Association between e-cigarette exposure and ventilation homogeneity in young adults: a cross-sectional study

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Lung clearance index may be a useful biomarker to measure the effects of e-cigarette use on ventilation distribution and to track early functional impairment of the small airways https://bit.ly/3CteODd

Cite this article as: Stanojevic S, Yung MH, Sahin B, *et al*. Association between e-cigarette exposure and ventilation homogeneity in young adults: a cross-sectional study. *Eur Respir J* 2025; 65: 2401675 [DOI: 10.1183/13993003.01675-2024].

This article has an editorial commentary: https://doi.org/10.1183/13993003.02482-2024

Received: 23 Aug 2024
Accepted: 8 Nov 2024

Abstract

Background The number of young people who use e-cigarettes is rising. It remains unclear whether e-cigarette use impairs lung function. We aimed to compare ventilation distribution between young adults exposed to e-cigarettes and an unexposed group.

Methods Study participants included otherwise healthy young adults (18–24 years) who self-reported e-cigarette use and unexposed participants who had no history of e-cigarette, tobacco or cannabis exposure. Exposure to e-cigarettes was defined using three measures: 1) ever-exposed, 2) daily use and 3) puff frequency, which includes none (unexposed), minimal (<2 puffs·h^{-1}), moderate (3–4 puffs·h^{-1}) and heavy (⩾5 puffs·h^{-1}). Ventilation distribution was measured using the multiple-breath washout test and reported as lung clearance index (LCI).

Results A total of 93 participants were recruited; 38 unexposed and 41 exposed participants had LCI measures. The exposed group consisted predominately of participants who used flavoured e-liquids (94.5%) that contained nicotine (93.5%). The magnitude and direction of the difference in LCI across the exposure definitions was similar. Compared with the unexposed group, in the unadjusted models LCI was higher in those with any e-cigarette use (mean difference 0.15, 95% CI −0.004–0.31), daily users (mean difference 0.10, 95% CI −0.08–0.28) and heavy users (mean difference 0.22, 95% CI 0.03–0.41).

Conclusion This preliminary work suggests that LCI may be a useful biomarker to measure the effects of e-cigarette use on ventilation distribution and to track early functional impairment of the small airways.

Introduction

E-cigarette use (*i.e.* vaping) amongst adolescents and young adults is rising in many places around the world [1]. E-cigarettes are promoted for harm reduction and as an alternative to combustible tobacco cigarettes [2]; however, the safety of these products remains unclear.

The potential effects of e-cigarette use on the pulmonary system have been recently summarised in two review articles [3, 4]. The combination of *in vitro* and *in vivo* evidence suggests that vaporisation of e-cigarette liquids (including glycol, vegetable glycerine, propylene, ethylene glycol, nicotine and chemicals required to create over 15 000 flavours) is associated with chronic inflammation, impaired mucociliary clearance and oxidative stress, amongst other cellular changes. The deposition of particles is likely to occur in the peripheral airways (airways <2 mm), and the early effects of chronic inflammation and impaired mucociliary clearance are likely to manifest in altered gas mixing and worsening ventilation inhomogeneity in the lung periphery [5, 6]. Standard pulmonary function tests (*e.g.* spirometry), predominately measuring airflow through large airways, are unlikely to detect early impairments in lung function that occur in the peripheral airways [7–10].

The multiple-breath washout (MBW) test is a sensitive measure of ventilation distribution, which reflects gas mixing efficiency and is particularly sensitive to peripheral airway pathology [11–13]. Previous research has shown that in people with obstructive lung conditions, the primary measure of ventilation distribution (*i.e.* lung clearance index (LCI)) is impaired many years before spirometry outcomes are, and is strongly correlated with both structural and functional changes observed using imaging tools [7, 14–17]. Based on the hypothesised mechanism of the effects of e-cigarette use on the pulmonary system, we aimed to compare ventilation distribution between otherwise healthy young adults who self-reported exposure to e-cigarettes and an unexposed group. We hypothesise that the exposed group will have worse ventilation inhomogeneity compared with the control group.

Methods

Study design

This prospective cross-sectional observational study was conducted from September 2022 to February 2024 in Halifax, NS, Canada. The study was approved by the Dalhousie University Health Sciences Research Ethics Board (2020-5077) and Nova Scotia Health Research Ethics Board (1029054). Written informed consent was obtained from each participant. Questionnaires and pulmonary function tests were performed at the same study visit.

Consultations with persons with lived experience

Two sessions with young people who use e-cigarettes were held in October 2020 to pilot the study protocol and questionnaires. Participants provided feedback on the terminology used and wording of each question to ensure these reflected current products and colloquial language. Due to the rapid changes in e-cigarette products available during the study period, two additional sessions were conducted in July 2023. The inclusion criteria and questionnaires were revised to reflect how products were used in the community (*e.g.* participants were not required to exclusively use pod-style devices as many e-cigarette users purchased liquid refillable devices or purchased disposable products).

Participant recruitment

Participants were recruited from the community using posters, social media posts and word of mouth. A CAD 50 gift card was provided as reimbursement to all participants who attended a study visit. The sample was a convenience sample and most of the study participants were university students or staff members.

Participants were eligible if they were 18–24 years of age and did not have a history of physician-diagnosed respiratory disease (*e.g.* asthma). Participants who self-reported e-cigarette use were considered exposed. Initially, participants who used combustible tobacco cigarettes and cannabis products were excluded; however, due to a high percentage of dual users in the community the exclusion criteria were modified after the first 20 participants completed the study. Healthy participants who did not report previous e-cigarette, combustible tobacco cigarette or cannabis products and did not report respiratory symptoms in the previous 2 weeks were considered unexposed.

Exposure definition

Based on the input from the community members, exposure was classified using three definitions: 1) self-reported ever-users of e-cigarettes, irrespective of duration and frequency, were considered as "ever-exposed"; 2) self-reported daily users; and 3) self-reported puff frequency, measured as the typical number of puffs taken per hour: <2 puffs·h^{-1} (minimal), 3–4 puffs·h^{-1} (moderate) and ⩾5 puffs·h^{-1} (heavy).

Outcome measures

Ventilation distribution was measured using the nitrogen MBW test according to the existing consensus statement and published protocols [18, 19]. The MBW test is performed during normal tidal breathing. During the test, the participant breathes 100% oxygen, and with each tidal breath the resident nitrogen in the lungs is washed out. The breath-by-breath concentration of nitrogen is calculated based on the oxygen and carbon dioxide that is directly measured by the device. The primary outcome, lung clearance index ($LCI_{2.5}$), reflects the number of lung turnovers required to reduce the end-tidal gas concentration of nitrogen to 1/40 (2.5%) of its starting concentration. LCI is calculated as the cumulative exhaled volume of gas divided by the functional residual capacity (FRC). The FRC reflects the volume within the lungs at the end of a tidal breath. A higher LCI indicates worse ventilation inhomogeneity and thus worse lung function. A test typically takes 30 min to perform, which includes at least two technically acceptable trials and a washout period between trials. Each trial was reviewed retrospectively for quality using a standardised protocol by a blinded reviewer (S. Stanojevic) [19]. In healthy individuals, LCI follows a normal distribution, whereas the distribution can be highly right skewed in people with advanced lung disease. There are published reference ranges for LCI and the upper limit of normal varies with age [20].

In addition, lung volumes and flows were measured using spirometry. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC were measured (without administration of bronchodilator) and reported according to current recommendations [21]. Spirometry outcomes were interpreted using Global Lung Function Initiative race-neutral reference equations [22]. All lung function measurements were performed according to international technical standards [11, 23] using an Exhalyzer D with Spiroware version 3.3.2 (Eco Medics, Duernten, Switzerland).

Questionnaire

Each participant filled out a questionnaire regarding their sociodemographic characteristics as well as previous environmental exposures (*e.g.* second-hand tobacco exposure and biomass cooking fuels). The questionnaire included frequency and duration of combustible tobacco use, combustible cannabis use and other inhaled exposures, as well as e-cigarette use habits (frequency, duration, device, puffs per hour, nicotine concentration and flavour use). We specifically asked whether participants were exposed to e-liquids that contained cannabis products.

Sample size

The study was initially powered to detect a 0.7-unit difference in LCI between exposed and unexposed groups for males and females separately, assuming a standard deviation of 0.5 units in the unexposed group and 1.0 units in the exposed group.

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the study population. Multivariable linear regression models were used to compare differences in MBW and spirometry outcomes between groups before and after adjusting for potential confounding factors (including combustible tobacco use and cannabis use). Sensitivity analyses included analyses of exclusive e-cigarette users, participants born in Canada and a sex-stratified analysis. A complete case analysis was conducted. Differences between groups were interpreted based on the magnitude and direction of the estimate, with 95% confidence intervals to facilitate interpretation of the precision of the estimates. Linear regression was used to describe the relationship between LCI and FEV_1 % pred. The models were adjusted for potential confounders (tobacco cigarette use, cannabis use and country of birth). The study was reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [24].

Results

A total of 93 participants (47 unexposed and 46 exposed) met the study inclusion criteria, 79 participants (38 unexposed and 41 exposed) had valid MBW tests, and 63 participants (30 unexposed and 33 exposed) had valid MBW and spirometry tests (figure 1). Overall, 85.0% (n=79) of all MBW and 83.9% (n=78) of all spirometry tests were deemed as acceptable. Three participants were not able to perform either MBW or spirometry. The exposed and unexposed groups were similar in terms of age, height and body mass index (table 1), whereas the exposed group had a higher proportion of participants born in Canada compared with the unexposed group.

Within the exposed group, participants reported e-cigarette use for a median (interquartile range) of 3 (2–4) years. More than a third of all exposed participants (39.0% (n=16)) exclusively used e-cigarettes, while 29.3% (n=12) reported smoking tobacco cigarettes (more than 100 lifetime cigarettes) and 51.2% (n=21) reported concurrent combustible cannabis product use. Participants who used combustible cannabis products also reported using e-liquids with tetrahydrocannabinol (THC) in combination with flavoured e-liquids. Over half of the participants in the exposed group reported daily e-cigarette use (68.3% (n=28)) and taking $\geqslant 5$ puffs·h^{-1} (58.5% (n=24)) (table 2). Within the exposed group, nearly all participants reported using flavours (92.7% (n=38)) and nicotine (95.1% (n=39)) in e-liquids. Participants reported using a combination of fruit, candy/dessert and mint flavours as well as flavourless e-liquids, and all reported using more than one type of flavour (results stratified by flavour or flavour type are not reported).

Multiple-breath washout

Of the participants with acceptable MBW data (n=79), LCI was higher (*i.e.* worse) in the exposed group compared with the unexposed group (table 3). Participants in the heaviest exposure group ($\geqslant 5$ puffs·h^{-1}) on average had the highest LCI (table 3). The magnitude and direction of the difference in LCI was consistent between exposure definitions (table 4 and figure 2). Compared with the unexposed group, LCI was higher in participants with any e-cigarette use (mean difference 0.15, 95% CI −0.004–0.31), daily users (mean difference 0.10, 95% CI −0.08–0.28) and heavy users (mean difference 0.22, 95% CI 0.03–0.41).

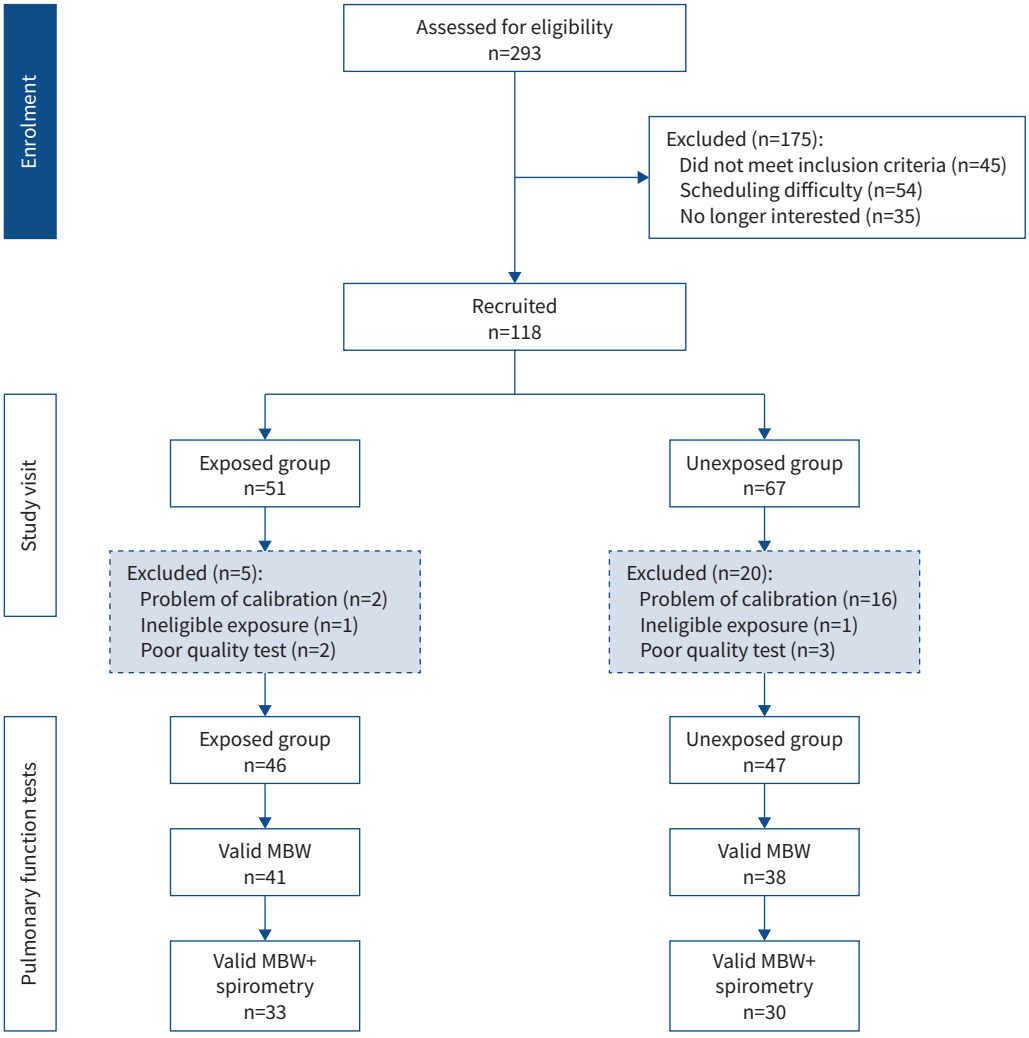

FIGURE 1 Summary of study participant recruitment and exclusion criteria. A total of 79 participants had acceptable multiple-breath washout (MBW) data. A total of 63 participants had acceptable MBW and spirometry data.

Adjusted analysis

Multivariable linear regression models for each exposure definition are presented in table 4. In all cases adjustment for combustible tobacco cigarette exposure or cannabis use attenuated the measure of effect. For example, adjusting for combustible tobacco cigarette exposure, the mean difference in LCI between the heavy exposure group and unexposed group was 0.19 (95% CI −0.01–0.40), and after adjustment for cannabis was 0.15 (95% CI −0.09–0.38).

TABLE 1 Summary of study population demographic characteristics

	Unexposed group (n=38)	Exposed group (n=41)
Female	18 (47.4)	21 (51.2)
Age (years)	20.8±1.7	20.5±1.8
Height (cm)	172.8±9.6	169.8±9.5
Body mass index (kg·m^{-2})	25.3±3.6	24.8±5.6
Born in Canada	16 (42.1)	22 (53.7)

Data are presented as n (%) or mean±SD.

TABLE 2 Summary of exposure history in the e-cigarette-exposed group (n=41)

Vaping history (years)	3 (2–4)
E-cigarette flavour use	38 (92.7)
E-cigarette nicotine use	39 (95.1)
Nicotine concentration	
0 mg	2 (5.0)
1–9 mg	4 (10.0)
10–49 mg	23 (57.5)
⩾50 mg	11 (27.5)
Cannabis product use	21 (51.2)
Combustible tobacco cigarette use (>100 cigarettes ever)	12 (29.3)
Self-reported puff frequency (puffs·h^{-1})	
<2 (minimal)	9 (22.0)
3–4 (moderate)	8 (19.5)
⩾5 (heavy)	24 (58.5)
E-cigarette use	
Daily	28 (68.3)
Weekly	9 (22.0)
Monthly	4 (9.8)

Data are presented as median (interquartile range) or n (%).

Sensitivity analyses

The magnitude of LCI difference was consistent in the subset of participants who did not use combustible tobacco cigarettes (mean difference 0.19, 95% CI 0.08–0.37; n=38 unexposed, n=19 exposed) and in the subset of participants born in Canada (mean difference 0.23, 95% CI 0.08–0.53; n=16 unexposed, n=14 exposed).

Male participants reported more combustible tobacco cigarette and cannabis product use, and a longer mean±SD e-cigarette use history (3.2±1.48 years) compared with female participants (2.48±1.03 years). Sex-stratified analyses showed the difference in LCI between exposed and unexposed male participants (mean difference 0.18, 95% CI 0.05–0.42) was larger than in female participants (mean difference 0.14, 95% CI 0.07–0.35).

Spirometry

Both FEV_1 and FVC % pred were higher (*i.e.* better) in the exposed group compared with the unexposed group, whereas FEV_1/FVC was similar between the two groups (table 2). Multivariable regression between e-cigarette exposure and each of the three spirometry outcomes did not detect a statistically significant association for any of the three exposure definitions (supplementary table S1); in all comparison the unexposed group had better spirometric lung function than the exposed group. For each unit increase in LCI, the FEV_1 % pred decreased by −11.2% (95% CI −20.2– −2.2%). The direction and magnitude of this association was similar even after adjustment for tobacco use, cannabis use and country of birth (slope coefficient −12.0, 95% CI −21.6– −2.4). The adjusted model only explained 17.7% of the variance in FEV_1 % pred.

TABLE 3 Descriptive summary of multiple-breath washout (MBW) and spirometry outcomes in each exposure group

	Unexposed group	Exposed group	Daily use	⩾5 puffs·h^{-1}
MBW	n=38	n=41	n=28	n=24
LCI	6.06±0.4	6.22±0.3	6.18±0.3	6.28±0.4
FRC (L)	2.92±0.9	2.85±0.8	2.90±0.8	2.66±0.8
Spirometry	n=30	n=33	n=21	n=21
FEV_1 % pred	99.8±14.3	102.8±13.4	105.2±12.8	101.8±12.8
FVC % pred	108.4±16.1	107.6±15.4	112.1±13.9	108.2±16.2
FEV_1/FVC	0.80±0.1	0.84±0.1	0.83±0.1	0.83±0.1

Data are presented as mean±SD, unless otherwise stated. LCI: lung clearance index; FRC: functional residual capacity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

TABLE 4 Multivariable regression models comparing lung clearance index (LCI) between unexposed and exposed participants

	Unexposed (n)	Exposed (n)	LCI mean difference (95% CI)		
			Unadjusted	Adjusted for tobacco use	Adjusted for cannabis use
Ever-exposed	38	41	0.15 (−0.004–0.31)	0.13 (−0.05–0.30)	0.10 (−0.10–0.29)
Daily	38	23	0.10 (−0.08–0.28)	0.10 (−0.10–0.29)	0.08 (−0.15–0.31)
Heavy users	38	24	0.22 (0.03–0.41)	0.19 (−0.01–0.40)	0.15 (−0.09–0.38)

Exposure was defined using three definitions: 1) self-reported ever-users of e-cigarettes, irrespective of duration and frequency, were considered as "ever-exposed"; 2) self-reported daily users, and 3) self-reported puff frequency, measured as heavy users (⩾5 puffs·h^{-1}). In each comparison the exposure group is compared with never-users.

Symptoms

Respiratory symptoms were recorded with the revised questionnaire only (n=21 in the exposed group). All but one participant in the exposed group (95% (n=20/21)) reported at least one respiratory symptom (either cough, mucous and phlegm, trouble breathing, sore lungs/throat, shortness of breath, chest pain or difficulty running). The most commonly reported symptom was cough (57% (n=12/21)), followed by mucous and phlegm (48% (n=10/21)), difficulty running (38% (n=8/21)) and shortness of breath (33% (n=7/21)). More than half (67% (n=14/21)) of participants reported at least one physical symptom (either nausea, upset stomach, dizziness or lack of endurance) and 52% (n=11/21) reported a cognitive symptom (either withdraw, anxiety, depression or dependency).

Discussion

Otherwise healthy young adults with relatively short exposure to daily e-cigarette use had on average worse ventilation inhomogeneity compared with healthy controls. Young adults who use e-cigarettes daily and were considered heavy users (⩾5 puffs·h^{-1}) had the highest LCI values and the largest differences in ventilation inhomogeneity relative to the unexposed group. Adjustment for potential confounding factors attenuated the magnitude of association, but the overall direction and magnitude of association were similar. These preliminary findings suggest that LCI may be a useful marker of physiological impairment of lung function in people who are exposed to e-cigarettes.

The overall difference in LCI between the e-cigarette-exposed and -unexposed groups was small but not negligible. In the subset of participants with recorded symptom data, nearly all reported at least one respiratory symptom. Further, the magnitude of difference observed between exposed and unexposed participants was dose dependent and consistent across several sensitivity analyses. Although individual LCI values were within the range observed in healthy individuals, the group differences suggest early changes in lung function after a relatively short exposure history (1–5 years). The average LCI observed in the exposed group was lower than observed in individuals diagnosed with COPD or bronchiectasis (LCI has been reported as 9–12 in these populations) [9, 25]. Previous studies were, however, done using a different device/software/tracer gas and so are not directly comparable. One longitudinal study has shown that an elevated LCI in early adulthood in the general population was associated with future development of obstructive pulmonary impairment and greater risk of hospitalisations for respiratory symptoms [26].

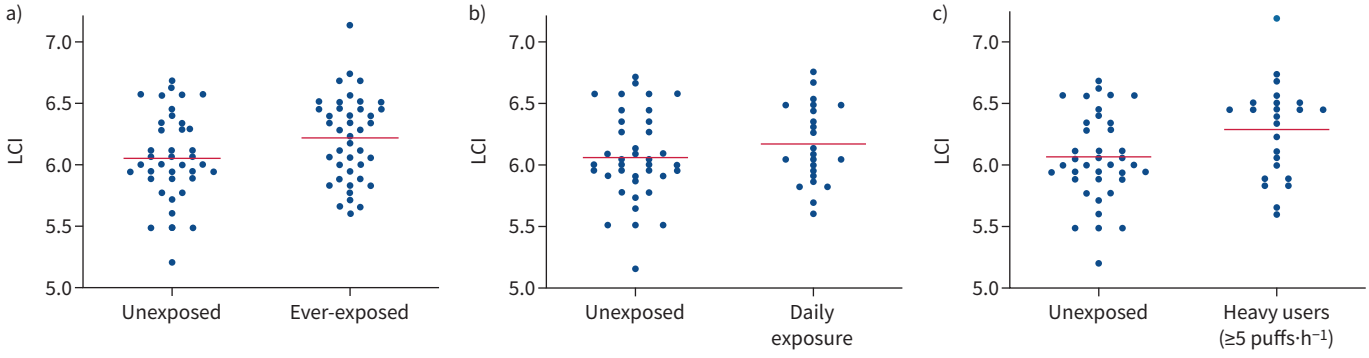

FIGURE 2 Stem-and-leaf plots of lung clearance index (LCI) between exposure groups: a) ever-exposed *versus* unexposed, b) daily exposure *versus* unexposed and c) heavy users (⩾5 puffs·h^{-1}) *versus* unexposed. The red line represents the mean LCI in each group.

Further, our findings align with the evidence published by Khizakke Puliyakote *et al.* [27] who observed changes in both ventilation (measured by relative dispersion) and perfusion (assessed using proton magnetic resonance imaging) in nine individuals exposed to e-cigarettes. The observed differences in ventilation inhomogeneity align mechanistically with evidence generated from *in vitro* and animal studies demonstrating increased inflammatory cytokines [28–30], decreased mucociliary clearance [31, 32] and airway hyperactivity [33–35].

Overall, the duration of exposure was relatively short (ranging between 1 and 5 years) and some individuals had very limited exposure, which may explain the small magnitude of difference between the groups. Further, the exposed group was heterogeneous in terms of the exposure itself, including the types of devices used, types of flavours, nicotine concentrations and cannabis product use. Individuals who exclusively used flavoured nicotine e-liquids, without any use of cannabis/THC products or combustible tobacco cigarettes, were relatively challenging to recruit in this age group. Nonetheless, the sensitivity analysis limited to the exclusive e-cigarette group was consistent in magnitude to the main results. The participants in this study are distinct from those who were reported to have e-cigarette or vaping use associated lung injury (EVALI) in 2019–2020 as most of our study participants used commercially available devices and e-liquids [36].

The long latency period between inhaled exposures and measurable morbidity and mortality established with inhaled environmental exposure, but unknown for e-cigarette use, may be another reason for the small magnitude of differences, especially the lack of difference between spirometry outcomes. Airflow obstruction, measured by spirometry, generally reflects impairment of the large airways, whereas ventilation inhomogeneity is sensitive to changes in the peripheral airways. At least two studies have directly compared spirometry outcomes between daily e-cigarette users and unexposed participants [37, 38]. Meo *et al.* [38] compared 30 male e-cigarette users (daily for at least 6 months) with unexposed participants and found reduced absolute measures of lung function (FEV_1, FEV_1/FVC and forced expiratory flow at 25–75% of FVC). Polosa *et al.* [37] reported a lower FEV_1 % pred (95.9% (n=9)) in e-cigarette users compared with unexposed participants (104.8% (n=12)) but the analyses were underpowered to detect significant differences between the groups. The limited population characteristics provided by both studies limited direct comparisons to understand potential differences in the characteristics of the unexposed groups.

A consistent commentary within the current literature is that e-cigarette exposure is very challenging to define and prone to measurement bias [39, 40]. The reliance on self-reported exposure may have underestimated the true exposure. After multiple consultation sessions with community partners, we defined e-cigarette exposure using puffs per hour to differentiate between casual and habitual users. Other studies have tried to create a pack-years equivalent definition, based on the number of days e-cigarettes are used, the times a device is picked up and the number of puffs per use [27]. Young people who contributed to our study design shared that it is difficult to recall e-cigarette use based on types of questions, as they do not reflect the typical ways in which people use e-cigarettes. Alternatively, others have suggested that the number of times e-liquid is replenished may provide a more accurate measure of e-liquid consumption [39–41]. Community partners from a wide age range (16–30 years) highlighted that even fourth-generation “pod” style devices can be modified, and e-liquids can be customised such that the exact flavour, nicotine concentration and quantity of e-liquid is difficult to quantify. Further, during our consultations young people noted that many individuals share devices, making it further challenging to track the number of “pods” used. Limiting the exposure definition to “ever” used e-cigarettes, or even “daily use”, may mask important dose-dependent associations. Self-report based on behaviour (*e.g.* how soon after you wake up do you want to use your e-cigarette) [42] or objective measures of the volatolomic profile of exhaled breath may provide more reliable measures of exposure.

Limitations

Overall, the study sample size was a small convivence sample, and participants were exposed to a range of e-cigarette devices and e-liquids, which limited the generalisability of these findings. During the 2-year study period, the products available (both devices and e-liquids) changed rapidly and it was not possible to attribute the exposure for an individual to a single device or e-liquid. We were unable to investigate whether any of these specific products were associated with worse ventilation inhomogeneity. There are now thousands of available flavours and vendors, and it was not possible to separate individual exposure to a specific flavour (or category of flavours) from any use. The limited sample size also limited the statistical power and the number of factors we could adjust for. The differences observed may be confounded by factors that we did not measure (*e.g.* early-life exposures and socioeconomic status). The exposure groups differed in terms of geographical ancestry and potentially unmeasured confounding factors such as socioeconomic status. Sensitivity analyses limited to the subgroup of study participants born in Canada

showed slightly larger differences in LCI. Further, in our study population many of the heavy e-cigarette users also used cannabis in various forms and it was not possible to completely separate the effects of e-liquid flavours that contain nicotine from those that contain forms of cannabis. As the population of e-liquid only users is small, especially in Canada where cannabis products are legal, it will be important to record details regarding cannabis exposure in order to conduct adequately powered adjusted analysis. In our subgroup (e-cigarette only users) analysis and adjusted regression analysis, the magnitude of difference between exposed and unexposed participants was similar, albeit the precision of the estimates was much wider in both of these analyses.

Although we observed statistically significant differences in LCI between the exposure groups, the clinical significance of these findings is not fully clear. These results provide details with respect to study design features, such as study population characteristics (inclusion criteria), sample size estimates and potential confounders for future studies. In addition, future longitudinal studies that include both measures of LCI and imaging studies may help to further explain the underlying pathophysiology and clinical significance.

Conclusions

This preliminary work suggests LCI may be a useful biomarker to measure the effects of e-cigarette use on ventilation distribution and to track early functional impairment of the small airways.

Data availability: De-identified data are available upon request.

Ethics statement: The study was approved by the Dalhousie University Health Sciences Research Ethics Board (2020-5077) and Nova Scotia Health Research Ethics Board (1029054).

Conflict of interest: S. Stanojevic reports grants from the ATS (Chair: ATS/ERS Updated Technical Standard on PFT interpretation), consulting fees from Chiesi Farmaceutici, speaker fees from Vyaire Medical, participation on a medical advisory board with Ndd Technologies, leadership roles with the ATS (Pulmonary Function Testing Committee) and ERS (Global Lung Function Initiative), and other non-financial interests as a statistical editor for *Thorax*, editorial board member for the *European Respiratory Journal*, and junior associate editor for the *Canadian Journal of Respiratory, Critical Care and Sleep Medicine*. The remaining authors have no potential conflicts of interest to disclose.

Support statement: This work was supported by Research Nova Scotia and the Canadian Research Initiative on Substance Matters (CRISM). Funding information for this article has been deposited with the Crossref Funder Registry.

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