18,513 (98.2)	
Other heart condition						<0.0001
Yes	12 (7.8)	48 (5.1)	108 (9.5)	792 (5.6)	960 (5.8)	
No	124 (92.3)	714 (94.9)	1226 (90.5)	15,807 (94.4)	17,871 (94.2)	

This table displays results from Wave 1, where participants were asked if they have ever been diagnosed with any of the above respiratory or cardiovascular conditions.

¹ Unweighted frequency.

² Weighted percentage.

³ Ever having been diagnosed with one or more of the following five conditions: asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or some other lung or respiratory condition.

⁴ Ever having been diagnosed with any of the following six conditions: high blood pressure, high cholesterol, stroke, heart attack (i.e., myocardial infarction) and/or need for bypass surgery, congestive heart failure, or some other heart condition. Includes need for bypass surgery.

⁵ P-values compare the baseline variables against the primary exposure in wave 1 (ENDS/Drug Use).

⁶ Currently use every day or some days.

⁷ In the past 30 days, any use of heroin, inhalants, solvents, or hallucinogens or use of non-prescribed prescription drugs such as painkillers, sedatives, or tranquilizers.

of ENDS among people who used drugs did not result in greater odds of cardiovascular ailments (AOR 0.99 [95% CI 0.78–1.25, $P = 0.93967$]).

When stratifying by sex of the individual, compared to females do not use drugs or ENDS, females who use both have 25% higher odds of an adverse cardiovascular condition (AOR 1.25 [95% CI 1.02–1.53], $P = 0.03465$). Males who only use drugs have 24% higher odds of a respiratory condition compared to males who use neither (AOR 1.24 [95% CI 1.02–1.50], $P = 0.02734$).

Looking at individual cardiovascular outcomes, dual use of drugs and ENDS was significantly associated with the odds of having a stroke (AOR 2.48 [95% CI 1.19–5.15], $P = 0.01516$; Supplemental Table 4.10) and marginally significantly associated with high blood pressure (AOR 1.26 [95% CI 0.98–1.61], $P = 0.0732$; Supplemental Table 4.6) compared to people who do not use drugs or ENDS.

Looking at individual categories of drug use, dual use of painkillers and ENDS (AOR 1.28 [95% CI 1.02–1.60], $P = 0.0336$) had the greatest

odds of developing adverse cardiovascular conditions compared to individuals who did not use either. Individuals who only used painkillers had higher odds of developing an adverse cardiovascular condition compared to individuals who used neither painkillers nor ENDS (AOR 1.33 [95% CI 1.14–1.57], $P = 0.00045$) and compared to individuals who only used ENDS (AOR 1.31 [95% CI 1.10–1.56], $P = 0.00215$).

4. Discussion

Our findings are largely consistent with the existing literature, which has linked both drug use (Yamanaka and Sadikot, 2013; Radke et al., 2014; Tseng et al., 2013) and vaping (Werner et al., 2020; Layden et al., 2020; Thiri6n-Romero et al., 2019; Blagev et al., 2019) independently with respiratory system ailments. Interestingly, we found that drug consumption is more strongly associated with the presence of respiratory symptoms than vaping after accounting for demographic and other

Table 2A
Substance use and other health characteristics over time.

Characteristic	Wave 2 (2014–15) n ¹ (% ²)	Wave 3 (2015–16) n ¹ (% ²)	Wave 4 (2016–17) n ¹ (% ²)	Wave 5 (2017–18) n ¹ (% ²)	p-value ⁹
Total ³	18,893 (100)	18,893 (100)	18,893 (100)	18,893 (100)	
Electronic nicotine product ⁴ and/or illicit drug ⁵ use [Primary Exposure]					
Both	368 (0.9)	299 (0.8)	226 (0.6)	194 (0.5)	0.8918
E. nicotine products only	1985 (5.1)	1370 (3.6)	1198 (3.1)	1660 (4.3)	<0.0001
Drugs only	1318 (5.9)	1536 (6.6)	1244 (5.1)	464 (1.5)	<0.0001
Neither	15,161 (88.1)	15,679 (89.0)	16,249 (91.2)	16,600 (93.8)	<0.0001
Health insurance					<0.0001
Yes	15,828 (88.6)	16,045 (89.8)	16,051 (89.7)	16,109 (90.2)	
No	2998 (11.4)	2732 (10.2)	2756 (10.3)	2695 (9.8)	
Cigarette use ⁶					<0.0001
Current	6535 (18.3)	6436 (19.8)	6368 (19.5)	5980 (18.3)	
Former	3608 (23.8)	3971 (27.1)	4254 (28.2)	4787 (29.9)	
Experimental/No use	8160 (57.9)	6911 (53.1)	6782 (52.2)	6673 (51.8)	
Other tobacco use ⁶					<0.0001
Current	1458 (4.1)	1284 (3.4)	1279 (3.4)	1103 (3.0)	
Former	2750 (11.4)	3061 (11.1)	3542 (12.7)	4010 (14.0)	
Experimental/No use	12,433 (84.5)	14,350 (85.5)	13,918 (83.9)	13,635 (83.0)	
Cannabis Use ⁷					<0.0001
Yes	3145 (8.7)	3228 (9.2)	3421 (9.8)	3738 (11.0)	
No	15,766 (91.3)	15,690 (90.8)	15,486 (90.2)	15,180 (89.0)	
Heavy Alcohol Use ⁸					<0.0001
Yes	2186 (7.3)	2067 (7.2)	1917 (6.3)	1878 (6.4)	
No	16,685 (92.7)	16,808 (92.8)	16,973 (93.7)	17,002 (93.6)	
Diabetes					0.0626
Yes	1947 (13.1)	1917 (12.6)	1976 (13.0)	1969 (13.2)	
No	16,936 (87.0)	16,961 (87.4)	16,909 (87.0)	16,905 (86.8)	

¹ Unweighted frequency.

² Weighted (and adjusted for complex survey design) percentage.

³ The final analytic sample excluded all participants lost to follow-up.

⁴ Currently use every day or some days.

⁵ In the past 30 days, any use of heroin, inhalants, solvents, or hallucinogens or use of non-prescribed prescription drugs such as painkillers, sedatives, or tranquilizers.

⁶ Current: Currently smoke every day or some days and have smoked >100 cigarettes in a lifetime or used another form of tobacco regularly in the past. Former: Currently do not smoke but have smoked >100 cigarettes in a lifetime or used another form of tobacco regularly in the past. Experimental: Currently smoke or formerly have smoked but have smoked ≤100 cigarettes in lifetime or never used another form of tobacco regularly in the past. No Use: Have never smoked.

⁷ Used THC products in the last 30 days.

⁸ Consume more than 4 drinks per day for men and more than 3 drinks per day for women, on days in which alcohol was consumed in the last 30 days.

⁹ P-values test whether exposure variable response distribution change across the waves.

confounding risk factors. Drug consumption has also been associated with sleep-disordered breathing, chronic respiratory failure, COPD and asthma (Grischott et al., 2019; Rose et al., 2014; Winhusen et al., 2020).

We found ENDS significantly increases the odds of respiratory symptoms but did not observe an interactive effect of dual ENDS and drug use. Past literature found an even greater effect on this relationship, with people who use ENDS having 75% greater odds of chronic bronchitis, emphysema, or COPD than those who do not use ENDS (Osei et al., 2020). Of note, certain respiratory outcomes such as COPD and emphysema take time to develop, and thus it is possible that a 5-year study is limited in discerning the actual effect of ENDS.

This study confirms previous findings from the literature demonstrating the connections between illicit drug use and prescription drug misuse with adverse cardiac-related outcomes (Baldini et al., 2012; Chen and Ashburn, 2015; Khodneva et al., 2016; Aquaro et al., 2011; Kevil et al., 2019). In slight disagreement with the current literature, which poses probable, albeit inconclusive, associations between vaping and cardiovascular ailments (Qasim et al., 2017; Alzahrani et al., 2018; MacDonald and Middlekauff, 2019; Peruzzi et al., 2020), we did not find an association between exclusive ENDS use and adverse cardiovascular outcomes. Moreover, dual ENDS and drug use had no significant interactive effect. This finding is mainly inferred from the result that people who used drugs and ENDS had around the same odds of cardiovascular ailments relative to those who only used drugs. That said, when assessing the cardiovascular conditions variable into specific conditions, we saw evidence of a strong interactive effect for the risk of stroke.

Past research indicates men use illicit drugs at higher rates than women and are more likely to be diagnosed with SUDs (WDR, 2020). While men may be more likely to use illicit drugs, because of genetic and societal factors, women who do use illicit drugs tend to start later in life and increase usage faster than men. By the time they enter substance abuse treatment, they typically have more severe medical problems than men (Greenfield et al., 2010). While these medical problems are likely not the same as those tested in this research, the difference in how men and women typically engage with substances could help explain why our results show women are more at risk of adverse respiratory conditions compared to men when using drugs, ENDS, or both.

4.1. Limitations

The changes in the PATH questionnaire over time may introduce measurement bias in the study, particularly through the outcome of respiratory and cardiovascular variables. For example, in wave 4, participants were only asked about having cardiovascular and respiratory conditions if they had seen a doctor in the last 12 months. Since many respondents had not seen a doctor in this time frame, and thus were not asked about their health conditions in this wave, we had to adjust for the non-responses, theoretically impacting our results. While we standardized the time period for drug use to usage in the last 30 days, we did not account for the frequency of use within that time period; thus, there would be no distinction between a respondent who uses, for example, cocaine once a month versus every day. In addition, the study focuses on

Table 2B
Summary statistics of adverse respiratory and cardiovascular conditions over time.

Characteristic	Wave 2 (2014–15) <i>n</i> ¹ (% ²)	Wave 3 (2015–16) <i>n</i> ¹ (% ²)	Wave 4 (2016–17) <i>n</i> ¹ (% ²)	Wave 5 (2017–18) <i>n</i> ¹ (% ²)	p-value ⁵
Respiratory ³					0.001
Yes	2481 (11.5)	2591 (12.1)	2194 (10.9)	2296 (11.4)	
No	16,374 (88.5)	16,279 (87.9)	16,694 (89.1)	16,572 (88.6)	
Asthma					<0.0001
Yes	1468 (6.8)	1498 (7.0)	1200 (6.0)	1213 (6.1)	
No	17,387 (93.2)	17,372 (93.0)	17,688 (94.0)	17,655 (93.9)	
Chronic bronchitis					0.0011
Yes	602 (2.7)	606 (2.5)	493 (2.1)	476 (2.1)	
No	18,253 (97.3)	18,264 (97.5)	18,395 (97.9)	18,392 (97.9)	
COPD					<0.0001
Yes	574 (2.5)	665 (2.9)	684 (3.0)	840 (3.7)	
No	18,281 (97.5)	18,205 (97.1)	18,204 (97.0)	18,028 (96.3)	
Emphysema					0.9333
Yes	253 (1.0)	250 (1.0)	241 (1.0)	254 (1.0)	
No	18,602 (99.0)	18,620 (99.0)	18,647 (99.0)	18,614 (99.0)	
Other lung or respiratory condition					0.0475
Yes	408 (2.1)	467 (2.6)	391 (2.1)	385 (2.2)	
No	18,447 (98.0)	18,403 (97.4)	18,497 (97.9)	18,483 (97.8)	
Cardiovascular ⁴					<0.0001
Yes	5001 (31.2)	5137 (32.5)	4710 (30.3)	5152 (33.1)	
No	13,858 (68.8)	13,730 (67.5)	14,169 (69.7)	13,707 (66.9)	
High blood pressure					<0.0001
Yes	3614 (22.4)	3732 (23.0)	3488 (22.3)	3814 (24.6)	
No	15,245 (77.6)	15,135 (77.0)	15,391 (77.7)	15,045 (75.4)	
High cholesterol					0.0006
Yes	2444 (16.5)	2605 (17.7)	2395 (16.2)	2602 (17.3)	
No	16,415 (83.5)	16,262 (82.3)	16,484 (83.8)	16,257 (82.7)	
Heart attack ⁵					0.8261
Yes	146 (0.8)	126 (0.8)	140 (0.9)	150 (0.8)	
No	18,713 (99.2)	18,741 (99.2)	18,739 (99.1)	18,709 (99.2)	
Congestive heart failure					<0.0001
Yes	190 (1.0)	189 (1.1)	210 (1.4)	273 (1.7)	
No	18,669 (99.0)	18,678 (98.9)	18,669 (98.6)	18,586 (98.3)	
Stroke					0.0006
Yes	145 (0.7)	140 (0.8)	129 (0.7)	181 (1.1)	
No	18,714 (99.3)	18,727 (99.2)	18,750 (99.3)	18,678 (98.9)	
Other heart condition					0.0004
Yes	602 (3.8)	630 (3.9)	602 (4.0)	714 (4.7)	
No	18,257 (96.2)	18,237 (96.1)	18,277 (96.1)	18,145 (95.3)	

¹ Unweighted frequency.

² Weighted column percentage.

³ Being diagnosed with one or more of the following five conditions in the past 12 months: asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or some other lung or respiratory condition.

⁴ Being diagnosed with any of the following six conditions in the past 12 months: high blood pressure, high cholesterol, stroke, heart attack (i.e., myocardial infarction) and/or need for bypass surgery, congestive heart failure, or some other heart condition. Includes need for bypass surgery.

⁵ P-values test whether adverse cardiovascular and respiratory condition variables change across waves.

dual ENDS and drug use, but does not account for any respondents who may have used more than one drug. The study period was only 5 years; thus, certain health conditions that take longer to develop, or get noticed by a doctor, may not be accurately represented in the results. The PATH questionnaire does not ask about using individual drugs but categorizes various drugs. This prevents a more precise analysis of how usage of the individual drugs could impact the included outcomes. Finally, the PATH questionnaire is self-reported, which could lead to overestimating certain variables related to drug use. We also do not have medical records to verify the accuracy of responses related to medical diagnoses.

4.2. Clinical significance

The clinical implications of this study point to the need for prevention and intervention strategies among individuals who use ENDS and drugs to reduce their risk of respiratory and cardiovascular complications. In this study, we found that individuals who used both drugs and ENDS had higher odds of respiratory complications compared to those who only used ENDS or those who did not use drugs or ENDS at all. While we did not find a significant synergistic effect on the development

of respiratory and cardiovascular complications for individuals who use drugs and ENDS, we did find this effect when looking specifically at COPD and stroke. Based on the direction of many of the non-significant findings, it is likely that with a larger sample size or more follow-up time, synergistic interactions would be significant.

Our call to further research synergistic interactions between ENDS and drugs is based on known interactions between nicotine and drugs. For example, heroin-dependent people who smoke cigarettes tend to increase nicotine consumption, citing their desire to maintain heroin pleasure as the primary reason (Li et al., 2010). On the other direction, people who currently and formerly smoked were more likely to have an OUD and consume opioids at higher doses than people who did not smoke (Young-Wolff et al., 2017). This could result from nicotine-inducing CYP450 enzymes, many of which metabolize opioids (Yoon et al., 2015). Thus, in the case of opioids, dual use with nicotine tends to increase the amount of substances consumed.

5. Conclusions

The health effects of vaping and drugs have been independently

Table 3

Adjusted odds ratio and risk difference estimates of adverse respiratory and cardiovascular conditions for dual use of electronic nicotine products and drugs.

Characteristic	Primary Outcome							
	Adverse Respiratory Conditions ¹				Adverse Cardiovascular Conditions ²			
	AOR ³ (95% CI ⁴)	p-value	ARD ⁷ % (95% CI ⁴)	p-value	AOR ³ (95% CI ⁴)	p-value	ARD ⁷ % (95% CI ⁴)	p-value
Electronic nicotine products ⁵ and/or drug ⁶ use								
Electronic nicotine products only vs. Neither	<i>1.11</i> (0.99–1.23)	0.07758	0.55 (−0.08–1.17)	<i>0.08874</i>	1.02 (0.90–1.15)	0.78548	0.27 (−1.68–2.21)	0.7863
Drugs only vs. Neither	1.36 (1.15–1.60)	0.00027	1.83 (0.73–2.94)	0.00115	1.24 (1.08–1.42)	0.00214	3.63 (1.20–6.06)	0.00337
Drugs only vs. Electronic nicotine products only	1.23 (1.03–1.47)	0.02488	1.29 (0.12–2.45)	0.03035	1.22 (1.04–1.42)	0.0117	3.36 (0.72–6.00)	0.01254
Both vs. Electronic nicotine products only	1.37 (1.09–1.73)	0.00698	2.09 (0.39–3.79)	0.01618	<i>1.21</i> (0.97–1.51)	<i>0.09642</i>	3.20 (−0.71–7.10)	0.10878
Both vs. Drugs only	1.12 (0.85–1.47)	0.43088	0.80 (−1.24–2.84)	0.44221	0.99 (0.78–1.25)	0.93967	−0.16 (−4.41–4.08)	0.93964
Both vs. Neither	1.52 (1.20–1.93)	0.00054	2.63 (0.86–4.41)	0.00357	<i>1.23</i> (0.99–1.52)	<i>0.05717</i>	<i>3.47</i> (−0.32–7.25)	<i>0.07258</i>

Bolded aOR/RD indicates statistical significance at a significance level of 5%. Italicized aOR/RD indicates borderline significance.

¹ Being diagnosed with one or more of the following in the past 12 months: asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or some other lung or respiratory condition.

² Being diagnosed with one or more of the following in the past 12 months: high blood pressure, high cholesterol, stroke, heart attack (i.e., myocardial infarction) and/or need for bypass surgery, congestive heart failure, or some other heart condition.

³ AOR: adjusted odds ratio: Adjusted for age, gender, race/ethnicity, region of residence, marital status, education, income, employment status, availability of health insurance, cigarette smoking, duration of smoking, heavy alcohol consumption, weight status, and diabetes.

⁴ CI: confidence interval.

⁵ Currently use every day or some days.

⁶ In the past 30 days, any use of heroin, inhalants, solvents, or hallucinogens or use of non-prescribed prescription drugs such as painkillers, sedatives, or tranquilizers.

⁷ ARD: adjusted risk difference. Adjusted for age, gender, race/ethnicity, region of residence, marital status, education, income, employment status, availability of health insurance, cigarette smoking, duration of smoking, heavy alcohol consumption, weight status, and diabetes.

Table 4

Adjusted odds ratio estimates of adverse respiratory and cardiovascular conditions for dual use of electronic nicotine products and drugs stratified by Sex.

Characteristic	Primary Outcome							
	Adverse Respiratory Conditions ¹				Adverse Cardiovascular Conditions ²			
	Male		Female		Male		Female	
	AOR ³ (95% CI ⁴)	p-value	AOR ³ (95% CI ⁴)	p-value	AOR ³ (95% CI ⁴)	p-value	AOR ³ (95% CI ⁴)	p-value
Electronic nicotine products ⁵ and/or drug ⁶ use								
Electronic nicotine products only vs. Neither	1.05 (0.87–1.27)	0.6031	1.15 (1.01–1.31)	0.04057	0.99 (0.85–1.16)	0.94437	1.02 (0.85–1.21)	0.86807
Drugs only vs. Neither	<i>1.21</i> (0.98–1.50)	<i>0.08357</i>	1.46 (1.16–1.83)	0.00114	1.24 (1.02–1.50)	0.02734	1.25 (1.02–1.53)	0.03465
Drugs only vs. Electronic nicotine products only	1.15 (0.86–1.54)	0.34608	1.27 (1.01–1.60)	0.04506	<i>1.25</i> (0.99–1.57)	<i>0.05581</i>	<i>1.23</i> (0.97–1.56)	<i>0.09415</i>
Both vs. Electronic nicotine products only	1.33 (0.92–1.91)	0.12833	1.42 (1.05–1.92)	0.02097	<i>1.34</i> (0.98–1.84)	<i>0.06536</i>	1.05 (0.75–1.46)	0.79014
Both vs. Drugs only	1.15 (0.78–1.72)	0.4806	1.12 (0.78–1.59)	0.53663	1.08 (0.76–1.54)	0.67916	0.85 (0.59–1.23)	0.39143
Both vs. Neither	<i>1.39</i> (0.99–1.97)	<i>0.06001</i>	1.63 (1.20–2.22)	0.00172	<i>1.34</i> (0.98–1.81)	<i>0.06316</i>	1.06 (0.79–1.42)	0.6832

Bolded aOR indicates statistical significance at a significance level of 5%, and italicized indicates borderline significance.

¹ Being diagnosed with one or more of the following in the past 12 months: asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or some other lung or respiratory condition.

² Being diagnosed with one or more of the following in the past 12 months: high blood pressure, high cholesterol, stroke, heart attack (i.e., myocardial infarction) and/or need for bypass surgery, congestive heart failure, or some other heart condition.

³ AOR: adjusted odds ratio: Adjusted for age, gender, race/ethnicity, region of residence, marital status, education, income, employment status, availability of health insurance, cigarette smoking, duration of smoking, heavy alcohol consumption, weight status, and diabetes.

⁴ CI: confidence interval.

⁵ Currently use every day or some days.

⁶ In the past 30 days, any use of heroin, inhalants, solvents, or hallucinogens or use of non-prescribed prescription drugs such as painkillers, sedatives, or tranquilizers.

studied, but not much is known concerning the acute and chronic effects of dual ENDS and drug use on the development of cardiovascular and respiratory symptoms. With ENDS growing in popularity, especially among young adults, and the ongoing drug epidemic, the effects of combined use on long-term health outcomes remain less understood. Future research using more extended time periods of study and accounting for more specific frequency and duration of use is required better to understand the potential interactive effects of dual use.

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Author Contributors

Each author contributed to the submission in the following manner. Study Concept: FQ Data Management: FQ, AN, WAB Statistical Analysis: FQ, AN, WAB Interpretation of data: FQ, AN, WAB, SA, KE Initial

drafting of manuscript: FQ, AN Editing/revision of manuscript: FQ, AN, WAB, SA, KE. All authors have made significant contributions to this manuscript and have approved this version for submission.

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Declaration of Competing Interest

None.

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Supplementary materials

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