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The home air in agriculture pediatric intervention (HAPI) trial: Rationale and methods

Erin E. Masterson[a,*], Lisa B. Younglove[a], Adriana Perez[b], Elizabeth Torres[c], Jennifer E. Krenz[a], Maria I. Tchong French[a], Anne M. Riederer[a], Paul D. Sampson[d], Nervana Metwali[e], Esther Min[a], Karen L. Jansen[a], Gino Aisenberg[f], Ryan S. Babadi[a], Stephanie A. Farquhar[a,g], Peter S. Thorne[e], Catherine J. Karr[a,h]

[a] Department of Environmental & Occupational Health Sciences, University of Washington, Seattle, WA, United States of America
[b] Yakima Valley Farm Worker's Clinic, Toppenish, WA, United States of America
[c] Northwest Communities Education Center, Radio KDNA, Granger, WA, United States of America
[d] Department of Statistics, University of Washington, Seattle, WA, United States of America
[e] Department of Occupational and Environmental Health, University of Iowa, Iowa City, IA, United States of America
[f] School of Social Work, University of Washington, Seattle, WA, United States of America
[g] Department of Health Services, University of Washington, Seattle, WA, United States of America
[h] Department of Pediatrics, University of Washington, Seattle, WA, United States of America

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ABSTRACT

Background: Data addressing air quality effects on children with asthma in rural U.S. communities are rare. Our community engaged research partnership previously demonstrated associations between neighborhood NH_3 and ambient $PM_{2.5}$ and asthma in the agricultural lower Yakima Valley of Washington. As a next step, the partnership desired an intervention approach to address concerns about pediatric asthma in this largely Latino immigrant, farm worker community.

Objective: The Home Air in Agriculture Pediatric Intervention (HAPI) sought to examine the effectiveness of enrichment of an existing asthma education program with portable high-efficiency particulate air (HEPA) cleaners designed to reduce $PM_{2.5}$ and NH_3. We investigated the effect of this enriched approach on these exposures and asthma health measures.

Design: We randomized children with poorly controlled asthma to a control arm (current asthma education program) or an intervention arm (current asthma education program + placement of two indoor air cleaners in the family's home). Outcomes included (1) 14-day integrated samples of indoor air contaminants ($PM_{2.5}$ and NH_3) at baseline and one-year follow-up and (2) child asthma health metrics at baseline, midpoint (4–6 months) and one-year follow-up. These included the Asthma Control Test, symptoms days, clinical utilization, oral corticosteroid use, pulmonary function, fractional exhaled nitric oxide, and urinary leukotriene E_4 concentration.

Discussion: To our knowledge, this is the first randomized HEPA cleaner intervention designed to assess NH_3 as well as $PM_{2.5}$ and to evaluate health outcomes of children with asthma in an agricultural region.

1. Introduction

While there is significant evidence for indoor and outdoor air contaminants influencing pediatric asthma morbidity in urban cohorts, data addressing air quality and health of children with asthma in rural United States (U.S.) communities are rare. In the agricultural lower Yakima Valley of Washington State, we previously reported that increases in ambient fine particular matter (PM) less than 2.5 μm in diameter ($PM_{2.5}$) and neighborhood levels of ammonia (NH_3) are associated with deficits in lung function and increased symptoms among children with asthma [1–5].

Recognizing that ambient pollutants may infiltrate indoor settings and since children typically spend the largest proportion of their time indoors, we designed the Home Air in Agriculture Pediatric Intervention (HAPI) Trial to address the home indoor environment in this community. Based on studies conducted among low-income urban

* Corresponding author.
E-mail address: emaster@uw.edu (E.E. Masterson).

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children, the evidence is strong for the effectiveness of home-based interventions to improve asthma health outcomes [6,7]. This is particularly true for interventions that provide education and focus on identification and reduction of indoor asthma triggers, including allergens (e.g., dust mites, cat, dog, mouse, cockroach) and airway irritants such as PM, NH_3, traffic-derived pollutants, and cigarette smoke [7].

Several studies have examined the effectiveness of portable high-efficiency particulate air (HEPA) filter and HEPA-type air cleaners, alone [8–17] or in concert with asthma education [18–22]. Studies focused on homes with wood stoves in rural and semi-urban communities found evidence for PM reduction with HEPA-type air cleaners [9,10,13,15,16,23], but not necessarily for improvement in asthma [11,19,24]. It is well-established that asthma interventions delivered by community health workers (CHW) consistently improve asthma-related health outcomes, including fewer symptoms, daytime activity limitations, and emergency/urgent care visits [25,26]. These typically involve home-based educational visits. HEPA interventions that have been combined with educational components have reported a reduction in asthma symptoms [18–20]. We leveraged an existing local CHW-based asthma education program and sought to examine the effectiveness of an additional portable HEPA cleaner intervention, designed to reduce $PM_{2.5}$ as well as NH_3, to the existing typical education program to reduce these indoor air contaminants and to improve asthma health.

2. Methods

2.1. Overview of design

We designed and carried out the HAPI Trial via a longstanding community engaged research partnership comprising the University of Washington's (UW) Pacific Northwest Agricultural Safety and Health (PNASH) Center and two community organizations. The Northwest Communities' Education Center (NCEC)/Radio KDNA is a Spanish language public radio station whose mission is to help and empower local disadvantaged communities to overcome barriers of literacy, language, discrimination, poverty, and illness. The Yakima Valley Farm Workers Clinic (YVFWC) provides clinical services to the majority of farm workers and their families and operates a CHW-delivered asthma home education program. Our UW staff provided study scientific oversight including training and quality assurance for all procedures. The YVFWC asthma education program served as the contact point for all participant interactions by phone and in person and conducted home-based asthma health assessments. The NCEC/Radio KDNA staff conducted residential exposure assessments and maintained an on-site field laboratory for sample processing and temporary storage.

A two-arm, randomized study design compared asthma control, lung function, unscheduled asthma-related clinical utilization, episodes of significant asthma exacerbation, asthma biomarkers, and household air quality among children with asthma who received the YVFWC CHW-delivered asthma education program to those who received portable HEPA cleaners for use in their homes in addition to the existing education program. Fig. 1 shows the basic structure of participant contact and data collection. We consented and enrolled participants at the YVFWC clinical site in Toppenish, WA. We then visited participants' homes to collect baseline measures and randomize participants to a study arm. Asthma health follow-up lasted for one year with assessments twice after randomization (mid-study year, end of study year). We collected 14-day integrated household air samples to measure $PM_{2.5}$ and NH_3 at baseline and at the end of the study year. We also assessed several covariates that describe factors known to influence asthma health. These included measurements of indoor inhalant allergens, endotoxin, and nitrogen dioxide (NO_2). In addition, we characterized baseline demographics, child atopy through skin prick testing, asthma health history, caregiver psychosocial stress, and home environment characteristics.

2.1.1. Study setting

The lower Yakima Valley in central Washington State is a highly productive region of intensive crop and dairy agriculture. Regional air quality is a concern, with episodic high daily $PM_{2.5}$, and high wintertime PM and NH_3 [27–29]. Sources include agricultural burning, wildfires, wood stove use, fugitive dusts, and secondary aerosol production from animal emissions [28]. The U.S. Environmental Protection Agency (EPA) has identified the area as a community impacted by environmental justice concerns based on the vulnerability of the population and the presence of environmental hazards [30].

For over a decade, our community engaged research partnership has focused on the environmental health of the immigrant Latino communities of farm workers and their families residing in this region. Pediatric asthma is a community-identified research priority that motivated this work as well as our prior asthma research [31].

2.1.2. Participant recruitment and eligibility

We identified potential participants from referrals to the YVFWC Asthma Education Program. The program identifies children with recent asthma emergency department (ED) visits to invite to the program. In addition, the program receives ongoing referrals from clinical providers and self-referral from community members. YVFWC staff contacted potential participant caregivers by phone and invited them to participate based on self-reported responses to screening eligibility criteria: (1) aged six to 12 years, (2) resided within 1/2 mile (800 m) of dairy or crop production, and (3) had poorly controlled asthma. We based the latter on a positive endorsement of: “more than four days with asthma symptoms in the prior two weeks”, “use of asthma rescue medications for more than four days in the prior two weeks”, “hospitalized or ED visit for asthma in the prior year”, and/or “unscheduled clinic visit due to an asthma attack in the past year”. We excluded children from the study who lived in more than one primary residence. The study was particularly interested in HEPA cleaner effectiveness in homes potentially impacted by ambient sources in an agricultural setting. Since indoor smoking can have a major influence on indoor PM, and smoking prevalence is relatively low in this population, we excluded homes with smokers [32].

We invited eligible participants to attend an enrollment visit at the YVFWC where we obtained informed consent.

2.1.3. Study visits, asthma education, and randomization

Fig. 1 illustrates the timeline and location of study encounters. We scheduled the first home visit as soon as possible after enrollment. This home visit comprised the baseline air sampling and asthma assessments, after which we randomized participants to a study arm. Next, we scheduled a mid-study home visit with asthma assessment which occurred approximately four to six months after enrollment. Finally, we scheduled a final home visit with follow-up air sampling and asthma assessments (end of study year assessment). Between the mid-study and final home visits, we made at least one retention call to each participant family.

All participants received the YVFWC asthma education program, a longstanding resource in this setting. This program includes content on (i) key mediators of asthma health, (ii) medication technique and adherence, and (iii) trigger identification and reduction recommendations. Historically provided as three in-home visits over three to four months, all children in the HAPI trial received the first education session in the clinic setting during the study enrollment visit. The program provided subsequent education at home, the second education session concurrent with the baseline study visit and the final education conducted independent of the study visits (approximately three months after enrollment). The program also provided the following to participants: a medication storage box and peak flow meter (asthma education session 1), a green cleaning kit (asthma education session 2), and dust mite covers for the child's pillow and mattress (asthma education session 3).

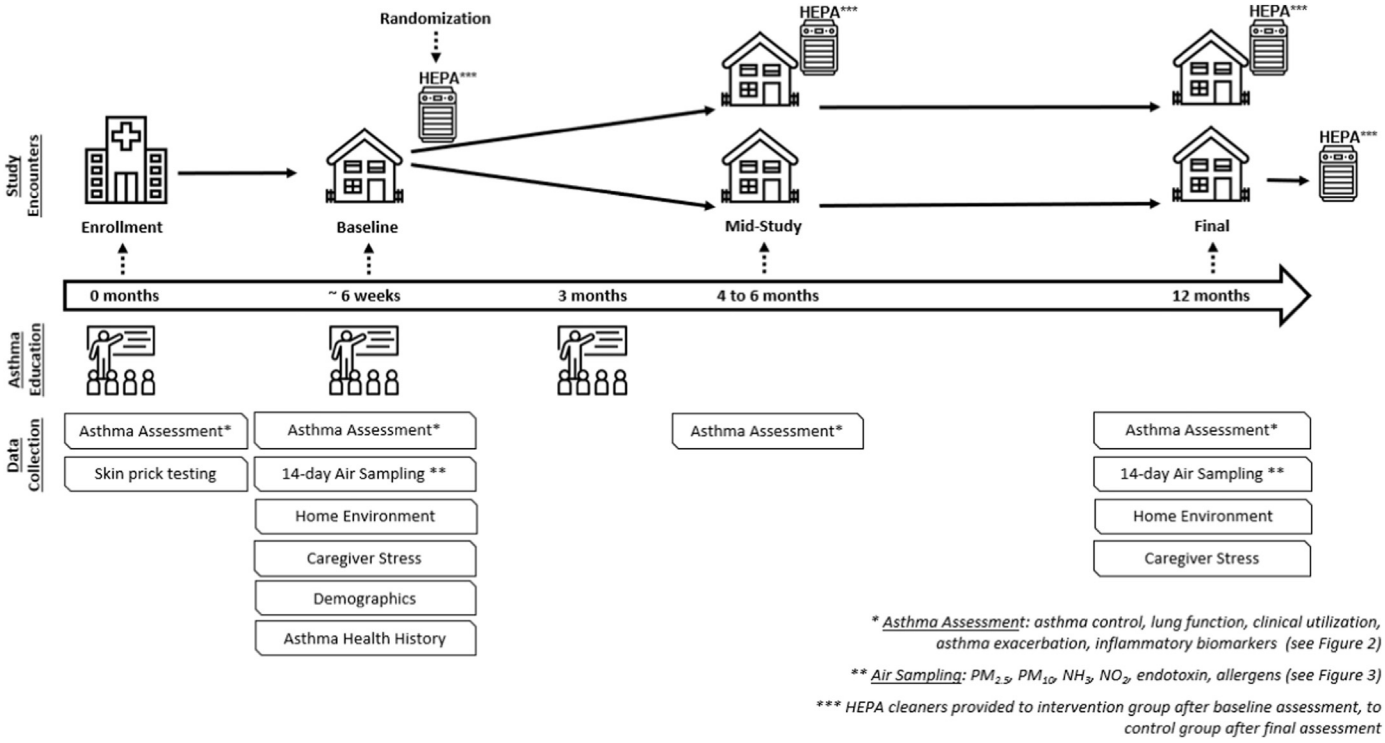

Fig. 1. HAPI trial overview.

We randomly assigned child participants to either (1) the HEPA cleaner intervention group with asthma education and provision of two indoor portable HEPA cleaners designed to reduce PM and NH_3 or (2) the control group (asthma education only). Our UW study staff prepared, sealed, and shuffled envelopes containing a card indicating control or intervention group. Prior to completion of the baseline 14-day air sampling, the UW study coordinator selected an envelope and provided the content (study arm assignment) to the field staff. After completion of the baseline sampling, field technicians installed two HEPA cleaners in the homes assigned to the intervention group. Families did not learn of their group assignment until after completion of the baseline assessment.

2.2. Intervention – Portable HEPA cleaner placement and use

HEPA filters are effective at reducing PM from both indoor and ambient sources [18,19]. We provided the Austin Air Pet Machine 410® as the portable HEPA cleaners for this study (Austin Air Systems Ltd., Buffalo, NY, USA). This commercially available unit had four-stage filtering including two pre-filters to remove medium and larger particles (e.g., pet dander, medium sized mold, pollen, and dust mite particles), a carbon/zeolite filter for removing NH_3 (and other pet odors, fumes), and a true HEPA filter rated for 99.97% removal of smaller particles (> 0.3 um) and 95% removal of particles > 0.1 um. The manufacturer noted the device could clean up to 1500 square feet of space and was rated for continuous use. The device included three fan speed options (high, medium, low).

The unit measured 58.4 cm high, 35.6 cm wide, and 35.6 cm deep, weighed 22.7 kg, and sat on easy-roll caster wheels. At the time of the intervention, units were purchased from the manufacturer for $350 USD each, a slight reduction from retail cost at that time. Field technicians placed the two air cleaners appropriately in the intervention group households, with one in the child's sleeping area and one in the home living area (20.3 cm from the wall, away from heating sources). Our field staff provided and discussed a fact sheet on using the air cleaner, which promoted optimal operation – continuous operation of both air cleaners, keeping the child's bedroom door closed and selecting the highest fan speed.

During the mid-study and final visits, we questioned intervention group participants about their typical use of the HEPA cleaner in the prior month (e.g., on/off, fan speed) by room (child's sleeping area, home living area). In addition, to monitor air cleaner use, we attached an Onset® HOBO UX90–004 Motor On/Off Data Logger (Onset Computer Corporation, Bourne, MA, USA) to all of the bedroom air cleaners and, due to budget constraints, approximately half of the living area HEPA cleaners; Austin Air technicians installed the loggers. The randomization envelopes included whether the units were to include a HOBO Data Logger.

2.3. Asthma health assessment: Disease history, baseline features, and trial follow up metrics

We assessed each participant's asthma health history as part of the baseline assessment. This included caregiver report of the child's asthma clinical utilization over the prior year and lifetime. In addition, the asthma educator recorded participants' prescribed asthma medications.

During the clinic enrollment visit, we conducted a skin prick test on study participants to determine atopy. The study staff instructed subjects to withhold antihistamines for 72 h prior to the test. The study physician (Karr) applied a disposable, multiple test skin prick applicator to the volar aspect of the participant's lower arm (Multi-Test II, Lincoln Diagnostics, Decatur, IL, USA) using six standard aeroallergens (dog epithelium; mixed mold containing Alternaria, Clad. sphaerosperum, mixed-Aspergillis (oryzae, repens, terreus, niger), and mixed-Penicillium (notatum, chrysogenum); mouse epithelium; mixed mite containing D. pteronyssinius and D. farina; mixed cockroach containing American and German; standardized cat hair) as well as histamine (positive control) and glycerinated phenol-saline (negative control) (ALK Abello, Horsholm, Denmark).

Fig. 2 lists the study metrics used to assess the effect of the intervention on asthma health. The measures include recommended metrics

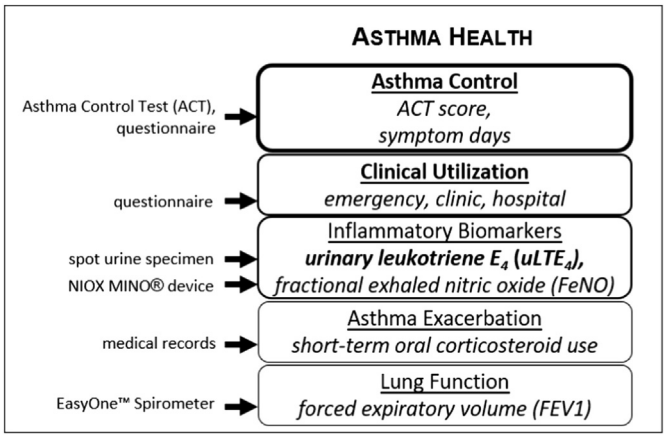

Fig. 2. HAPI trial asthma health measures.

for asthma clinical trials [33], including asthma control [34,35], lung function [36], unscheduled asthma-related clinical utilization [37], episodes of significant asthma exacerbation [38], and asthma biomarkers [39].

The enrollment visit (clinic) provided an opportunity for participants to become familiar with the measures requiring effort (spirometry, exhaled nitric oxide, urine specimen collection) and a study "run in" period after the first education session which covered proper medication use and ensured participants had their recommended medications. The trial's baseline, mid-study, and final asthma health assessments took place in the home. We also recorded questionnaire responses from caregivers on clinical utilization over the duration of follow-up (from randomization to end of study year). We reviewed medical records to determine short-term oral corticosteroid use by each participant during the one-year study follow-up as a measure of a significant exacerbation. We identified two primary subjective and two primary objective outcomes a priori: (1) asthma control measured using a composite instrument (Asthma Control Test, based on 4-week recall), (2) caregiver report of symptom days in the prior two weeks, (3) clinical utilization, and (4) urinary leukotriene E_4 ($uLTE_4$) concentrations [40–42]. We describe all of the health outcome measures in detail below.

2.3.1. Asthma control

The Asthma Control Test (ACT) is a well-validated, reliable, and recommended composite instrument for assessing control of asthma available in both Spanish and English [34,43]. We administered the five-item ACT to participants at least 12 years of age at enrollment and the seven-item Childhood Asthma Control Test (cACT) to children aged four to 11 years at enrollment and their caregiver. Child age at enrollment determined which test was applied for all data collection time points. For both tests, participants were asked to recall the prior four weeks. Higher scores indicate greater asthma control. Well-controlled asthma is defined as a composite score greater than 19 on both the ACT and cACT.

Asthma symptom days is a commonly assessed and recommended outcome in asthma intervention studies [35]. We asked caregivers to recall the number of days in the prior two weeks their child had particular asthma symptoms, including wheezing, coughing, tightness in the chest, shortness of breath, waking up at night because of asthma symptoms, or slowing down from usual activities because of asthma.

2.3.2. Clinical utilization

During the trial follow-up visits, staff asked caregivers if their child had a scheduled or unscheduled ("urgent") clinical visit with a doctor or health care provider, ED visit, or overnight hospitalization for asthma symptoms since the last in-home visit [37]. They recorded the numbers and types of visits caregivers reported.

2.3.3. Inflammatory markers of asthma

We measured both an established, clinically approved (fractional exhaled nitric oxide, FeNO) and an emerging ($uLTE_4$) biomarker of asthma-associated inflammation [44].

We used the portable NIOX VERO® (Aerocrine Inc., Stockholm, Sweden) for direct measurement of FeNO. We measured FeNO prior to spirometry in all participants. We interpreted results as low, intermediate, or high inflammation according to child age using ATS guidelines [45].

We also collected a spot sample of urine at each asthma assessment and measured specific gravity using a hand-held digital refractometer (ATAGO Co. Ltd., Bellevue, WA, USA). We then aliquoted and stored samples at −20 °C prior to submitting the urine samples to the National Institute of Health's Children's Health Exposure Analysis Resource (CHEAR) for quantification of $uLTE_4$ using an enzyme-linked immunosorbent assay (No. 501060; Cayman Chemical, Ann Arbor, Michigan). We saved additional aliquots for potential future analyses of interest.

2.3.4. Asthma exacerbation

We reviewed participant medical records for receipt of prescription for a course of oral corticosteroid during the trial as a measure of a significant asthma exacerbation [38].

2.3.5. Lung function

We measured lung function using the EasyOne spirometer (NDD Technologies, Andover, MA) according to current American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [36,46,47]. We conducted a minimum of three exhalations with acceptable starts, complete exhalation, and no coughs until we achieved at least two exhalations with acceptable repeatability.

2.4. Home environment assessment

We assessed participants' homes for features relevant to asthma health through caregiver survey, home walk-through (observational checklist), and 14-day integrated air sampling conducted at the baseline and final home visits approximately one year later. The latter was a primary study outcome.

2.4.1. Indoor air contaminant assessment

The primary contaminants of interest were $PM_{2.5}$ and NH_3 in the child's sleeping area, while secondary exposure outcomes included $PM_{2.5}$ in the living area, and PM_{10} and PM_{coarse} (PM_{10}-$PM_{2.5}$) in the sleeping area (Fig. 3). We also assessed established indoor asthma triggers as covariates of interest. These included NO_2, endotoxin, and common indoor inhalant allergens (dust mites (Mite Group 2), cat (Fel d 1), dog (Can f 1), mouse (Mus m 1), cockroach (Bla g 2), mold (Alt a 1)) in the child's sleeping area. We measured outdoor NH_3 to evaluate the potential influence of ambient agricultural sources on indoor NH_3 concentrations.

We selected and positioned sampling equipment to minimize participant burden (e.g., low noise, streamlined/out-of-the-way placement, no maintenance or technician checks required during sampling) and to represent exposures in the child's breathing zone (i.e., approximately 1 m from the floor). We attached the PM, NO_2 and NH_3 sampling devices to an intravenous (IV) pole on wheels, with the PM sampler enclosed in a small metal cage to protect it from damage or interference. We placed Electrostatic Dust Collectors (EDCs) [48] on a flat surface in the child's sleeping area and used these to collect settled dust for subsequent endotoxin and target allergens analysis. We collected 14-day baseline and follow-up samples one year apart (same season). We typically set up sampling equipment on a Tuesday, Wednesday or Thursday so households would have the same proportion of weekdays

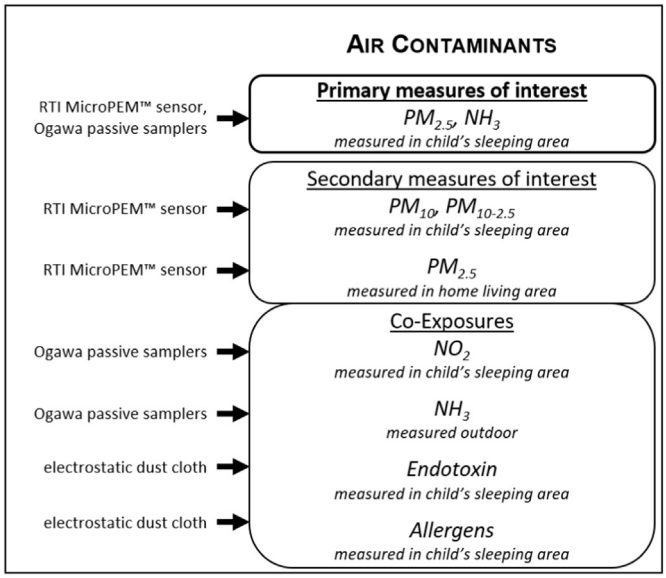

Fig. 3. HAPI Trial Air Contaminant Exposure Measures.

vs. weekends in their 14-day samples.

General quality assurance/quality control (QA/QC) measures included detailed written field, laboratory, and data management protocols, field and laboratory staff training, detailed field and laboratory logbooks, chain-of-custody sample tracking, periodic internal audits, National Institute of Standards and Technology traceable calibration standards (or equivalent where applicable), laboratory and field blanks, matrix spikes, and replicate samples. We will publish detailed sampling and analytical methods for each contaminant in future work, as we summarize briefly below.

2.4.2. Particulate matter (PM)

We collected gravimetric PM samples using MicroPEM v. 3.2A samplers (RTI International, Research Triangle Park, NC, USA) with mini $PM_{2.5}$ and PM_{10} impactors. Primarily designed for personal exposure measurements, we used the MicroPEMs as area monitors due to their small size, quiet pump and good agreement with reference methods [49–51]. We hung two MicroPEMs (one for $PM_{2.5}$, one for PM_{10}) in the child's sleeping area, and one for $PM_{2.5}$ in the living area, with flow rates set to 0.5 L/min using a TSI 4100 flow meter (TSI Incorporated, Shoreview, MN). We loaded the MicroPEMs with 25-mm Teflon filters, which were pre- and post-weighed to the nearest 0.5 μg following standard procedures in a temperature- and humidity-controlled laboratory at the UW [52,53]. We calculated PM concentrations ($\mu g/m^3$) by dividing the post and pre filter mass difference by the volume of air drawn through the MicroPEM over the sample duration at the measured flow rate.

2.4.3. Ammonia (NH_3) and nitrogen dioxide (NO_2)

Ogawa passive samplers (i.e., badges) (Ogawa USA, Pompano Beach, FL, USA) were used to sample gaseous NH_3 and NO_2 in the child's sleeping area, and NH_3 outdoors in close proximity to the residence. Ogawas have performed well in validation studies against active methods for measuring NH_3 at low concentrations in ambient air [54,55], although validation studies are lacking for household indoor air where NH_3 concentrations are typically higher [56–59]. We chose the Ogawas over an active method because they are lower cost, noiseless, do not need electricity, and can be left unattended for long periods [55,60]. Badges (one for each analyte) were pinned to a piece of cloth and hung from the IV pole just above the MicroPEMs. Technicians were careful to make sure both ends received airflow and to place them away from sources that could potentially bias the measurements (e.g., water, gas stoves). At the end of the sampling period, badges were removed and transported cold to the field laboratory then to UW for analysis following manufacturer protocols [61,62].

2.4.4. Endotoxin and allergens

Endotoxin and common indoor allergens in the child's sleeping area were measured using EDCs, comprised of two fiber electrostatic cloths inside a polypropylene folder. These simple, low-cost devices have been validated for passive sampling of bioaerosols in homes [63–65]. EDCs were supplied by the Thorne Laboratory at the University of Iowa (UI) (Iowa City, IA, USA). EDCs were placed on a flat surface in the child's sleeping area if available, such as on a dresser, desk, or nightstand. If a flat surface was not available, then field staff placed the EDC on the flat surface of a portable TV tray table that was provided. At the end of the sampling period, EDCs were collected, transported cold to the field laboratory, then shipped cold to UI for extraction and endotoxin analysis using the kinetic chromogenic Limulus amebocyte lysate assay [48,66,67]. An aliquot of the extract was removed, stored at −20 °C, then shipped frozen to the UW for analysis of the target allergens (dust mite (Mite Group 2, preferentially Der p 2 but may also include Der f 2), cat (Fel d 1), dog (Can f 1), mouse (Mus m 1), cockroach (Bla g 2), and mold (Alt a 1) using MARIA multiplex arrays for indoor allergens (Indoor Biotechnologies, Charlottesville, VA, USA) [68,69]. This method has been shown to be 10 to 40 times more sensitive for Mite Group 2 and Fel d 1, respectively, than traditional ELISA methods [69].

2.4.5. Psychosocial stress

Pediatric asthma outcomes may be influenced by caregiver exposure to psychosocial stress (including negative life events, depression, traumatic events and violence, chronic financial strain, and discrimination) [70–72]. We administered a psychosocial questionnaire to the primary caregiver as part of the baseline and final home visits to assess personal and community stressors. This questionnaire consisted of 38 questions derived from several validated tools and organized into six discrete sections: (i) stress associated with having a child with asthma [73], (ii) perceptions of safety [74,75], (iii) stresses relevant specifically to Latino immigrant communities [76], (iv) violence exposure [77], (v) caregiver overall perceived stress [78], and (vi) depression symptom checklist [79].

2.4.6. Home observation and caregiver report of household features and activities

During the baseline and final home visits, we collected information on each participant's home environment. This included a home environmental checklist (HEC), an observational checklist adapted from the U.S. EPA Asthma Home Environment Checklist (HEC) [80]. The HEC modules include: (a) Building Exterior/Outside, (b) General (number of bedrooms, any cleaning to prepare for study visit, recent home improvements), (c) Dust and Cleaning practices and frequency, (d) Ventilation and Moisture, (e) Pets and Pests, (f) Heat Sources used, maintenance and condition, (g) Chemical and Irritants used in the home, and (h) a Home Walk-Through that described and assessed the condition of home flooring, odors, structural issues and other damage, and cleanliness by room (child's sleeping area, living area, kitchen, bathroom).

We also administered a questionnaire to caregivers regarding typical activities within the household by three time periods throughout the day (6 am-12 pm, 12 pm–6 pm, 6 pm-6 am). Our field staff asked caregivers to report on the day prior at all home visits. The activities included having windows open, use of the stove and oven, sweeping and vacuuming, use of air conditioning, candles, incense, and the amount of time the child spent awake at home.

2.5. Human subjects

2.5.1. Informed consent, incentives, and return of results

The UW Human Subjects Division and the YVFWC Research Review Committee approved the study protocol. Study participants who agreed to share clinical record data signed Health Insurance Portability and Accountability Act (HIPAA) forms.

The HAPI trial provided participating families incentives in the form of $50 at each of the data collection encounters, up to $200 per family. Intervention families could elect to keep the HEPA cleaners or have them removed by our field staff at study completion. The HAPI study offered control families a HEPA cleaner with instructions on use at study completion.

2.5.2. Data safety monitoring

At the time of submission (2013), given the intervention was to modify exposure only and the small size of the study, the project was deemed not a clinical trial and did not merit or require a formal Data Safety Monitoring Committee. There were no safety implications with the intervention. The PI, the study core partners, and the community advisory board handled reports and complaints from study participants regarding the use of the HEPA cleaners during the trial. Our social work co-investigator created a plan for follow-up with caregivers who revealed suicidal ideation, emotional or psychological distress, or expressed potential to harm others during the psychosocial assessment component of the data collection.

2.6. Statistical considerations

The planned primary analyses for the HAPI trial is to determine if access to in-home HEPA cleaners (1) reduced indoor $PM_{2.5}$ and NH_3 for participating children living in a rural agricultural community, and (2) improved asthma-related health outcomes over and above the existing, “usual” asthma education program.

2.6.1. Sample size and power calculations

We conducted power calculations for demonstrating an effect on $PM_{2.5}$ and asthma control in a sample of 30 control participants and 30 HEPA intervention participants. We examined prior studies of similar intervention study designs on the effects of HEPA cleaners on PM which provide a range of expected intervention effects (30–50%) and coefficients of variation (CV) (60–80%) [18–20]. Computed power values for $\alpha = 0.05$ level, two sample *t*-tests (carried out on the log scale) with possible intervention effects from 35% to 50%, and CV from 60% to 80% were calculated. Power exceeded 0.80 for all scenarios except those for the lowest effect size (35%) and a few with the highest CVs. Actual analyses will use more efficient linear mixed effects models accounting for relevant covariate effects. We conclude that we have sufficient power to detect meaningful changes in $PM_{2.5}$ levels between groups.

For the primary outcome metric of asthma control (ACT/cACT), we carried out a power calculation to demonstrate the results expected in analyses of the effects of the intervention for the proposed study design with participants divided approximately evenly between control and intervention groups. It has been suggested that a minimally clinically important difference in child ACT is 2 points [81,82]. We estimated, for a sample size of 60 participants, that we would have 0.81 power to detect a 2-point improvement in the cACT, comparing baseline with the mean of mid-study and final study assessments in a model that ignores (or assumes prior adjustment for) demographic and seasonal effects. We based this calculation on estimated between- and within-subject standard deviations of 3.76 and 2.46, respectively, derived from the middle ranges of overall standard deviations and ICCs reported in related studies [82–86].

2.6.2. Data analysis plans

We will examine control/intervention group differences (i.e., randomization effectiveness) through descriptive analyses with appropriate tabular and graphical approaches as well as associations among the following groups of variables: demographics, health history, psychosocial stress, home environment features, key environmental contaminant levels known to influence asthma, and asthma-related outcomes. We will transform variables with skewed or heteroscedastic distributions as appropriate.

Next, we will examine the effect of control/intervention group on air contaminants in the home. Our primary air contaminant outcomes are $PM_{2.5}$ and NH_3 concentrations in the child's sleeping area. Using an intention-to-treat approach, we will fit analysis of covariance (ANCOVA) models comparing indoor concentrations at follow-up in the control vs. HEPA-assigned households, adjusting for baseline concentrations. We hypothesize indoor concentrations of these contaminants will be lower in the HEPA-assigned households.

We will also perform sensitivity analyses to investigate the influence of temperature, relative humidity, occurrence of local wildfires during sampling periods, and other potentially important variables on the control/intervention group-contaminant concentration associations. Information on local wildfires will be obtained from the regional air authority and publicly available data from the nearest regulatory $PM_{2.5}$ monitor (Toppenish, WA) operated by the Yakama Nation and Washington State Department of Ecology.

Finally, to examine the effect of control/intervention group on health outcomes, we will employ longitudinal statistical models that account for baseline measurements and potential seasonal effects in an intention to treat analysis. Asthma control, measured by the ACT (prior four weeks) and the number of symptom days reported in the prior two weeks on parental survey, urinary LTE_4 concentrations and clinical utilization for asthma care are the primary outcomes of interest. We will also examine additional asthma-related outcomes (see Fig. 2). We hypothesize that following randomization, the intervention group will be less likely to have poorly controlled asthma, have fewer symptoms days in the past two weeks, have better lung function, require fewer courses of oral corticosteroids, have fewer unscheduled clinical visits (ED, clinic, hospital), and have lower concentrations of inflammatory markers (FeNO, $uLTE_4$). We will consider additional exposure covariates (i.e., NO_2, coarse PM, PM_{10}, endotoxin, and allergens) in models as confounders, if baseline levels suggest randomization regarding these factors was not a success. We will also explore effect modification by atopy, use of a controller medication at baseline, and caregiver stress. Secondary analyses will examine if analysis of intervention status on health outcomes and exposures were influenced by frequency of HEPA use and timing of HEPA use (e.g. night vs day).

2.7. Dissemination of findings

The community partner organizations and community advisory board has identified appropriate audiences and methods for disseminating results and providing ongoing advice on culturally appropriate messaging. Audiences identified for overall study result report-back include the study participants, medical provider community, the broader Yakima Valley community, the Confederated Tribes and Bands of the Yakama Nation, and local public health and air quality control agencies. The dissemination plan includes community events, health fairs, infographics, brief radio reports through Radio KDNA, meetings with agency leaders and development of a *radionovela*.

We provided individual feedback to all participant caregivers at the time of testing for the asthma related health assessments that provide immediate results and clinically relevant interpretation (e.g., spirometry, FeNO, ACT scores, skin prick testing). At the end of the study year, staff reviewed the health results again with the caregiver participants and discussed actionable items such as adhering to the child's asthma management plan. We also returned baseline measurements of

individual household indoor $PM_{2.5}$ and NH_3 levels to participants as both written reports and verbal feedback.

2.8. Study evaluation

At the end of the participant's study year, we administered a survey to caregivers regarding their impressions of the study experience. In addition, we conducted an in-depth phone evaluation with a subset of caregivers (every eighth participant, after study completion, $N = 7$). Questions for the in-depth phone evaluation included acceptability of intervention and environmental sampling methods.

3. Discussion

To our knowledge, this is the first portable HEPA cleaner trial in a rural agricultural setting and the first to evaluate the effect of HEPA filters on NH_3 in addition to PM. In our study, we measure both indoor $PM_{2.5}$ and NH_3, which may reflect ambient sources of air pollution from proximal sources infiltrating homes as well as specific indoor sources. We examined the influence of the HEPA intervention on both contaminants as many HEPA air cleaners include components to reduce pet odors such as NH_3. The impact of these filters on indoor concentrations of NH_3 in addition to $PM_{2.5}$ have not previously been reported, so we aimed to advance our understanding of the influence of these air cleaners on both contaminants as well as health.

Overall, the pediatric asthma and environmental trigger literature is dominated by non-rural cohorts despite evidence that asthma morbidity may be as high or higher among low income rural children with asthma in the United States [87–89]. While many of the triggers previously identified may reflect poor housing conditions, rural agricultural communities may have unique sources to address. For example, we identified relationships between neighborhood levels of NH_3 and asthma outcomes in the setting of this trial [1,2]. This study includes a relatively comprehensive evaluation of residential features associated with indoor air quality and asthma health. This provides an opportunity to address any key confounders or effect modifiers and provides a unique opportunity for better understanding the role of the home environment on this understudied population of children with high asthma morbidity.

The trial design builds on prior literature that suggests the use of portable HEPA cleaners reduces indoor PM [9,10,13,15,16,18–22] and may improve asthma outcomes for children [11,19,24]. The effectiveness of HEPA cleaners on reducing PM (including $PM_{2.5}$) in the homes of children with asthma is relatively consistent, although the effect magnitude varies among studies. In addition to PM, we include an innovative component to examine the potential influence of a commercially available air cleaner on NH_3. We also employ both well-established measures of asthma health outcomes as well as a more novel biomarker of asthma health: $uLTE_4$ [42].

The effectiveness of portable HEPA cleaners on asthma health outcomes is mixed [11,19,24]. Many studies have shown the benefits of asthma education that includes identification of individual child triggers and individualized plans for addressing their triggers [25,26]. However, only two previous trials have examined the effect of portable HEPA cleaners combined with an in-home asthma education program [18–20]; of these, only Butz et al. (2011) and Eggleston, et al. (2005) examined effects on asthma symptoms (and found reductions). Although Batterman et al. (2013) examined indoor air quality (not asthma outcomes), they reported large variability in filter use across participating homes, noting how filter use increased when a CHW program was implemented and recommending that active HEPA use monitoring be part of future interventions [20,21].

Increasingly, children in communities across the United States have access to asthma education programs provided by clinical sites or public health agencies. We designed our study to assess whether adding portable HEPA cleaners could further improve indoor air quality and asthma outcomes for these children. Our community-engaged practices also provided an opportunity for successful engagement and retention of a difficult to reach population of Latino immigrant children with asthma in rural agricultural Washington State. The community partners were involved in all stages of study design and conduct, ensuring practices that are feasible and acceptable to the participants. Furthermore, by anchoring the study in a longstanding asthma education program, we are fostering effective translation of study findings to the local program and similar programs across the nation.

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Authors' contributions

CJK, the Principal Investigator (PI), conceived of and designed the present study. EEM and CJK drafted the manuscript. LY, AP, ET, JK, MTF, AMR, PS, NM, EM, KJ, GA, RSB, SF, and PST contributed to the conception and design of the study, collection of data and the drafting of this manuscript. All co-authors revised the manuscript for intellectual content and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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