BMJ Open

Protocol for the air purification for eosinophilic COPD study (APECS): a randomised controlled trial of home air filtration by HEPA

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To cite: Saeed MS, Denoncourt CM, Chao IA, *et al*. Protocol for the air purification for eosinophilic COPD study (APECS): a randomised controlled trial of home air filtration by HEPA. *BMJ Open* 2024;**14**:e074655. doi:10.1136/bmjopen-2023-074655

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-074655).

Received 12 April 2023
Accepted 30 November 2023

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ABSTRACT

Introduction Exposure to particulate matter (PM) pollution has been associated with lower lung function in adults with chronic obstructive pulmonary disease (COPD). Patients with eosinophilic COPD have been found to have higher levels of airway inflammation, greater responsiveness to anti-inflammatory steroid inhalers and a greater lung function response to PM pollution exposure compared with those with lower eosinophil levels. This study will evaluate if reducing home PM exposure by high-efficiency particulate air (HEPA) air filtration improves respiratory health in eosinophilic COPD.

Methods and analysis The Air Purification for Eosinophilic COPD Study (APECS) is a double-blinded randomised placebo-controlled trial that will enrol 160 participants with eosinophilic COPD living in the area of Boston, Massachusetts. Real and sham air purifiers will be placed in the bedroom and living rooms of the participants in the intervention and control group, respectively, for 12 months. The primary trial outcome will be the change in forced expiratory volume in 1 s (FEV_1). Lung function will be assessed twice preintervention and three times during the intervention phase (at 7 days, 6 months and 12 months postrandomisation). Secondary trial outcomes include changes in (1) health status by St. George's Respiratory Questionnaire; (2) respiratory symptoms by Breathlessness, Cough and Sputum Scale (BCSS); and (3) 6-Minute Walk Test (6MWT). Inflammatory mediators were measured in the nasal epithelial lining fluid (NELF). Indoor PM will be measured in the home for the week preceding each study visit. The data will be analysed to contrast changes in outcomes in the intervention and control groups using a repeated measures framework.

Ethics and dissemination Ethical approval was obtained from the Institutional Review Board of Beth Israel Deaconess Medical Centre (protocol #2019P0001129). The results of the APECS trial will be presented at scientific conferences and published in peer-reviewed journals.

Trial registration NCT04252235. Version: October 2023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first double-blinded, randomised controlled trial of air purification for moderate-to-severe eosinophilic chronic obstructive pulmonary disease (COPD), a population at risk of respiratory health effects of air pollution.
⇒ The year-long intervention allows for the evaluation of long-term impact of air purification across seasons on indoor air quality and repeated measures of respiratory health.
⇒ Since our clinical trial does not exclude patients with adult-onset asthma, our results will be generalisable to the 'real world' population of former smokers with eosinophilic COPD, many of whom also report a diagnosis of asthma.
⇒ There is no minimum or maximum threshold for indoor particulate levels for participants enrolled in this study, and therefore some homes may have low indoor particulate matter levels and receive minimal air quality benefit, while others may have high indoor levels (eg, due to secondhand tobacco smoke exposure, fireplace use or candle burning in the home).
⇒ This study only aims to reduce particulate matter exposure while at home, including particulate matter from the outdoors that enters the home. It does not address potentially harmful gaseous pollution at home or pollution exposures that occur while outside the home, such as occupational exposures.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an incurable, progressive and debilitating disease affecting more than 15% of the population over age 40 in the USA.[1] In spite of smoking cessation strategies and medical advances in the treatment of COPD, COPD-related mortality has increased in the USA and is the third leading cause of death.[2] The clinical approach to treating COPD has

changed in recent years based on the identification of different subtypes of COPD. Higher levels of eosinophils in the blood have emerged as a clinical tool to identify an inflammatory subtype of COPD.[3] Eosinophilic COPD patients have been found to have more airway remodelling and higher rates of exacerbations[4–6] compared with non-eosinophilic COPD patients and are targeted for medical therapy, especially inhaled corticosteroids for those with frequent exacerbations.[3 7–10] However, there may be a role for non-pharmacologic interventions to reduce noxious stimuli, such as air pollution and aeroallergens, that may cause lower lung function, increased airway inflammation and worse respiratory symptoms in the eosinophilic COPD subtype.[11–13]

Several randomised controlled trials have investigated whether indoor air purification can improve symptoms and reduce exacerbations in patients with obstructive lung diseases who spend most of their time inside. Most of these trials were conducted in children with asthma and have found improvements in peak flow, nasal and/or respiratory symptoms.[14–16] At the time of this publication, only one large randomised controlled trial has evaluated air purification in patients with moderate to severe COPD and demonstrated reduced respiratory symptoms, lower rates of COPD exacerbation and less rescue medication use after 6 months of air purification.[17]

We designed this double-blinded, placebo-controlled trial of high-efficiency particulate air (HEPA) filter intervention to test the hypothesis that reducing long-term exposure to indoor PM improves lung function in eosinophilic COPD.[18 19] Our clinical trial is novel because we focus specifically on patients with the eosinophilic subtype of COPD, who may be especially susceptible to air pollution[11] and may benefit the most from air purification. This study will allow us to directly test a non-pharmacological intervention aimed at reducing airborne exposures, potentially establishing a new treatment option for former smokers with eosinophilic COPD that prevents, rather than palliates, airway inflammation.

METHODS AND ANALYSIS

Study design

This will be a double-blinded, randomised controlled clinical trial, in which participants will be equally divided into the active or sham (placebo) group. Beth Israel Deaconess Medical Centre (BIDMC) of Boston, MA, will be the primary study site. Recruitment will be conducted at BIDMC and several Boston area hospitals. The study will begin in March 2021 with an estimated completion in June 2025.

The study will consist of two clinic visits at the BIDMC Clinical Research Centre (study entry visit and study exit visit at 12 months postrandomisation) and three home visits (at the time of randomisation, at 7 days and 6 months postrandomisation). The first home visit (day 0) at which participants will be randomised (and receive two real or sham air purifiers) will occur approximately 3 months after the first clinic visit at BIDMC. All study participants will provide two baseline 7-day air quality measurements (at 3 months preintervention and the week prior to randomisation) and three air quality measurements postrandomisation during the time period when the real versus sham air purifiers are in the home (at 7 days, 6 months and 12 months). Figure 1 provides an overview of

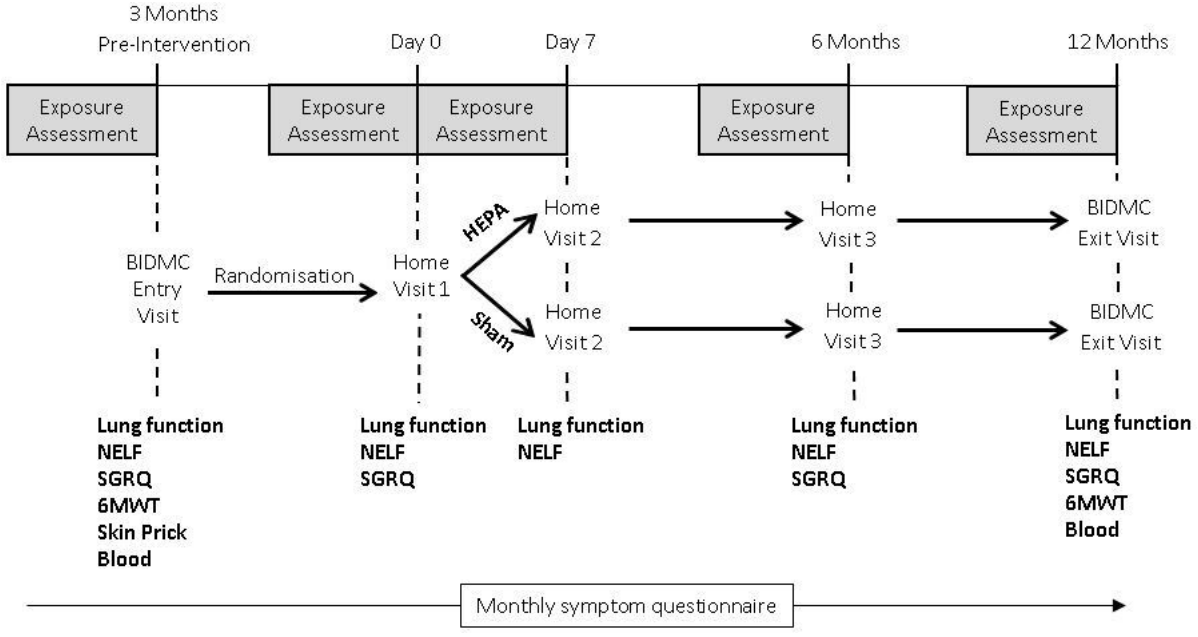

Figure 1 Study design for air purification trial in eosinophilic COPD (n=160). For each exposure assessment, a 7-day air sample will be collected for particle mass by gravimetry, elemental analysis of $PM_{2.5}$ by X-ray fluorescence and black carbon (BC) by light transmission. COPD, chronic obstructive pulmonary disease; HEPA, high-efficiency particulate air; 6MWT, 6-Minute Walk Test; NELF, nasal epithelial lining fluid; SGRQ, St. George's Respiratory Questionnaire.

Box 1 Inclusion and exclusion criteria for study enrolment

Inclusion Criteria
⇒ Age of 40 years or older
⇒ Physician diagnosis of COPD
⇒ GOLD Stage II–IV airflow obstruction: FEV_1 <80% predicted, FEV_1/FVC <70%
⇒ Former smoking with tobacco exposure of >10 pack-years
⇒ Absolute eosinophil count ≥150 cells/µL (≥0.015 x 10^9/L) at screening or in the previous year

Exclusion Criteria
⇒ Inability to complete monthly questionnaire
⇒ Inability to perform lung function testing
⇒ Current use of HEPA purifier
⇒ Current tobacco smoking, e-cigarette use or vaping
⇒ End-stage chronic disease with life expectancy <2 years as determined by PI judgement
⇒ Living in location other than home (eg, long-term care facility)
⇒ Moving residences within the 15-month duration of the trial

the study visit timeline with tests that will be performed at each visit.

The treatment assignments will be generated by the data coordinating centre at Boston Children's Hospital (BCH) using permuted block randomisation (with block sizes of 8 to ensure balance by season). On day 0, a designed unblinded BIDMC staff member will be informed by secure email of the intervention status and selects either two active or two sham air purifiers to place in the participant's home, one in the living room and one in the bedroom. The actual allocation must not be disclosed to the study participant or any other study personnel, nor should there be any written or verbal disclosure of the allocation code (stored at BCH) in any of the corresponding study documents. The intervention (active) air purifier is a CowayAirmega 400S True HEPA Air Purifier, which captures particles down to 0.1 µm in size and is designed to accommodate rooms up to 1560 square feet. Sham Coway filtration devices are engineered by the Harvard School of Public Health to replicate the sound and appearance of a functional filtration device. All health measurements will be obtained by a research assistant or research nurse who is blinded with respect to intervention status.

Participants and recruitment

Potentially eligible participants will be screened from the electronic medical record using the inclusion and exclusion criteria listed in box 1. Potential participants will then be contacted by phone or mail, after which a member of the study team will complete the screening process by phone. Potentially eligible participants who do not meet eosinophil criteria based on clinical laboratory testing obtained in the previous year will be invited to have a screening blood test to determine study eligibility (eosinophil count >150 cells/µL or >0.15 x 10^9/L). Participants meeting all study entry criteria who wish to participate in the trial will complete informed consent via phone or in person with research staff prior to receiving the air sampler before the BIDMC entry visit (figure 1).

Participant engagement will be maintained through monthly survey questionnaires (online or by phone) and the five study visits. In addition, the participants will be compensated a total of $450 by study completion. To maintain retention, there will be a 3-month baseline run-in phase during which we will assess if participants are able to complete the monthly questionnaires and schedule their first home visit. Participants unable to complete these assessments will not undergo randomisation or remain in the study. We will aim to recruit 160 participants with eosinophilic COPD following the criteria below. Exposure and outcome measures at each visit are shown in table 1.

Exposure assessments

Five indoor air samples will be collected 1 week before each visit using a calibrated stationary preassembled air sampler, the Harvard PRPS99, operated at 5 L/min. It will collect fine, coarse and large particles in a single device, with impaction stages with 50% cut points at >10, 2.5–10 and <2.5 µm.[20] Teflon filters and polyurethane foam (PUF) discs will be equilibrated and weighed before and after sample collection on an electronic microbalance (Model MT-5, Mettler Toledo, Rainin LLC, Oakland, California, USA) in the controlled temperature and humidity lab at the Harvard School of Public Health, after preparation under a clean air positive flow hood. We will measure the 7-day average mass concentration of $PM_{2.5}$, $PM_{2.5–10}$ and PM_{10+} in µg per m^3 of air sample. The black carbon (BC) concentration on the Teflon filter will be determined by the SootScan OT21 Transmissometer (Magee Scientific, Berkeley, California, USA).[21 22] Trace elemental concentrations will be measured from the Teflon filter using an energy-dispersive X-ray fluorescence (EDXRF) analyzer (Epsilon 5, MarvernPanalytical, UK).

Settled dust will be collected from the participant's living and bedroom by vacuuming approximately 100 cm squared (1 US square foot) area for 2 min. This will be performed twice in the bedroom and twice in the living room at randomisation and 6 months postrandomisation. Samples will be collected into Dustream collection filters and tubes (Indoor Biotechnologies #DU-FL-2, Charlottesville, Virginia, USA)[23 24] and stored at −80°C.

To document participant activity patterns and time spent outside the home, we will administer a brief questionnaire every 3 months to assess where participants typically spend their time (eg, home, work, commuting and outdoors) during weekdays and weekends. We will also assess exposure to pets every month.

Clinical trial outcomes

The primary trial outcome will be the change in forced expiratory volume in 1 s (FEV_1). The secondary outcomes will include the changes in (1) health status, quantified using the St. George's Respiratory Questionnaire

Table 1 Clinical measures and exposure data collected at each study visit

Visit	Clinic 1	Home 1	Home 2	Home 3	Clinic 2
Timing	**3 months prerandomisation**	**Day 0 day of randomisation**	**7 days postrandomisation**	**6 months postrandomisation**	**12 months postrandomisation**
Vitals	x	x	x	x	x
PFTs	x	x	x	x	x
NELF	x	x	x	x	x
FeNO	x	x	x	x	x
Medication questionnaire	x				x
Demographical, housing and medical history questionnaires	x				
Blood samples	x				x
Skin prick	x				
Nasal brush	x				x
6MWT	x				x
Sterile nasal swab		x		x	
Home dust collection		x		x	
7-day air sample preceding visit	x	x	x	x	x

FeNO, fractional exhaled nitric oxide; 6MWT, 6-Minute Walk Test; NELF, nasal epithelial lining fluid; PFTs, pulmonary function testings.

(SGRQ)[25 26]; (2) respiratory symptoms, measured through the Breathlessness, Cough and Sputum Scale (BCSS)[27]; and (3) functional capacity assessed by the 6-Minute Walk Test (6MWT) (online supplemental table 1).[28–30] Other outcome measures will include nasal inflammatory mediators measured in the nasal epithelial lining fluid (NELF) by nasosorption.[31 32]

Health measurements

Spirometry

Lung function will be obtained at all five study visits. Baseline (preintervention) lung function will be measured twice (at the study entry visit at BIDMC and 3 months later at day 0 home visit when real/sham air purifiers are installed).

A trained research assistant will obtain pulmonary function testing (PFT) using a portable EasyOne Plus Diagnostic Spirometer (ndd Medical Technologies, Switzerland). It has built-in quality assurance and incentive software and has been validated and used extensively in research, including the Burden of Obstructive Lung Disease Initiative.[33–35] The EasyOne Plus Diagnostic Spirometer is not influenced by temperature, humidity or barometric pressure. It requires three reproducible efforts per completed test. We will collect a maximum of five trials per test. We will record FEV_1, peak expiratory flow rate and forced vital capacity (FVC). The forced expiratory ratio (FEV_1/FVC) will also be calculated.

Nasal Epithelial Lining Fluid (NELF)

A trained research assistant will collect NELF, as described by Rebuli.[31 32] Each nostril will be briefly moistened with 100 µL of 0.9% sterile normal saline solution. An absorbent, fibrous matrix of Leukosorb medium (Pall Scientific, Port Washington, New York, USA), cut to fit within the nasal passages, will be inserted into each nostril until the indicator mark is at the base of each nare. The nostrils will be clamped shut with a padded nose clip for 2 min. Both strips will then be removed and placed in separate sterile 1.5 mL cryovials and stored at −80°C at BIDMC. Two paired NELF samples will be collected at all clinic and home visits. NELF samples will be analysed for inflammatory mediators and for metals.

Fractional exhaled nitrous oxide (FeNO)

FeNO (Circassia AB, Sweden) measurement will be used as an assessment of airway inflammation and will be conducted by a research assistant. We will use the portable NIOX VERO device and obtain two exhaled nitric oxide measurements at each visit, from which an average will be taken.

Skin prick

A research assistant will perform a skin prick test using standard procedures and protocols using the MultiTest II device (Lincoln Diagnostics, Decatur, Illinois).[36] The skin prick test will be performed at the first clinic visit. A panel of 14 common allergens will be tested: *Alternaria tenuis*, *Aspergillus fumigatus*, dog epithelium, *Cladosporium*, cat hair, box elder, dust mite mix, cockroach mix, mouse epithelium, *Penicillium*, red birch, short ragweed, timothy grass and white oak. Histamine will serve as the positive control and saline as the negative control. Atopy will be defined as having at least one positive skin reaction.

Nasal swab

We will collect sterile nasal swabs at randomisation and 6 months postrandomisation. We will swab each anterior nare for 5 s using sterile PurFlock Ultra Flocked Swabs (Puritan Medical Products Company, Guilford, Maine).[37] Samples will be stored in a 1.0 mL Cryotube at −80°C.

Nasal brush

A research nurse at the BIDMC Clinical Research Centre will perform nasal brushing at the clinic visits. The participant will be asked to blow their nose. The research nurse will insert a sterile cytology brush (Medical Packing Corporation, Camarillo, California) into the inferior turbinate and move the brush in a circular motion for 10–15 s. If there is blood or mucus on the brush, the procedure will be repeated in the other nare. Samples will be vortexed for 60 s and stored in the cell lysis buffer RLT Plus by Qiagen (Hilden, Germany) in a 1.4 mL Micronic vial at −80°C at BIDMC.

6-Minute Walk Test (6MWT)

The research assistant will perform a 6MWT with the participant at the two clinic visits (at study entry and 12 months postrandomisation). This test was developed for people with respiratory disease and will measure the distance that a person can walk on a flat surface in a period of 6 min.[28–30]

Blood samples

At the clinic visits, blood will be collected and analysed at a clinical laboratory for cell count with differential and serum IgE. In addition, whole blood samples will be collected and stored in trace metal-free tubes. A whole blood sample will be collected in a Paxgene tube. Additionally, we will collect plasma, to be stored as 6–1 mL aliquots in 1.8 mL cryovials and buffy coat samples to be stored as 3–1 mL aliquots in 1.8 mL cryovials. All samples will be stored at −80°C.

Questionnaire assessments

The change in health status will be quantified using the SGRQ, a validated 50-item questionnaire scored from 0 to 100, with higher scores indicating more health impairment, with a 3-month recall that measures respiratory symptoms, limitations in daily life and perceived well-being in patients with COPD.[25 26] SGRQ will be administered via electronic questionnaire at baseline (3 months before intervention and on the day of intervention) and postintervention (at 6 months, 9 months and 12 months). The change in respiratory symptoms will be measured monthly through the Breathlessness, Cough and Sputum Scale (BCSS) administered electronically. The BCSS has been validated to assess the severity of COPD symptoms

(breathlessness, cough and sputum)[27] and is scored between 0 and 12, with higher scores indicating greater symptom severity. The Modified Medical Research Council (mMRC) Dyspnoea Scale will also be administered every 3 months to ask participants to describe disability due to breathlessness.[38] In addition, a COVID-19 questionnaire will be administered every 3 months to ask about a COVID-19 diagnosis or treatment in the last 3 months. Each month, we also ask about the severity of COPD symptoms, any new healthcare diagnoses, any hospitalisations and any changes to medications.

Power calculations

We plan to enrol 160 participants with eosinophilic COPD. For the primary outcome of change in forced expiratory volume in 1 s (FEV_1), we estimated power using a simulation-based approach that repeatedly generated data under a linear mixed model applied to all of the data collected for each individual, including two baseline and three postrandomisation lung function measurements. We calculated the proportion of time; we rejected the null hypothesis of no intervention effect within this modelling framework. With an alpha=0.05 and a total of n=160 participants, we estimate that we will have 80% power to detect an intervention effect of at least 20 mL in FEV_1 and 90% power to detect a difference of 24 mL in FEV_1 due to the intervention. If we have a dropout rate of 12.5%, we will have 80% power to detect an intervention effect of at least 22 mL and 90% power for an effect of at least 26 mL in a completers-only analysis among 140 participants. We anticipate that our 1-year indoor air quality intervention will result in a difference in FEV_1 that is greater than the effect associated with variability in daily and annual air pollution levels in observational studies.[39–42] Still, we are adequately powered to detect an effect size as small as what is reported in these studies.

For our secondary outcome of change in health status measured by SGRQ, with an alpha=0.05, a total of n=160 participants (80 per arm) and SD of SGRQ change of 8.7,[17] we will have 80% power to detect a 3.9-point difference and 90% power to detect a 4.5-point difference in SGRQ when testing the group postrandomisation effect in a linear mixed model framework. If we have a dropout rate of 12.5%, we will have >80% power to detect an intervention effect of at least 4.2 points and 90% power to detect a 4.8-point difference in a completers-only analysis among 140 participants. Our true power will be even higher than this due to the repeated measures of SGRQ (two baseline and two postrandomisation) in our study. For clinical trials in COPD, a mean SGRQ change score of 4 units is considered a valid threshold of beneficial treatment.[43]

Data analysis plan

Our primary analysis will contrast changes in outcome levels in the HEPA intervention and control (sham) arms. For our primary outcome of FEV_1, we will obtain two baseline measures (3 months apart) and three observations postintervention for each participant (spanning 12 months), which will make it possible to assess the effects of the intervention while controlling for the season of measurement. Our primary and secondary outcomes are all continuous measures (change in FEV_1, functional status by SGRQ score, 6MWT, symptom score). We will apply linear mixed-effect models to investigate the effect of air purification on outcome variables:

$$Y_{ij}=b0 + b1\ grp_i + b2\ grp_i \times post_j + b3\, z_{ij} + w_i + {}_{eij},$$

where Y_{ij} is any continuous outcome for participant i at visit j; grp_i indicates active or sham air purifier; $post_j$ is an indicator variable for postrandomisation (vs prerandomisation) for a given visit; and z_{ij} is a vector of potential confounders on the day of visit, including season. In this model, the b1 indicates the difference in outcome at baseline and allows us to check for imbalance in the randomisation. In the likely event that there is balance in outcomes at baseline and the main effect of grp_i is absent, we can refit the model removing this main effect. The b2for the grp_i * $post_j$ interaction is the term of scientific interest and indicates how postrandomisation versus prerandomisation changes in FEV_1 differ in the intervention versus control arms. The term w_i represents a normally distributed subject-specific random effect to account for intraindividual correlations among repeated measurements taken on the same individual, and e_{ij} is a normally distributed within-subject error. In the event of crossovers, the primary analysis will be intention to treat.

Standard regression diagnostics for longitudinal residuals will be employed to check the normality assumption and assumed variance-covariance structure of the residuals, and more flexible structures will be used when necessary. Continuous outcomes will be transformed to meet assumptions of normality required for modelling. Outliers will be identified using the generalised extreme Studentized deviation procedure. If outliers have a substantial influence, we will run sensitivity analyses excluding them.

In secondary analyses, we will examine if the effect of HEPA filtration on respiratory health is modified by time spent at home, characteristics of the home, indoor pollution exposures (eg, gas stove use, secondhand smoke exposure) and occupational exposures.

Ethics and confidentiality

Institutional Review Board (IRB) approval was obtained through BIDMC (2019P001129). Participating study sites have ceded approval to the BIDMC IRB, consistent with current US National Institutes of Health (NIH) policy. We will employ multiple strategies to minimise all potential risks to the participants. Following ethical and IRB guidelines, a participant's confidentiality will be maintained and respected throughout the study. A unique identifier, rather than the name of the participant, will be used for the collection of data and labelling of specimens. Likewise, all of the databases will use the same identifier with the exception of one database which will contain the tracking and contact information of the

participants. Boston Children's Hospital will serve as the data coordinating centre for the study. All of the databases will be secured on a network drive, and access will only be granted to study staff on a need-to-know basis in all the institutions. Confidentiality and privacy will be maintained with state-of-the-art, password-protected REDCap system used by NIH clinical trial studies. The data reported in medical journals and scientific conferences will be presented in aggregate, and no individual participant will be identified.

Publication of results and data-sharing plan

The study findings will be published in peer-reviewed scientific journals and presentations in scientific and medical conferences. Authorship eligibility will be consistent with scientific norms. Requests for data-sharing and post hoc analyses will be considered after the study is complete and database closed. We will use data-sharing agreements to restrict the transfer of data, requiring that data be used only for research purposes.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Acknowledgements We would like to thank the following individuals who contributed to the early success of the study: Anna Stanley-Lee, Amparito Cunningham, Amro Aglan, Maura Alvarez Baumgartner, Kelly Chen, Mostafa Aglan, Hilary Zetlen, Alexandra Purcell, Katherine Poole, Aleeya Shamsi, Natalie Baker, Ramon H Guillen and the staff of the BIDMC Clinical Research Centre.

Contributors MBR conceived of the study. WP provided expertise in environmental clinical trial design and field work. BAC determined the primary statistical analysis plan. PK, C-MK, JMW and STF determined the exposure assessment plan. IJ and MER provided expertise in nasal fluid and nasal cell collection methodology and analysis. MBR, KFG, JPL, AJS and NJN planned the recruitment and data management protocols for the study. MSS, IAC, CMD and SS helped with the implementation and wrote the initial draft of the manuscript. All authors contributed to refinement of the study and critically reviewed and proofread the final manuscript.

Funding Supported by National Institute of Environmental Health Sciences grants R01ES031252, P30ES000002 and P30ES010126. Skin prick supplies have been provided by Lincoln Diagnostics (Decatur, IL). Coway USA (Los Angeles, CA) subsidised the air purifier cost. This work is further supported by the Harvard Catalyst/Harvard Clinical and Translational Science Center and Harvard University and its affiliated academic healthcare centres.

Competing interests MBR, WP, MER, IJ, BAC and PK report research grant funding from the NIH. MBR reports receiving expert testimony fees from the Conservation Law Foundation. BAC and PK report research funding from the US EPA outside the submitted work. WP reports receiving consulting fees from Regeneron, Sanofi, Novartis, Genentech, AstraZeneca and GlaxoSmithKline, all outside the submitted work. No other disclosures were reported.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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