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The Canadian Lung Outcomes in Users of Vaping Devices (CLOUD) Study: protocol for a prospective, observational cohort study

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ABSTRACT

Introduction The rapid growth in popularity of e-cigarettes over the past decade has prompted concerns about their impact on long-term respiratory health. Small airway injury is suspected to be a direct consequence of e-cigarette use and may be quantifiable by novel structural and functional diagnostic modalities.

Methods and analysis In a multicentre observational longitudinal study, participants will be enrolled in either an adolescent (ages ≥12 and <19 years) or an adult arm (≥19 years old) and followed over 3 years across three time points (baseline, 18 months and 36 months). In the adolescent arm, a total of 50 e-cigarette and 50 non-e-cigarette users will be enrolled across 4 sites. In the adult arm, a total of 100 e-cigarette users, 100 non-e-cigarette users, and an additional 100 combustible cigarette-only users and 100 dual combustible cigarette-e-cigarette users will be enrolled across 5 sites. Participants will undergo respiratory questionnaires, pulmonary function tests, oscillometry, cardiopulmonary exercise testing, hyperpolarised 129-xenon gas MRI and blood collection. In adolescent participants only, multiple breath washout and induced sputum collection will be performed. Adult participants will also undergo inspiratory/expiratory chest CT and bronchoscopy. The primary endpoint will be a composite of small airway dysfunction according to oscillometry, cardiopulmonary testing and/or chest imaging parameters.

Ethics and dissemination This protocol has been approved by The University of British Columbia-Providence Health Care Research Ethics Board (Certificate H24-00374). The use of hyperpolarised 129-xenon gas in this study has been approved by Health Canada (Certificate HC6-024-c291776). Written documentation of informed consent will be required prior to study initiation. We will seek to enrol adolescent participants who are capable of providing informed consent with an optional support statement from a parent encouraged but not required. Study findings will be disseminated to medical/scientific audiences through scientific conferences and published manuscripts respecting the Strengthening the Reporting of Observational Studies in Epidemiology statement, to youths through outreach events at high schools and community programmes and through social media, and to adults through lung health community events.

Trial registration number NCT06819969.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This multicentre study will capture multimodal outputs of respiratory health in Canadian adolescents and adults who use e-cigarettes using novel diagnostic and imaging techniques.
⇒ The study design has been informed by input from persons with lived vaping experience, Indigenous representatives, public health advocates and youth volunteers.
⇒ As a 3-year longitudinal study, dropout over the course of the study may occur.
⇒ Changes in vaping and smoking habits over the course of the study as well as the high degree of variability in vaping practices between individuals may complicate downstream analyses.

INTRODUCTION

The invention of e-cigarettes in 2003 upended the trajectory of a decades-long public health campaign against combustible cigarette smoking. Promoted as a safer method of inhaling nicotine compared with cigarettes and as smoking cessation tools, e-cigarettes

have substantially grown in popularity with rates of uptake now exceeding those of cigarette smoking.[1] In Canada, 6% of Canadians aged 15 years and older have vaped in the past 30 days.[2] Younger Canadians appear to be the most susceptible to these habits, with 14% of those aged 15–19 years and 18% of those aged 20–24 years reporting past 30-day use.[2] Indigenous populations are also disproportionately affected by the spread of vaping which may place them at higher risk for potential downstream respiratory complications.[3–5] As Canadians increasingly reach for e-cigarettes, especially at younger ages and not just for the purposes of smoking cessation, greater clarity into the pulmonary toxicities of vaping is urgently needed.

The Canadian Lung Outcomes in Users of Vaping Devices (CLOUD) Study is a pan-Canadian, multicentre, multidisciplinary and longitudinal approach to studying vaping from cell to society. By designing an observational cohort that bridges the adolescent and adult populations, we aim to address two pressing, yet distinct questions on vaping across the lifespan: (1) In adolescents and youths for whom vaping may be their first entry into inhalational exposures, what respiratory injuries might arise? (2) For adults, in whom the landscape of vaping is contextualised by cigarette smoking cessation efforts, to what degree, if at all, do e-cigarettes reduce the known pulmonary injuries associated with cigarette smoking, the leading cause of preventable death globally? Transitioning from cigarettes to e-cigarettes to complete abstinence from any inhaled products is not straightforward for many, with those using both cigarettes and e-cigarettes having up to an approximately 65% probability of remaining dual users by 1 year.[6 7]

The challenge in studying vaping and achieving an accurate depiction of its pulmonary consequences lies in the heterogeneity of vaping practices across populations. From the types of devices and e-liquids to flavours and concentrations, this variability adds an unprecedented level of complexity. Moreover, vaping products have changed dramatically over the last decade.[8] The characterisation of the respiratory effects of e-cigarettes also remains superficial and a more comprehensive phenotyping of vaping-exposed lungs across the lifespan using novel imaging and pulmonary function techniques, dynamic exercise testing, and airway cell sequencing would significantly enhance our understanding of the potential harms. As with combustible cigarette smoking, the small airways (characterised by a diameter <2 mm) may be particularly vulnerable during vaping given their high degree of exposure to particulate matter.[9] These regions of the lung may harbour the earliest signs of injury, ultimately setting the stage for future obstructive airways disease.

Objectives

The objective of the CLOUD Study is to characterise small airway injury in adolescent and adult Canadians who use e-cigarettes. Specifically, our goals are to:

1. Characterise the structural and functional disruptions associated with e-cigarette use using oscillometry, multiple breath washout (MBW), chest CT, hyperpolarised 129-xenon (^{129}Xe) MRI, cardiopulmonary exercise testing (CPET) and bronchoscopy.
2. Determine the association between e-cigarette use and respiratory outcomes, including symptom burdens, exacerbation-like respiratory events, and school and work absences.
3. Characterise the epigenetic and transcriptomic disruptions associated with e-cigarette use in blood, sputum, airway epithelium and lung immune cells.

METHODS AND ANALYSIS

Overview

The CLOUD Study is a prospective, observational cohort study that will enrol both e-cigarette and non-e-cigarette users to undergo detailed respiratory symptom, physiologic, imaging and biospecimen collection over a 3-year period. Visits will occur at baseline, 18 months and 36 months. The protocol design is detailed in figure 1. The projected enrolment for adolescent participants (ages ≥12 and <19 years) is 50 e-cigarette users and 50 non-e-cigarette users. The projected enrolment for adults (≥19 years) is 100 dual e-cigarette and combustible cigarette users, 100 e-cigarette-only users, 100 combustible cigarette-only users and 100 non-smoking and non-e-cigarette users.

Study centres

The CLOUD Study will take place at six academic hospital centres across Canada. Four of these sites (BC Children's Hospital, the University of Alberta, The Hospital for Sick Children and the Université de Sherbrooke) will enrol adolescent participants between the ages of 12 and 18 years, while five sites (The University of British Columbia, the University of Alberta, McMaster University, the Ottawa Hospital Research Institute and the Université de Sherbrooke) will enrol adult participants >18 years.

Eligibility criteria

For the adolescent arm, participants will be enrolled if they are ≥12 and <19 years old and if they (1) use neither combustible cigarettes nor e-cigarettes or (2) use e-cigarettes exclusively. Exclusion criteria include anyone with a contraindication to pulmonary function testing and CPET, individuals who have smoked combustible cannabis within the last month and/or have a combustible cannabis smoking history of >1 joint-year, individuals who have smoked combustible cigarettes within the last 6 months and individuals with a physician-diagnosed chronic lung disease (such as asthma, cystic fibrosis or bronchopulmonary dysplasia).

For the adult arm, participants will be enrolled if they are ≥19 years old and if they (1) use neither combustible cigarettes nor e-cigarettes; (2) use combustible cigarettes exclusively, never using e-cigarettes; (3) use e-cigarettes exclusively, never using combustible cigarettes; or (4) use

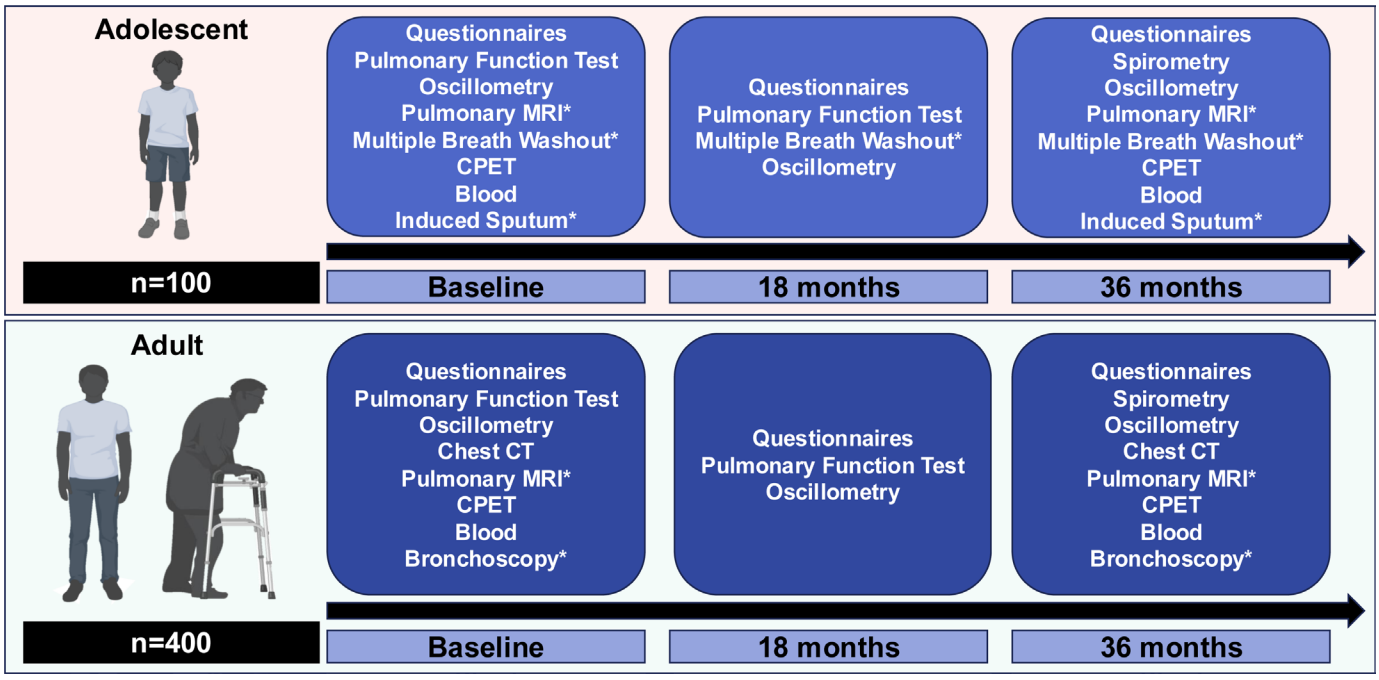

Figure 1 Study overview. *Multiple breath washout, induced sputum, MRI and bronchoscopy are available at select sites. CPET, cardiopulmonary exercise test. Figure created with the assistance of BioRender.

both combustible cigarettes and e-cigarettes currently. Exclusion criteria include anyone with a contraindication to pulmonary function testing and CPET, individuals who have smoked combustible cannabis within the last month and/or have a combustible cannabis smoking history of >1 joint-year and individuals currently undergoing treatment for lung cancer.

For either arm, the inability to provide written informed consent will also be an exclusion criterion. No limitations will be placed on the type of e-liquids used by participants; for example, e-cigarette users of nicotine, tetrahydrocannabinol and cannabidiol will be all enrolled. As this study is intended to mirror real-world experiences with vaping, no limitations will also be placed on vaping/smoking cessation or resumption over the course of the 3-year observational period.

Informed consent

Written informed consent will be obtained from all participants. For adolescents, informed consent will be obtained from participants who are capable of providing it, with an optional support statement from a parent encouraged but not required.

Data collection

A full description of respiratory tests and key outcomes is provided in table 1.

Clinical data

All participants will undergo detailed demographic, exposure and medical history questionnaires at each of the three study time points. Vaping histories will be captured in multiple ways, including the types of devices used, the frequency of vaping, and the composition and flavourings of e-liquids. For adolescent participants, these questionnaires will be administered without parental presence to ensure accurate reporting. Measures of vaping dependence will also be captured using a modified Fagerstrom test.[10]

Validated respiratory symptom questionnaires for adult participants will include the St. George's Respiratory Questionnaire (SGRQ),[11] the COPD Assessment Test,[12] the modified Medical Research Council dyspnoea scale,[13] the International Physical Activity Questionnaire (short form)[14] and the McMaster Cough Severity Questionnaire.[15] Adolescent participants will complete the American Thoracic Society Questionnaire, an eight-item tool assessing cough, wheezing, phlegm production, shortness of breath and chest tightness.[16] This questionnaire has been validated in adolescents who smoke, with scores positively correlating with measures of dependence and severity of habit[17] and declining following smoking cessation.[18] A modified SGRQ and Visual Analogue Scale[19] evaluating shortness of breath, wheezing, chest tightness, cough, sputum production and sputum purulence will also be completed by adolescent participants. Every 3 months, participants will be contacted to fill out an online survey capturing exacerbation-like respiratory events, defined as (1) changes in at least one major respiratory symptom and (2) the use of antibiotics and/or systemic corticosteroids or health services (physician visit, emergency room or hospitalisation[20]) over the previous 3-month period and any work or school absences secondary to respiratory problems.

Pulmonary function and exercise data

All participants will undergo pulmonary function testing at baseline, 18 months and 36 months.[21] Oscillometry will be performed in all participants at baseline, 18

Table 1 Key respiratory variables collected in the CLOUD Study

Test	Key outcome variables	Study groups
Pulmonary function testing	FEV_1/FVC FEV_1 FEV_3/FEV_6 FVC Total lung capacity Diffusion capacity	All participants
Oscillometry	R5–R20	All participants
Multiple breath washout	Lung clearance index	Adolescent participants (two sites)
^{129}Xe hyperpolarised pulmonary MRI	Ventilation defect percent RBC to membrane ratio Membrane to gas ratio RBC to gas ratio Apparent diffusion coefficient	Adult participants (two sites) Adolescent participants (two sites)
Cardiopulmonary exercise test	Peak VO_2 %predicted V_E/VCO_2 nadir	All participants
CT imaging	Parametric response mapping functional small airways disease (PRM^{fSAD}) Relative area of the lung with attenuation below −856 Hounsfield units (RA856) Quantitative and qualitative emphysema Pulmonary vascular volume Mucus score Total airway count	Adult participants
Induced sputum methylation and transcriptome	Epigenetic age Differentially methylated and expressed genes	Adolescent participants (three sites)
Bronchial epithelial cell and bronchoalveolar lavage methylation and transcriptome	Epigenetic age Differentially methylated and expressed genes	Adult participants (three sites)
Blood methylation and transcriptome	Epigenetic age Differentially methylated and expressed genes	All participants

FEV_1, forced expiratory volume in 1 s; FEV3, forced expiratory volume in 3 s; FEV_6, forced expiratory volume in 6 s; FVC, forced vital capacity; R5–R20, fall in resistance from 5 to 20 Hz; V_E/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption at peak exercise.

months and 36 months, using the tremoFlo C-100 system (THORASYS Thoracic Medical Systems, Montreal, QC). Measurements will be performed according to the recommended guidelines set by the European Respiratory Society (ERS).[22] Total and central airway resistance will be measured at 5 and 20 Hz (R5 and R20, respectively), and peripheral airways resistance as R5–20. Two adolescent sites (BC Children's Hospital and The Hospital for Sick Children) will also perform a substudy of MBW according to the technical standards outlined by the American Thoracic Society (ATS)/ERS[23] using an Exhalyzer D (Eco Physics, Durnten, Switzerland). All participants will undergo a CPET at baseline and 36 months on a cycle ergometer according to ATS/American College of Chest Physicians guidelines.[24] This will consist of a 6 min resting period, followed by a 1 min warm-up of unloaded pedalling, then 10–25 W/minute stepwise increases in work rate to symptom limitation. Standard cardiac, metabolic, ventilatory and gas exchange parameters will be measured and averaged every 30 s. Operating lung volumes will be derived from inspiratory capacity manoeuvres collected every 2 min as previously described.[25 26] Dyspnoea intensity, leg discomfort and unpleasantness ratings will be evaluated at rest and throughout each stage of exercise using the modified 0–10 category ratio Borg scale.[27]

Imaging data

Adolescent participants at two sites (BC Children's Hospital and The Hospital for Sick Children) and adult participants at two sites (The University of British Columbia and McMaster University) will undergo hyperpolarised ^{129}Xe MRI at baseline and at 36 months. All sites are aligned under the ^{129}Xe MRI Clinical Trials Consortium (129xectc.org) such that equipment and protocols are harmonised. Conventional anatomical proton (^{1}H), functional ^{129}Xe and functional proton MRI will be performed on whole-body 3-Tesla MRI systems according to established guidelines.[28] All adult participants will undergo chest CT imaging at baseline and 36 months. Images will be acquired during a static breath-hold at

full inspiration and expiration, then reconstructed using a slice thickness of 0.625–1.25 mm. Images will be quantified using VIDA Insights software (VIDA Diagnostics, Inc., Iowa). Qualitative reads under the direction of a clinical radiologist (JL) will also be performed to detect clinically important nodules, bronchiectasis, emphysema and fibrosis. All image reading and analysis will be performed centrally to ensure standardisation across the study centres.

Biospecimens

Blood and lung biospecimens will be collected at baseline and at 36 months. Blood collection will include serum, plasma and buffy coat and will be performed in all participants. Adolescent participants will undergo induced sputum collection. An optional bronchoscopy substudy will be performed in adults at three centres (The University of British Columbia, McMaster University and the Université de Sherbrooke) during which oral washes, airway epithelial brushings and bronchoalveolar lavage will be collected, according to previously published protocols.[29–33] Biospecimen collection and processing will be carried out using harmonised protocols across all sites. Samples will be stored at −80°C until use. DNA methylation from blood and lung specimens will be profiled using the Illumina MethylationEPIC array, which encompasses >930 000 CpG sites. Total RNA from specimens will undergo whole transcriptome sequencing using the Illumina NextSeq 2000 platform.

Primary outcomes

Our primary endpoint will be a composite measure of small airways dysfunction, in which participants meeting at least one of the following criteria will be considered to have small airways dysfunction. For adolescent participants, these measures will include (1) a change in resistance from 5 to 20 Hz (R5–R20) >upper limit of normal (ULN) on oscillometry[34] or (2) peak oxygen consumption (VO_2) <lower limit of normal (LLN) plus a ventilatory response or minute ventilation/carbon dioxide production (V_E/VCO_2) nadir >ULN.[35] For adult participants, these measures will include (1) R5–R20>ULN,[36] (2) disease probability measure functional small airways disease (fSAD) >10% on chest CT,[37–39] or (3) peak VO_2<84% predicted (considered abnormally low)[24] plus a V_E/VCO_2 nadir>ULN.[40] The proportion of participants meeting at least one of the criteria for small airways dysfunction at any time point will be compared between the vaping and control groups using χ^2 tests. Multivariable logistic regressions will be used to adjust for possible covariates, such as age, sex and their interaction with vaping/smoking groups. Variables will be assessed through univariable logistic regression, and those with significant ($p<0.05$) associations will be included as covariates in the multivariable logistic regression while respecting the 10 events per variable rule. Statistical significance will be determined at $p<0.05$.

Secondary outcomes

Multivariable logistic regression analyses will be used to determine whether vaping is associated with other proposed measures of small airways dysfunction such as FEV_3/FEV_6[41] and FEV_3/FVC <LLN[42] or a lung clearance index >ULN on MBW.[43] We will also determine the relationship between vaping and prevalence of a post-bronchodilator FEV_1/FVC<LLN at each time point and with a faster rate of FEV_1 decline over 3 years. Diffusing capacity, residual volume and total lung capacity will also be measured at baseline and tested for their associations with vaping using linear regression models. Symptom scores and their respective changes over 3 years will be compared among study groups using a one-way ANOVA followed by post hoc Tukey's test to evaluate for between-group differences as well as linear regressions to adjust for possible covariates. Respiratory event frequency and school/work absenteeism will be compared among study groups using negative binomial regression models. Secondary CT imaging characteristics such as quantitative and qualitative emphysema, total airway count, airway morphology, pulmonary vascular volume[44] and mucus score[45] will be compared among the study groups using ANOVA followed by post hoc Tukey's tests as well as linear regressions. Similar methods will be used to compare ^{129}XeMRI measurements including ventilation defect percentage,[46] RBC to membrane ratio, membrane to gas ratio, RBC to gas ratio[47] and apparent diffusion coefficient.[48] Blood, induced sputum, bronchial epithelial cell and bronchoalveolar lavage cell methylation profiles will be used to calculate epigenetic age according to established epigenetic clock algorithms[49] and compared between study groups using ANOVA tests. Methylation profiles will also be used in conjunction with whole transcriptome sequencing of these biospecimens to identify both differentially methylated and expressed genes associated with vaping through robust linear regression models. Differential cell proportions in bronchoalveolar lavage fluid and induced sputum samples will also be compared between the groups using χ^2 tests. Statistical significance will be determined at a $p<0.05$ for clinical outcomes, and at a Benjamini-Hochberg false discovery rate <0.05 for differential methylation as well as gene expression analyses. All analyses will be done in R. Results will be presented as effect size with 95% CIs.

Sample size estimation

The preliminary CPET data acquired by our team demonstrated an absolute difference of 16% of those having VO_2<84% predicted between the vaping and control groups. To detect a difference between the ENDS and control groups by χ^2 test assuming 5% significance, we will require a sample size of 50 in each group to achieve 85% power and 100 in each group to achieve 99% power. We have thus designed our sample size groups to achieve appropriate power in this study, while accounting for a conservative estimate of 10% dropout per year.

Data management

Deidentified data will be collected through a central secure REDCap website housed at the University of British Columbia. Data will be encrypted and password protected for sharing. CT and MRI images will be transferred and stored on a secure cloud housed by VIDA Diagnostics. Anonymised data will be shared on open platforms.

Patient and public involvement

Questionnaires and study advertisements were developed with input and guidance from two individuals with lived experiences using e-cigarettes as well as a seven-member youth advisory council made up of high school students across British Columbia (https://chartlab.ca/yac/). A specific questionnaire addressing the unique impact of e-cigarette use on Indigenous communities was developed with the input and guidance from members of the Westbank First Nation. These members of our team will be providing assistance with outreach and knowledge translation events over the course of the study.

ETHICS AND DISSEMINATION

This protocol has been approved by the University of British Columbia-Providence Health Care Research Ethics Board (Certificate H24-00374). The use of hyperpolarised ^{129}Xe gas in this study has been approved by Health Canada (Certificate HC6-024-c291776).

Consent forms describing in detail the study procedures and risks will be given to each participant and written documentation of informed consent will be required prior to study initiation. Each participant will have sufficient opportunity to discuss the study, have all of their questions addressed and consider the information in the consent process prior to agreeing to participate. Participants will be able to withdraw consent at any time during the course of the study without prejudice. We will seek to enrol adolescent participants who are capable of providing informed consent with an optional support statement from a parent encouraged but not required.

The findings of this study will have important implications for estimated 68 million individuals around the world who use e-cigarettes.[50] We will work closely with our youth advisory council both during and after the study to devise events, forums and social media materials to disseminate study findings. Youth-specific knowledge mobilisation modalities will include accessible, highly visible and digestible platforms like YouTube, TikTok, and Instagram (delivered in short segments and presented by peers) and youth-driven outreach events at high schools and community programmes. Our team also consists of persons with lived vaping experience who will help devise lay infographics to share study results. We will hold public forums both in person and virtually across Canada to discuss our findings with the assistance of the British Columbia Lung Foundation, the Alberta Lung Association, the Lung Health Foundation, Association pulmonaire du Québec, the Canadian Lung Association, the Canadian Respiratory Research Network and the Canadian Thoracic Society. Finally, our work will have special interest to healthcare providers and respiratory scientists. We will thus present study findings at leading national and international respiratory research conferences and publish our manuscripts in both general medical and respiratory journals, respecting the Strengthening the Reporting of Observational Studies in Epidemiology statement.[51] Given the immediate relevance of our study results for public health, we plan to share these with provincial school boards; provincial and federal ministries of health, youth, education, and Indigenous Affairs; the Public Health Agency of Canada and Health Canada.

DISCUSSION

The current literature on vaping is insufficient to properly inform Canadians on its impact on lung health. These knowledge gaps exist at a time when e-cigarettes are increasingly popular, making the need for high-quality, comprehensive research ever more urgent. Our study will comprehensively phenotype Canadians who use e-cigarettes, address multiple levels of potential lung harm and provide crucial and timely guidance for them and their healthcare providers. Our key deliverables include:

1. An integrated physiologic and CT-MR imaging approach to uncovering the structural and functional dynamics of e-cigarette use;
2. A deep characterisation of cardiopulmonary exercise abnormalities associated with e-cigarette use;
3. An integrated multi ‘omics evaluation of airway samples from both adolescent and adult participants who use e-cigarettes, providing insight into the molecular damage that can occur with vaping;
4. A legacy cohort of longitudinal biospecimens collected across the lifespan, allowing for ongoing opportunities to study the effects of vaping on health.

A study team consisting of adult and paediatric respirologists, adolescent medicine specialists, addiction specialists, epidemiologists, biostatisticians, behavioural scientists, nurses, lung imaging scientists, radiologists, respiratory and exercise physiologists, molecular biologists, persons with lived experience, Indigenous advisors, public health advocates, trainees and youth representatives has been developed to ensure a multidisciplinary approach.

Nonetheless, we anticipate several challenges. First, as a longitudinal study over 3 years, we expect that there will be attrition. Strategies to prevent attrition will include (1) a health report provided to participants each year explaining results and implications for their medical care, (2) financial compensation for their time and (3) a yearly newsletter updating participants on the study’s progress and key findings. These incentives will help to recruit not just participants who use e-cigarettes but also control participants. To address the unique challenges that can arise with adolescent participation, our youth advisory council will advise on recruitment and retention

strategies. Other methods to promote paediatric participation will include youth-specific social media engagement, in-school education and awareness programmes, and offering documented volunteer hours as reward for participation.

We also recognise the complexity of inhalational habits among Canadians, which may also include not just traditional cigarettes, but other tobacco products (eg, cigars, cigarillos and hookah), cannabis smoking and illicit drugs. Distinguishing an attributable injury signature to solely e-cigarette use will be a challenge in the face of these competing risks. We will endeavour to uncover the unique contribution of vaping to lung injury by excluding current cannabis smoking, by using tobacco and illicit drug smoking status as covariates in our statistical models and by performing stratified analyses by tobacco and illicit smoking status.

We anticipate that participants in our study will also have a wide variation in vaping habits which will need to be accounted for in our analyses. We have thus structured our questionnaires to capture all sources of variability. Additional mitigating strategies include the use of serum samples to quantify cannabis and nicotine exposure through tetrahydrocannabinol and cotinine measurements, respectively. Subgroup analyses by severity of exposure groups will then be performed to determine whether individuals with higher measurable exposures have greater lung injuries.

Notwithstanding these challenges and limitations, we will create one of the most deeply phenotyped respiratory cohorts on vaping to date. The potential of this study falls long beyond the proposed study period, as we will generate biospecimens and datasets immediately available for secondary analyses. We are thus well positioned to address the future questions that will inevitably arise as our nation's journey with e-cigarettes evolves.

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Contributors JML is responsible for the content of this study as the guarantor. PB, JML, DDS, and JHR planned the study. JML, DDS, JHR and PB wrote the manuscript. XL provided the statistical analysis. All authors provided contributions to the design of the study and edited/revised the manuscript.

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Competing interests SC reports the following: he has received non-restricted research grants from the NIHR Oxford BRC, the Quebec Respiratory Health Research Network, the Association Pulmonaire du Québec, the Academy of Medical Sciences, AstraZeneca, bioMérieux, and Sanofi-Genyme-Regeneron; he is the holder of the Association Pulmonaire du Québec's Research Chair in Respiratory Medicine and is a Clinical research scholar of the Fonds de recherche du Québec; he received speaker honoraria from AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, and Valeo Pharma; he received consultancy fees for FirstThought, AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, Access Biotechnology and Access Industries; he has received sponsorship to attend/speak at international scientific meetings by/for AstraZeneca and Sanofi-Regeneron. He is an advisory board member and will have stock options for Biometry Inc – a company which is developing a FeNO device (myBiometry). He advised the Institut national d'excellence en santé et services sociaux (INESSS) for an update of the asthma general practice information booklet for general practitioners, and is a member of the asthma steering committee of the Canadian Thoracic Society. RLE reports the following: she has received research grants as trainee salary awards from Michael Smith Health Research BC, Canadian Respiratory Research Network, and Natural Sciences and Engineering Research Council of Canada; she received personal consulting fees from VIDA Diagnostics Inc; she has received support for attending meetings and travel from the Canadian Institutes of Health Research (Institute of Circulatory and Respiratory Health). XL reports receiving support for the present manuscript from the Canadian Institutes of Health Research. SC reports the following: he has received support for the present manuscript as a Principal Investigator research salary from Fonds de Recherche du Quebec and an unrestricted research grant from and position as endowed research chair for the Association PUlmonaire du Quebec. Additional unrestricted research grants received include those from the Sanofi-Regeneron, Quebec Respiratory Health Research Network, bioMérieux, Noix, Association Pulmonaire du Québec, National Institutes of Health Research (NIHR), Academy of Medical Sciences, and Air Intersectorialité Respiratoire son Québec Network; he has received consulting fees from FirstThought, AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, AccessBiotechnology and Access Industries; he has received speaker honoraria from AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, and ValeoPharma; he has received support for attending meetings and travel from AstraZeneca; he has participated as a medical advisor holding stock options for myBiometry; he has participated as an advisor for a general practise information booklet on asthma for the Institut National d'Excellence en Santé et Services Sociaux; he maintains stock options for myBiometry. MKS reports the following: he has received research grants from the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and University Hospital Foundation; he has received honoraria <$5000 for lectures in pulmonary rehabilitation. SS reports the following: she has received support for the present manuscript from the Canadian Institutes of Health Research; she has received grant payments to the institution from Cyclomedica Australia Pty

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REFERENCES

1 Canadian tobacco and nicotine survey (CTNS): summary of results for 2022. Ottawa, ON Health Canada; 2023.
2 Canadian community health survey. 2023. Available: https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1310009601 [Accessed 04 Dec 2024].
3 Seo YS, Chang YP. Racial and Ethnic Differences in E-Cigarette and Cigarette Use Among Adolescents. *J Immigr Minor Health* 2022;24:713–20.
4 Thompson S, Smith J, Lee K, *et al*. Industry sponsored harm reduction conference courts Indigenous peoples in Canada. *Tob Control* 2020;29:e130–1.
5 Struik LL, Werstuik ST, Sundstrom A, *et al*. Factors that influence the decision to vape among Indigenous youth. *BMC Public Health* 2022;22:641.
6 Brouwer AF, Jeon J, Hirschtick JL, *et al*. Transitions between cigarette, ENDS and dual use in adults in the PATH study (waves 1–4): multistate transition modelling accounting for complex survey design. *Tob Control* 2022;31:424–31.
7 Farber HJ, Rábade Castedo C, Jimenez-Ruiz CA, *et al*. The Fallacy of Electronic Cigarettes for Tobacco Dependence. *Ann Am Thorac Soc* 2024;21:1372–4.
8 Etter JF. An 8-year longitudinal study of long-term, continuous users of electronic cigarettes. *Addict Behav* 2024;149:107891.
9 Singh D. Small Airway Disease in Patients with Chronic Obstructive Pulmonary Disease. *Tuberc Respir Dis* 2017;80:317.
10 Rahman AU, Mohamed MHN, Jamshed S, *et al*. The Development and Assessment of Modified Fagerstrom Test for Nicotine Dependence Scale among Malaysian Single Electronic Cigarette Users. *J Pharm Bioallied Sci* 2020;12:S671–5.
11 Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005;2:75–9.
12 Jones PW, Harding G, Berry P, *et al*. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–54.
13 Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;93:580–6.
14 Craig CL, Marshall AL, Sjöström M, *et al*. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.
15 Kum E, Guyatt GH, Abdulqawi R, *et al*. The McMaster Cough Severity Questionnaire (MCSQ): a cough severity instrument for patients with refractory chronic cough. *Eur Respir J* 2025;65:2401565.
16 Comstock GW, Tockman MS, Helsing KJ, *et al*. Standardized respiratory questionnaires: comparison of the old with the new. *Am Rev Respir Dis* 1979;119:45–53.
17 Cassidy RN, Roberts ME, Colby SM. Validation of a Respiratory Symptom Questionnaire in Adolescent Smokers. *Tob Regul Sci* 2015;1:121–8.
18 Calabro KS, Prokhorov AV. Respiratory Symptoms After Smoking Cessation among College Students. *Pediatr Allergy Immunol Pulmonol* 2011;24:215–9.
19 Rhee H, Belyea M, Mammen J. Visual analogue scale (VAS) as a monitoring tool for daily changes in asthma symptoms in adolescents: a prospective study. *Allergy Asthma Clin Immunol* 2017;13:24.
20 Labonté LE, Tan WC, Li PZ, *et al*. Undiagnosed Chronic Obstructive Pulmonary Disease Contributes to the Burden of Health Care Use. Data from the CanCOLD Study. *Am J Respir Crit Care Med* 2016;194:285–98.
21 Stanojevic S, Kaminsky DA, Miller MR, *et al*. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J* 2022;60:2101499.
22 King GG, Bates J, Berger KI, *et al*. Technical standards for respiratory oscillometry. *Eur Respir J* 2020;55:1900753.
23 Robinson PD, Latzin P, Verbanck S, *et al*. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *Eur Respir J* 2013;41:507–22.
24 American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med* 2003;167:211–77.
25 Guenette JA, Chin RC, Cory JM, *et al*. Inspiratory Capacity during Exercise: Measurement, Analysis, and Interpretation. *Pulm Med* 2013;2013:956081.
26 Stickland MK, Neder JA, Guenette JA, *et al*. Using Cardiopulmonary Exercise Testing to Understand Dyspnea and Exercise Intolerance in Respiratory Disease. *Chest* 2022;161:1505–16.
27 Borg GAV. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377.
28 Niedbalski PJ, Hall CS, Castro M, *et al*. Protocols for multi-site trials using hyperpolarized ^{129}Xe MRI for imaging of ventilation, alveolar-airspace size, and gas exchange: A position paper from the ^{129}Xe MRI clinical trials consortium. *Magn Reson Med* 2021;86:2966–86.

29 McWilliams A, Tammemagi MC, Mayo JR, *et al*. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med* 2013;369:910–9.
30 Hernández Cordero AI, Yang CX, Yang J, *et al*. Airway Aging and Methylation Disruptions in HIV-associated Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2022;206:150–60.
31 Marshall EA, Filho FSL, Sin DD, *et al*. Distinct bronchial microbiome precedes clinical diagnosis of lung cancer. *Mol Cancer* 2022;21:68.
32 Leitao Filho FS, Takiguchi H, Akata K, *et al*. Effects of Inhaled Corticosteroid/Long-Acting β(2)-Agonist Combination on the Airway Microbiome of Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2021;204:1143–52.
33 Leung JM, Yang CX, Tam A, *et al*. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur Respir J* 2020;55:2000688.
34 Ducharme FM, Smyrnova A, Lawson CC, *et al*. Reference values for respiratory sinusoidal oscillometry in children aged 3 to 17 years. *Pediatr Pulmonol* 2022;57:2092–102.
35 Blanchard J, Blais S, Chetaille P, *et al*. New Reference Values for Cardiopulmonary Exercise Testing in Children. *Med Sci Sports Exerc* 2018;50:1125–33.
36 Oostveen E, Boda K, van der Grinten CPM, *et al*. Respiratory impedance in healthy subjects: baseline values and bronchodilator response. *Eur Respir J* 2013;42:1513–23.
37 Yang Y, Ge H, Lu J, *et al*. Structural features on quantitative chest computed tomography of patients with maximal mid-expiratory flow impairment in a normal lung function population. *BMC Pulm Med* 2023;23:86.
38 Kirby M, Yin Y, Tschirren J, *et al*. A Novel Method of Estimating Small Airway Disease Using Inspiratory-to-Expiratory Computed Tomography. *Respiration* 2017;94:336–45.
39 Comellas AP, Newell JD Jr, Kirby M, *et al*. Residual Volume versus FRC Computed Tomography Assessment of Functional Small Airway Disease in Smokers with and without Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2023;207:1536–9.
40 Sun XG, Hansen JE, Garatachea N, *et al*. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med* 2002;166:1443–8.
41 Yee N, Markovic D, Buhr RG, *et al*. Significance of FEV3/FEV6 in Recognition of Early Airway Disease in Smokers at Risk of Development of COPD. *Chest* 2022;161:949–59.
42 Knox-Brown B, Patel J, Potts J, *et al*. Small airways obstruction and its risk factors in the Burden of Obstructive Lung Disease (BOLD) study: a multinational cross-sectional study. *Lancet Glob Health* 2023;11:e69–82.
43 Kentgens A-C, Latzin P, Anagnostopoulou P, *et al*. Normative multiple-breath washout data in school-aged children corrected for sensor error. *Eur Respir J* 2022;60:2102398.
44 Synn AJ, Li W, San José Estépar R, *et al*. Radiographic pulmonary vessel volume, lung function and airways disease in the Framingham Heart Study. *Eur Respir J* 2019;54:1900408.
45 Dunican EM, Elicker BM, Gierada DS, *et al*. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest* 2018;128:997–1009.
46 Kirby M, Svenningsen S, Owrangi A, *et al*. Hyperpolarized 3He and 129Xe MR imaging in healthy volunteers and patients with chronic obstructive pulmonary disease. *Radiology* 2012;265:600–10.
47 Kaushik SS, Freeman MS, Cleveland ZI, *et al*. Probing the regional distribution of pulmonary gas exchange through single-breath gas- and dissolved-phase 129Xe MR imaging. *J Appl Physiol (1985)* 2013;115:850–60.
48 Kaushik SS, Cleveland ZI, Cofer GP, *et al*. Diffusion-weighted hyperpolarized 129Xe MRI in healthy volunteers and subjects with chronic obstructive pulmonary disease. *Magn Reson Med* 2011;65:1154–65.
49 Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol* 2013;14:R115.
50 Jerzyński T, Stimson GV, Shapiro H, *et al*. Estimation of the global number of e-cigarette users in 2020. *Harm Reduct J* 2021;18:109.
51 von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *Ann Intern Med* 2007;147:573–7.