BMJ Open Respiratory Research

Air quality, Environment and Respiratory Outcomes in Bronchopulmonary Dysplasia, the AERO-BPD cohort study: design and adaptation during the SARS-CoV-2 pandemic

Hana B Ruran,[1] Gary Adamkiewicz,[2] Amparito Cunningham,[3] Carter R Petty,[4] Kimberly F Greco,[4] Sigfus Gunnlaugsson,[1,5] Natalie Stamatiadis,[1] Gabriella Sierra,[1] Jose Vallarino,[2] Marty Alvarez,[2] Lystra P Hayden,[1,5] Catherine A Sheils,[1,5] Edie Weller,[4,5] Wanda Phipatanakul ,[3,5] Jonathan M Gaffin[1,5]

To cite: Ruran HB, Adamkiewicz G, Cunningham A, *et al*. Air quality, Environment and Respiratory Outcomes in Bronchopulmonary Dysplasia, the AERO-BPD cohort study: design and adaptation during the SARS-CoV-2 pandemic. *BMJ Open Resp Res* 2021;8:e000915. doi:10.1136/bmjresp-2021-000915

Received 24 February 2021
Accepted 7 June 2021

For numbered affiliations see end of article.

Correspondence to
Dr Jonathan M Gaffin; jonathan.gaffin@childrens.harvard.edu

ABSTRACT

Introduction Almost half of all school-age children with bronchopulmonary dysplasia (BPD) have asthma-like symptoms and more suffer from lung function deficits. While air pollution and indoor respiratory irritants are known to affect high-risk populations of children, few studies have objectively evaluated environmental contributions to long-term respiratory morbidity in this population. This study aimed to examine the role of indoor environmental exposures on respiratory morbidity in children with BPD.

Methods and analysis The Air quality, Environment and Respiratory Ouctomes in BPD (AERO-BPD) study is a prospective, single-centre observational study that will enrol a unique cohort of 240 children with BPD and carefully characterise participants and their indoor home environmental exposures. Measures of indoor air quality constituents will assess the relationship of nitrogen dioxide (NO_2), particulate matter ($PM_{2.5}$), nitric oxide (NO), temperature and humidity, as well as dust concentrations of allergens, with concurrently measured respiratory symptoms and lung function. Adaptations to the research protocol due to the SARS-CoV-2 pandemic included remote home environment and participant assessments.

Ethics and dissemination Study protocol was approved by the Boston Children's Hospital Committee on Clinical Investigation. Dissemination will be in the form of peer-reviewed publications and participant information products.

Trial registration number NCT04107701.

INTRODUCTION

Advances in neonatal medicine have resulted in the improved survival of infants born at earlier gestational ages; however, despite these interventions, the rate of bronchopulmonary dysplasia (BPD) has not declined and is one of the most common complications of preterm birth. Chronic lung disease of prematurity is evident in a growing population of children with respiratory health impairment. During the first 2 years of life, there is a 50% risk of readmission if the patient has the diagnosis of BPD. This risk continues with almost half of all school-age children with BPD develop asthma or asthma symptoms.[1] An even greater proportion has poor lung function at school age.[2–6] Several recent studies associate childhood lung function as the main precursor of adult pulmonary function[7–10] in birth cohorts and asthmatic populations. The knowledge that indoor air quality is associated with respiratory symptoms, bronchiolitis, healthcare utilisation and impaired lung function in children, particularly in asthmatic populations, is widespread, but children with BPD are largely excluded from asthma epidemiologic and clinical studies and may not have the same response to pollutant exposures. As of now, long-term respiratory research in BPD has focused on neonatal factors, yet neonatal insults only partially explain the later childhood health outcomes. Therefore, determining potentially modifiable environmental contributions to respiratory morbidity and lung function in school-age children with BPD is urgently needed.

Improved neonatal care to premature infants over the past 3 decades increased survivorship without improvement in prevalence of BPD[11] or long-term respiratory morbidity into childhood, leading to a growing population of children with respiratory health problems.[12 13] Two recent preterm birth cohorts from Sweden[14] and Australia[15] demonstrated current respiratory symptoms in 40% and 52% of preterm children

at school age, respectively, clearly indicating the rate of long-term respiratory morbidity is high despite improved neonatal care. With approximately 30 000 infants per year born in the USA with birth weights under 1500 g (very low birth weight) or extreme prematurity (<28 weeks' gestation)[16 17] and rates of BPD are estimated at over 40% for these infants,[12] a growing population of at least 12 000 children per year are at high risk of long-term respiratory morbidity. It is estimated that almost half of survivors suffer from asthma or asthma-like symptoms at school age and up to 60% have abnormal lung function.

Debate exists as to whether children with a history of chronic lung disease of prematurity truly develop asthma or if they suffer from a separate asthma-like condition.[18] Children with BPD have similar symptomatology and lung function impairment[2] but lack typical features of childhood asthma—personal or family history of atopy, aeroallergen sensitisation and elevated markers of allergic airway inflammation. Several cohorts have demonstrated normal levels of FeNO in school-age children with BPD,[19 20] significantly lower than comparable patients with asthma,[21] and low levels of aeroallergen sensitivity.[19] Regardless of definition, the rates of respiratory morbidity, whether defined as physician diagnosis of asthma[1 22 23] or as report of current asthma-like symptoms,[11 14 15] are similarly high.

While childhood asthma is known to have strong environmental contributions to both inception and morbidity of disease, little is known about the environmental contributions to respiratory morbidity in children with BPD. This absence of information is due to several phenomena. First, children born prematurely are frequently excluded from large birth cohort studies of allergy and asthma in order to remove subjects with a comorbid respiratory condition. Second, studies of preterm infants have primarily investigated neonatal survival and early life determinants of early life morbidity. In the few studies that analyse factors related to long-term respiratory health, the NICU-centric (neonatal intensive care unit) approach typically only allows for neonatal risk factors to be assessed. Home-based environmental determinants of asthma development in children with BPD have been limited to tobacco smoke exposure,[11] pet ownership and respiratory viral infections[1] in infancy, assessed by parental questionnaire. For non-BPD cohorts, exposure to ambient air pollutants has been associated with asthma development, asthma symptoms and asthma exacerbations.[24–31] Moreover, home-based measurements of nitrogen dioxide (NO_2) and other pollutants with indoor sources have been associated with asthma symptom severity[25 32–34] in children, even at modest levels of exposure.[33] Across many locations, indoor exposure to environmental pollutants has been associated with increased incident asthma diagnosis,[35] asthma symptoms[33 36] and asthma severity[32] in children. The most consistent associations have been with NO_2,[32 33 36] ozone and $PM_{2.5}$.[37]

Studies of healthcare utilisation support the symptomatic findings. Ambient air quality is associated with incidence of emergency department visits and hospitalisations[38] and episodes of bronchiolitis[39 40] in children. In fact, Strickland and colleagues[41] found that associations between ambient pollutant concentrations and paediatric emergency visits for asthma exacerbations were largest among children born preterm, suggesting a uniquely vulnerable population of children. This finding highlights the importance of studying personal exposure to air pollution in this high-risk paediatric population, beyond just those with asthma. We have similarly found that that preterm children in the School Inner City Asthma study are at higher risk for pollution-related health effects than non-preterm children with asthma in the same cohort.[42] Effect modification of preterm gestational age (GA) <37 weeks was seen on the relationship of indoor black carbon (BC) exposure with greater asthma symptoms and a significantly lower forced expiratory volume in one second (FEV_1) percent predicted in preterm children than term children with exposure to $PM_{2.5}$.[42] These data suggest preterm children are a subpopulation of asthmatics more highly vulnerable to the effects of poor air quality with increased symptoms and lower lung function. Moreover, these data suggest that findings from childhood asthma environmental health and medical intervention studies cannot be generalised from asthma to BPD. Therefore, investigating air quality and health outcomes specific to the BPD population is important and is currently a substantial knowledge gap.

This study fulfils several unmet needs and knowledge gaps. It will be the first study to objectively evaluate the role of home environmental exposures on school-age children with BPD. This unique study design will pair objective in-home assessment of pollutant and allergen exposures with objective outcome measures of lung function and prospectively assessed symptomatology—something that is currently lacking in the BPD literature.

METHODS AND ANALYSIS

Overview

The motivation for this study is to begin to unravel the basis for the increased prevalence of asthma-like symptoms and lung function abnormalities outside of neonatal events among school-age children with BPD. There are two primary study objectives:

1. Quantify the contributions of home environmental exposures on respiratory morbidity in children with BPD.
2. Determine the effect of indoor air quality on lung function in children with BPD.

The study will focus on the role of indoor irritants, while also considering factors such as indoor temperature and humidity, indoor allergens, medical history and family social characteristics. Objective lung function, prospective respiratory symptom assessments and environmental measurements will be made concurrently over two 7-day periods using novel and low burden objective monitoring

in 240 children. Atopic status will be characterised and BPD severity as potential effect modifiers. These data will provide the needed information to develop interventions aimed at improving long-term respiratory outcomes in patients with BPD.

Study design

Two hundred and forty school-age children with a diagnosis of BPD will be recruited to participate in an epidemiologic cohort study of one clinic-based and two home-based assessments. Measurements will be made to find associations of home environmental exposures with respiratory symptoms and lung function across repeated timepoints, including effect-modifying factors. Longitudinal analyses will explore variation (over 14 days) in respiratory symptom outcomes and pulmonary function in association with changes in environmental exposures, measured in two seasons to address known seasonal variation in both exposure and outcome measures.

Study population

Inclusion criteria

- Must be 6–12 years old at the time of enrolment.
- Born <32 weeks' GA.
- Diagnosed with BPD by requiring greater than 28 days of oxygen or other respiratory support (ventilator or continuous positive airway pressure (CPAP)) in the neonatal period.

Exclusion criteria

- History of major airway or chest surgery, such as tracheostomy, open heart surgery, lung surgeries, spinal surgeries (not including patent ductus arteriosis closure).
- Physical or mental impairment that will prevent subject from successfully conducting spirometry.
- Plans to move out of state within the next 9 months.

Recruitment

Families of potentially eligible children will be contacted by letter and phone. A short screening survey will be administered by phone to further ascertain study eligibility. Families who are eligible and interested in the study will be scheduled for a clinic visit at our well-established Boston Children's Hospital (BCH) Clinical Research Unit. Round-trip transportation will be arranged to overcome transportation barriers and families will be reimbursed for their time. Reminder phone calls will be made 2 days prior to the visit, when staff will confirm absence of an acute illness over the prior 2 weeks. Children will be asked to refrain from use of certain medications prior to the visit (that interfere with spirometry). The definition of BPD used for enrolment is based on the 2001 National Institute of Child Health and Human Development (NICHD) workshop categorised BPD based on severity, gestational age and post-menstrual age assessment of BPD severity.[43] Acknowledging that the optimal BPD definition has recently been the topic of debate,[44] we selected the 2001 NICHD definition because it was the consensus definition at the time of birth for the majority of children eligible to participate in this study and remains the primary validated[45] consensus-based definition in clinical practice. Confirmation of eligibility is performed by reviewing the subject's birth and neonatal medical records at the time of enrolment.

Protocol overview

Clinical, social and physiological data will be collected at the research clinic visit and outcome assessments of symptoms and lung function, as well as environmental data will be collected during two in-home visits, which will consist of a home environmental audit, dust sampling and 7 days of ambient air sampling (see figure 1). Staff will be trained, certified and monitored over time in the collection of each measurement, following written procedures, as developed for the SICAS[46] and SICAS-2[47] trials.

Clinic examination

The following will be collected at the research clinic visit: standardised questionnaires regarding health, medical history, demographic and family characteristics; objective tests of atopy and lung function; anthropometry; oropharyngeal examination and biological samples (urine, blood). Participants will undergo the following,

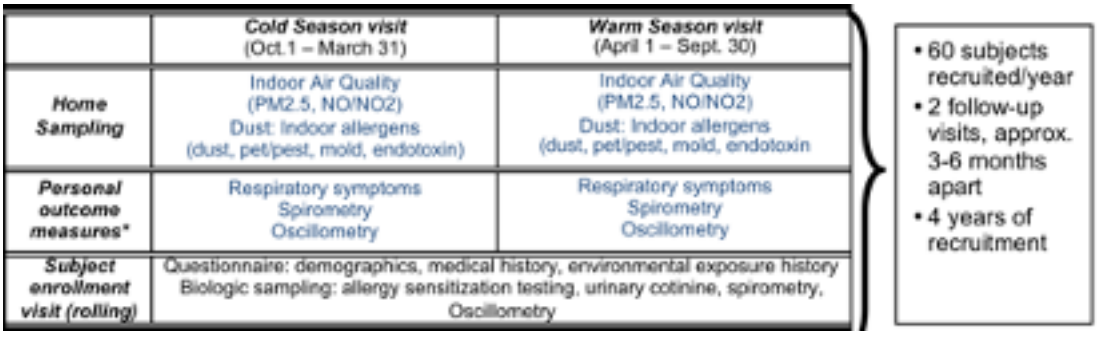

Figure 1 Schema depicting study timeline for each recruitment year. *Personal outcomes measured at the home sampling visits. Order of 'cold' and 'warm' sampling visits will vary based on enrolment season.

in the order listed: (1) brief orientation to testing facility and informed consent/assent; (2) urine collection; (3) anthropometry, oropharyngeal examination; (4) oscillometry; (5) pre-bronchodilator and post-bronchodilator spirometry; (6) venipuncture; (7) questionnaires.

Urine collection

The child (with parental assistance) will be instructed to void into a collection device.

Anthropometry

The child's weight (to 0.1 kg) and standing height (to 0.1 cm) will be measured using a calibrated digital electronic scale and stadiometer, respectively. Measures will be repeated three times, and average values will be used.

Oscillometry

Oscillometry will be performed by standard procedure[47] using the Tremoflo device (Thorasys, Montreal, Canada), calibrated daily with test load. After brief orientation, at least reproducible efforts will be recorded. The following parameters will be recorded from the best effort R_5, R_{20}, $R_{5\text{-}20}$, f_{res}, AX_5.

Spirometry

Spirometry will be performed according to ATS (American Thoracic Society) guidelines.[48] At least reproducible flow-volume loops will be obtained using a portable spirometer (Pneumotrac; Morgan Scientific, Haverhill, Massachusetts, USA), calibrated daily, using quality standards[49] and the Global Lung Initiative reference equations.[50] After baseline manoeuvres, 2.5 mg of albuterol will be administered via nebuliser (or 4 inhalations of albuterol 90 mcg by metered dose inhaler with aerochamber, if nebuliser therapy prohibited) and spirometry will be repeated 10–15 min later to obtain post-bronchodilator forced vital capacity (FVC), FEV_1 and forced expiratory flow $(FEF)_{25\text{-}75}$. Children will be asked to withhold short-acting bronchodilator medications for 6 hours and long-acting bronchodilator medications for 48 hours prior to testing.

Venipuncture

A 30 mL venous blood sample will be obtained using paediatric procedures. Within 1 hour, the sample is spun and aliquoted into vials for plasma and cell samples. Samples will be assayed for total immunoglobulin E (IgE) and a panel of common aeroallergens to determine respiratory sensitisation via Phadia ImmunoCAP assay (Thermo Fisher, Uppsala, Sweden). Specific IgE >0.35 kU will be considered positive for sensitisation; children with any positive tests will be considered atopic.

Questionnaires

Standardised assessments include those for respiratory symptoms; allergy; medical, family and social history; medications; home and neighbourhood characteristics; frequency of respiratory illnesses/infections; and healthcare utilisation. All instruments will be completed by the parent and child, when appropriate for age, with assistance by research staff as needed. Questionnaires and their relationship to our aims are shown in table 1.

Home visit

Two in-home sampling visits will be scheduled to occur in a warm season (April–September) and a cold season (October–March), separated by at least 3 months. A two-member research team will visit the family at a convenient time to the family. At the start of each sampling period the team will (1) conduct a home environmental audit; (2) set up an air monitor to measure indoor air quality and thermal conditions (7 days) in the child's bedroom; and (3) instruct the child and parent to complete the daily symptom and household activities diary. Staff members will visit the family at the completion of the 7-day collection period, at which time they will (1) retrieve monitoring devices; (2) collect symptom and activity diaries; (3) administer questionnaires to capture the primary outcome—maximum symptom days over the prior 2 weeks, as well as updated medical and healthcare utilisation information since the prior encounter; (4) collect a vacuumed dust sample from the bedroom for allergen assays: (5) perform spirometry with a portable spirometer (Pneumotrac; Morgan Scientific, Haverhill, Massachusetts, USA) calibrated daily, using quality standards[49] and the Global Lung Initiative reference equations[50] and oscillometry by Tremoflo device (Thorasys, Montreal, Canada). Staff will contact the family after the first two nights to troubleshoot any problems and reinforce the protocol.

Home audit

Staff will use a structured checklist completed during a home 'walk through' to characterise the home physical and social environment (15–20 min). The checklist will be adapted from one developed by Dr Adamkiewicz that includes 100 precoded categories (observed/not observed: evident mould, pests, kitchen/bathroom ventilation characteristics, combustion sources, chemical exposures).[51]

Air quality monitoring

Portable indoor air quality (IAQ) monitors that provide real-time measurements, developed by collaborators at the TH Chan Harvard School of Public Health,[52] will be placed on the child's bedroom shelf away from direct radiator contact and will monitor $PM_{2.5}$, NO_2,

Table 1 Summary of measurements

Domain	Instrument/Indices
Outcomes	
Respiratory morbidity	2-week symptom recall. The **primary outcome** for aim 1 is maximum symptom days in the prior 2 weeks[59–62] assessed at completion of home sampling visits, defined as the largest value among the following three variables: number of days with wheezing, tightness in the chest, or cough; number of nights with disturbed sleep as a result of breathing symptoms; and number of days on which the child had to slow down or discontinue play activities because of breathing symptoms Composite Asthma Score Index (asthmatic children only): Assesses impairment, risk and level of controller therapy, graded per national asthma guidelines (EPR-3) across domains: day symptoms, night symptoms, controller treatment, lung function measurements and exacerbations[65] Daily symptom diary: Catalogue of respiratory symptoms experienced for the duration of the sampling period
Lung function	**Primary: Spirometry** (FEV_1, FVC, FEF_{25-75}, FEV_1/FVC); Forced oscillometry (R_5, R20, R_{5-20}, f_{res}, AX_5)
Household physical environment (primary exposures)	
Household temperature, humidity, ventilation, particulates, NO_2	Indoor Environment Monitors: Awair-Omni weather stations for temperature, relative humidity, CO_2, VOC and $PM_{2.5}$; AlphaSense sensors with dataloggers using electrochemical (NO, NO_2, CO_2) sensors (OPC-N2; Harvard Mini-PEM). Mean daily levels, peaks, variances, and for $PM_{2.5}$, also integrated levels over 7 days Home Audit and Housing Scale Score[51]: Survey focused on housing types and characteristics. Specific indices derived from self-report and visual inspection, including ventilation, moulds, pests, smoking, and combustion by-products.
Household dust allergens and endotoxin	Bedroom Dust: Allergens: Der p1, Der f1, Mite Group 2, Bla g2, Fel d1, Can f1, Mus m1, Rat n1 (MARIA assay,[56] Bio-Rad); endotoxin (enzyme immunoassay averages (log transformed; upper quartiles)[58])
Time-activity log	Hourly Time-Activity Diary: Diary of activities performed in the home during the sampling periods, including child sleep time, cooking and cleaning activities
Household conditions	House Audit: Noise, light, shades, bedroom configuration base on interview and visual inspection[66]
Secondhand smoke	Urinary Cotinine: ELISA (Abnova, Walnut, CA; sensitivity 1 ng/mL) and questionnaire
Neighbourhood physical environment (secondary exposures)	
Neighbourhood walkability, poverty, disorder, social cohesion, crime	Neighbourhood Questionnaire: Includes neighbourhood safety (feeling safe walking in the neighbourhood) Geographic Information System: Geocoding factors contributing to neighbourhood disadvantage and fragmentation (% vacant house units, owner-occupied housing, etc)[67]
Child characteristics (modifiers, confounders)	
Atopy (specific sensitisation)	Total IgE, Phadiatop with reflex allergen-specific IgE levels for positive results (ImmunoCAP, Phadia AB): House dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), cockroach (*Blattella germanica*), cat, dog dander, mouse urine, *Aspergillus*, *Alternaria*, *Penicillium*, *Cladosporium sphaerospermum*, grass pollen, tree pollen and short ragweed
Respiratory symptoms/asthma (prevalence, severity)	International Study Of Asthma And Allergies In Childhood (ISAAC) asthma core questions: Score of ≥5 on the eight-item global wheezing questions has a sensitivity of 95% and specificity of 100% for identifying asthma[68 69] Composite Asthma Score Index (asthmatic children only, detailed above)[65] Paediatric sleep questionnaire[70] Modified asthma control test[71]
Rhinitis	ISAAC rhinitis core questions[69 72 73]
Respiratory illnesses	SICAS healthcare utilisation and respiratory infections (last 12 months)[74]
Adiposity	Exam: height, weight (BMI percentiles)
General health	SICAS Medical History and Medications Questionnaire[46] PROMIS Global Health 7[75 76] PROMIS Profile 25[77] Patient Health Questionnaire-4 (PHQ-4)[64]
Demographics	Parent-reported questionnaire

BMI, body mass index; FEF, forced expiratory flow; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

NO, carbon dioxide (CO_2), temperature and humidity during the 7-day monitoring period. Sensors will output to data loggers every 5 min. We also will measure $PM_{2.5}$ mass integrated/averaged over the 7-day monitoring period using standard methods[53 54] and in real time. NO and NO_2 will be calibrated quarterly and replaced every 18 months, CO_2 will be calibrated annually and all sensors will be assessed for any signal drift.

Dust collection and allergen/endotoxin assays

Dust for allergens and endotoxin will be obtained by vacuuming a 2 m^2 area in the child's bedroom plus bedding using an Oreck XL handheld vacuum with a special dust collector (DACI laboratory, JHU) fitted into the inlet hose of the vacuum using a standardised protocol,[55] consisting of vacuuming each surface for 5 min. Samples will be weighed in an environmentally controlled laboratory and extracted. Allergen concentrations will be measured using the MARIA assay[56] (using a Universal Allergen Standard), on a Bio-Plex Bead Suspension Array System that allows simultaneous capture and detection of multiple allergens in a single sample. Endotoxin (which stimulates airway inflammation[57] will be measured by enzyme immunoassay as previously described.[58] Dust samples will be banked appropriately, providing opportunities for future evaluation of the exposome, such as microbiome analyses.

Statistical plan

A summary of the key exposures, outcomes, confounders and modifiers is shown (table 1). Most indices will be analysed as continuous exposures or as quartiles of their distributions; when clinical thresholds exist, indices will be dichotomised.

Data analysis plan

Analyses will include (1) quantification of associations between home environment exposures and the prevalence and respiratory symptom severity and lung function; (2) assessment of whether the associations between home environmental exposures and respiratory symptoms or lung function are modified by atopy, BPD severity, neonatal medical course (ventilation, length of oxygen exposure) and selected family and neighbourhood exposures. Sensitivity analyses will evaluate the robustness of inferences and will explore variation by BPD severity in stratified analyses.

The main analyses under both aims can be unified under the general approach of quantifying repeated measures analyses of associations between home environment exposure (X) and respiratory-related outcome (Y). The primary symptom outcome is maximum symptom days in the prior 2 weeks, adapted from asthma epidemiology and intervention studies for similar age groups[59–62]: maximal number of days with symptoms in the weeks before the visit is defined as the largest value among the following three variables: number of days with wheezing, tightness in the chest or cough; number of nights with disturbed sleep as a result of breathing symptoms; and number of days on which the child had to slow down or discontinue play activities because of breathing symptoms. In the absence of disease-specific validated outcome measures for BPD, we adapted instruments frequently used in asthma epidemiology studies (maximum asthma symptom days, childhood asthma control test) to solicit more general respiratory symptoms that are frequently encountered in this population and overlap with asthma symptoms. While these ask specifically about cough, wheeze and chest tightness, they also solicit information about exertional impairment and sleep disruption from 'breathing issues' more generally. The daily diary completed during the exposure assessment period includes daily questions about cough, wheeze and shortness of breath. The primary lung function outcome for associations with temporally related lung function measure is specifically FEV_1 percent predicted.

Linear (for continuous outcomes) and generalised linear (for count outcomes) models will be used to assess the repeated-measures associations between environment exposures X and respiratory outcomes Y, adjusting for age, sex, race, ethnicity, family income, parent education, season and BPD severity. Other covariates (confounders, mediators; table 1) will also be considered. We will first estimate the association between each individual exposure and respiratory outcome, then assess the overall effect combining multiple environment exposures. Variable selection will be conducted with statistical approaches guided by biological rationale and conceptual considerations. A two-stage approach will be used. First, we will use variable selection techniques based on covariates only, such as cluster analysis or principal component analysis, eliminating variables that are highly correlated to avoid collinearity in subsequent modelling. We will then use cross-validated variable selection techniques to build models involving multiple environment exposures.

Effect modification will be explored using interaction tests and stratified analyses, assessing factors including BPD severity and atopy. BPD severity will be assigned based on consensus guideline[45] and extracted from the primary medical record. Atopy will be defined by having one or more positive specific IgE >0.35 kU to the panel of allergens. We will also examine if associations between specific allergen levels and respiratory outcomes are stronger in those with a specific sensitivity (by IgE) to that allergen.

Secondary outcomes will consider the effect of indoor exposures on annualised healthcare utilisation for urgent respiratory care, annualised number of respiratory illnesses. Additional measures of lung function will be evaluated in relation to indoor air quality exposures: FEV_1/FVC ratio, and FVC percent predicted; oscillometry measures: R_5, R_{20}, $R_{5\text{-}20}$, f_{res}, AX_5.

Power considerations

The proposed statistical analysis assessing the impact of environmental exposures on respiratory-related outcomes is based on generalised estimating equations to account for correlation among clustered observations at the subject level with assumptions derived from similar studies.[36 42 62 63] Based on these assumptions, a sample of 240 enrolled subjects, a 20 ppb change in NO_2 will

provide 89% and 87% power to detect a 1.0 maximum symptom day difference and a 3% FEV_1 percent predicted difference, respectively. A 30 µg/m^3 change in $PM_{2.5}$ would provide 99% power to detect an association with either 1.0 maximum symptom day or 3% FEV_1 percent predicted. We do not expect that confounders will significantly reduce our power. Our indoor school data showed that only between 1% and 9% of the variation in exposures was explained by demographic data and season.

SARS-CoV-2 adaptation

Enrolment was halted in early March 2020 due to the SARS-CoV-2 pandemic. Both state and medical centre restrictions on the use of the hospital-based clinical research unit and on the performance of home environmental assessments limited the capability to complete the planned assessments as part of the original protocol. Moreover, participants became reluctant to participate in in-person/in-home clinical research due to concerns over social distancing and risk of attending hospital research clinic visits. In order to maintain the research objectives, study integrity and ensure the safety of the participants and research staff,[64] the protocol was altered to augment recruitment, enable remote enrolment and provide minimal-contact home sampling and health outcome assessment.

In order to broaden our recruitment base, we partnered with local NICU and large paediatric practices to advertise the study and directly recruit from patient rosters. Expanding recruitment to sites outside of Boston Children's Hospital also augments generalisability and minimises potential bias of only recruiting from a tertiary care medical facility.

Given the anticipated local/institutional restrictions for in-person study visit conduct, compounded by likely ongoing participant concerns about coming to the clinical research centre for study visits, approaches were developed to allow performing the informed consent process remotely. Interested participants are mailed/emailed study information, including the informed consent document, for their pre-review. Following this, study team members use video conferencing software to conduct a visit that allows for a complete discussion of study participation and conduct the informed consent acquisition process, including using electronic signature platforms for participants to sign the consent documents.

During mandatory or preferred times of social distancing, enrolment procedures can be performed remotely. In this situation, all questionnaire assessments will be performed via a virtual meeting. Research laboratory flexibility was expanded to allow labs to be drawn at a remote site affiliated with BCH, limiting the need for participants to come to the main academic medical centre for blood draws. When able, brief visits to obtain objective assessments (anthropomorphic data, spirometry and oscillometry) are performed at the clinical research unit, minimising the time for participants and staff to be in close contact at the hospital.

Adaptations to the home sampling visits allow for complete data collection without research staff entering the home and with minimal in-person interaction. Vacuum dust sampling is performed by providing families with a vacuum outfitted with dust traps for parents to perform the procedure. Written instruction (provided in English and Spanish) and a virtual video interface allow the study staff to guide the family through the procedure. Similarly, curbside IAQ monitor setup is performed by dropping off the monitor at the family's home with written instructions for set-up and a virtual platform used to guide appropriate deployment in the child's bedroom. The in-person home environmental walkthrough inventory was adapted to a virtual visit in which the participant's caregiver assists in the physical evaluation of the home environment either using their own device or a study-provided tablet with video-conferencing capability. The research team guides the walkthrough and evaluation by instructing the caregiver to point the camera at the relevant areas of investigation.

Spirometry and oscillometry are typically performed with the participant performing specific breathing manoeuvres in close proximity to the research staff while the staff actively coaches the research subject through the manoeuvre. Ensuring the integrity of the primary spirometry endpoint is paramount. In an effort to achieve remote collection of FEV_1 measurements, remote spirometry with the ZEPHYR$_x$ (https://www.zephyrx.com/) MIR spirometer device was implemented. This is an app-based home spirometry system with live coaching ability (ie, video conferencing embedded in the app so research staff can coach in real time). The device is United States Food and Drug Administration (FDA) approved and security has been vetted by BCH clinical research innovation group. The device is currently being used and piloted in several clinical and research capacities, including a multicentre NIH research consortium, the NHLBI PreCISE network (NCT04129931; https://preciseasthma.org/). Furthermore, airway oscillometry allows adaptation and distancing options to collect this information at a six foot distance from the subject. Moreover, this manoeuvre does not require a forced exhalation, is less likely to induce coughing and therefore unlikely to generate an aerosol of secretions.

Patient and public involvement

The motivation for conducting this research protocol was highly influenced by the investigators' clinical practice evaluating and managing the respiratory health of children with BPD and recognising the frustrating lack of evidence basis for environmental assessment and intervention in this high-risk group of children. This protocol did not include explicit patient or public involvement in the initial design of the study protocol; however, the recruitment methodology was designed to honour and

respect the personal nature of protected health information and patient and family preferences for being contacted to learn about research opportunities. Methodological adjustments to the protocol in response to the SARS-CoV-2 pandemic were made to ensure the health and safety of participants in line with public health recommendations from local and national governing bodies. The findings of this research will be presented in academic settings, including conferences and peer-reviewed journals. A small group of participants will be invited to assist the research team in producing a patient-level mode of dissemination of the main study results to inform participants and linked communities after publication of the primary manuscript.

Ethics and dissemination

The study was approved by the Boston Children's Hospital Committee on Clinical Investigation IRB # P00029918, and informed consent and assent were obtained prior to performing any study procedures. The team will disseminate results to the scientific and lay community interested in indoor air quality or BPD in order to avoid unintentional duplication of research. Collaboration will be fostered with investigators who could make use of the collected data and protocols to further scientific discovery in this field.

All results derived from the proposed research will be shared through presentation and discussion at national and international research conferences, as well as through publication in peer-reviewed journals. Results will be presented at national and international scientific meetings focused on organisations interested in environmental health or paediatric respiratory health research. It is also anticipated that at least one to two major publications reporting the primary objectives of this research project and several secondary analysis publications will be generated. Additionally, according to the NIH Policy on Enhancing Public Access to Archived Publications Resulting from NIH Funded Research, all final manuscripts on acceptance for publication will be submitted to the NIH National Library of Medicine PubMed Central (PMC) database, making these openly accessible to the scientific and lay community. Data collected during the course of the proposed study will be made available to the scientific public on submission of a written formal request for data to the principal investigator and coinvestigators of this study. Following the publication of the main study findings, a patient-level communication will describe the key results and be available to participants and linked communities.

DISCUSSION

The AERO-BPD study was designed to provide a solid foundation for further investigation of environmental exposures and long-term respiratory morbidity in BPD—a novel area of investigation. As the population of children surviving preterm birth increases due to improved neonatal practices, the population of children at risk for long-term respiratory morbidity and poor lung function, so too, will increase. This has enormous implications on the surviving children, families and medical providers charged with caring for these patients, and the healthcare system, as a whole, as this growing segment of the population demands greater resource expenditure over their lifetime. The AERO-BPD study was designed to identify specific harmful components of the indoor environment associated with increased respiratory morbidity in children with BPD and to understand how indoor pollutants will negatively affect lung function in children with BPD, independent of other known epidemiologic risk factors.

Impact and future directions

School-age children with BPD suffer substantial respiratory morbidity—both as symptoms and lung function impairment. Yet, there is a current lack of evidence basis for factors contributing to this morbidity beyond the NICU experience. Identifying modifiable risk factors, such as poor indoor air quality, and designing interventions to mitigate their effects are of utmost importance to all stakeholders. The impact of these findings will be to identify modifiable risk factors affecting respiratory morbidity in this growing high-risk group of children. These data will be the platform from which targeted interventions can be tested to improve long-term morbidity and will provide greatly needed evidence basis for practicing clinicians, patients and policymakers. Findings from this research will improve our understanding of the environmental influence on children with BPD and offer results from which intervention trials may be designed and a foundation for evidence-based clinical recommendations. In addition to further studies on environmental exposure, this study will provide a foundation for future specific intervention studies to test mitigation strategies for indoor pollutants to improve respiratory health in this population. Furthermore, findings from this study will provide an evidence basis for recommendations related to respiratory health in BPD that currently does not exist and inform guideline creation and public policy.

Author affiliations
[1]Boston Children's Hospital Division of Pulmonary and Respiratory Diseases, Boston, Massachusetts, USA
[2]Department of Environmental Health, Harvard University T H Chan School of Public Health, Boston, Massachusetts, USA
[3]Boston Children's Hospital Division of Immunology, Boston, Massachusetts, USA
[4]Boston Children's Hospital, Biostatistics and Research Design Center, Institutional Centers for Clinical and Translational Research, Boston, Massachusetts, USA
[5]Harvard Medical School, Boston, Massachusetts, USA

Contributors Concept and design: JG, WP, GA, EW, CAS, LPH, SG. Acquisition of data/adaptation: All authors. Drafting of the manuscript: HBR, JG, WP. Critical revision of the manuscript for important intellectual content: All authors. Statistical

methods: CRP, EW. Environmental methods: GA, JV, MA. Obtained funding: SG. Administrative, technical or material support: All authors. Study supervision: SG, AC.

Funding This work was supported by the NIH R01ES030100 (SG), P30ES000002 and 1P50MD010428 (GA), K24 AI 106822 (WP) and K23 HL136851 (LPH).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Wanda Phipatanakul http://orcid.org/0000-0001-8639-0473

REFERENCES

1 Ng DK, Lau WY, Lee SL. Pulmonary sequelae in long-term survivors of bronchopulmonary dysplasia. *Pediatr Int* 2000;42:603–7.
2 Broström EB, Thunqvist P, Adenfelt G, *et al*. Obstructive lung disease in children with mild to severe BPD. *Respir Med* 2010;104:362–70.
3 Giacoia GP, Venkataraman PS, West-Wilson KI, *et al*. Follow-Up of school-age children with bronchopulmonary dysplasia. *J Pediatr* 1997;130:400–8.
4 Gross SJ, Iannuzzi DM, Kveselis DA, *et al*. Effect of preterm birth on pulmonary function at school age: a prospective controlled study. *J Pediatr* 1998;133:188–92.
5 Hacking DF, Gibson A-M, Robertson C, *et al*. Respiratory function at age 8-9 after extremely low birthweight or preterm birth in Victoria in 1997. *Pediatr Pulmonol* 2013;48:449–55.
6 Cazzato S, Ridolfi L, Bernardi F, *et al*. Lung function outcome at school age in very low birth weight children. *Pediatr Pulmonol* 2013;48:830–7.
7 Vollsæter M, Røksund OD, Eide GE, *et al*. Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax* 2013;68:767–76.
8 McGeachie MJ, Yates KP, Zhou X, *et al*. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med Overseas Ed* 2016;374:1842–52.
9 Stern DA, Morgan WJ, Wright AL, *et al*. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370:758–64.
10 Martinez FD. Early-Life origins of chronic obstructive pulmonary disease. *N Engl J Med* 2016;375:871–8.
11 Palta M, Sadek-Badawi M, Sheehy M. Respiratory symptoms at age 8 years in a cohort of very low birth weight children. *Am J Epidemiol* 2001;154:521–9.
12 Stoll BJ, Hansen NI, Bell EF, *et al*. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. *Pediatrics* 2010;126:443–56.
13 Collaco JM, McGrath-Morrow SA. Respiratory phenotypes for preterm infants, children, and adults: bronchopulmonary dysplasia and more. *Ann Am Thorac Soc* 2018;15:530–8.
14 Thunqvist P, Tufvesson E, Bjermer L, *et al*. Lung function after extremely preterm birth-A population-based cohort study (express). *Pediatr Pulmonol* 2018;53:64–72.
15 Simpson SJ, Logie KM, O'Dea CA, *et al*. Altered lung structure and function in mid-childhood survivors of very preterm birth. *Thorax* 2017;72:702–11.
16 Murphy SL, Mathews TJ, Martin JA, *et al*. Annual summary of vital statistics: 2013–2014. *Pediatrics* 2017;139:e20163239.
17 Martin JA, Hamilton BE, Osterman MJK, Hyattsville MD. Births in the United States, 2016. *NCHS Data Brief* 2017:1-8.
18 Smith J. An update on bronchopulmonary dysplasia: is there a relationship to the development of childhood asthma? *Med Hypotheses* 2003;61:495–502.
19 Lum S, Kirkby J, Welsh L, *et al*. Nature and severity of lung function abnormalities in extremely pre-term children at 11 years of age. *Eur Respir J* 2011;37:1199–207.
20 Baraldi E, Bonetto G, Zacchello F, *et al*. Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. *Am J Respir Crit Care Med* 2005;171:68–72.
21 Nordlund B, James A, Ebersjö C, *et al*. Differences and similarities between bronchopulmonary dysplasia and asthma in schoolchildren. *Pediatr Pulmonol* 2017;52:1179–86.
22 Korhonen P, Laitinen J, HyoUdynmaa E, *et al*. Respiratory outcome in school-aged, very-low-birth-weight children in the surfactant era. *Acta Paediatr* 2004;93:316–21.
23 Fawke J, Lum S, Kirkby J, *et al*. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med* 2010;182:237–45.
24 Franklin PJ. Indoor air quality and respiratory health of children. *Paediatr Respir Rev* 2007;8:281–6.
25 O'Connor GT, Neas L, Vaughn B, *et al*. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008;121:1133–9. S0091-6749(08)00407-7 [pii].
26 Brunekreef B. Health effects of air pollution observed in cohort studies in Europe. *J Expo Sci Environ Epidemiol* 2007;17:S61–5.
27 Rice MB, Rifas-Shiman SL, Oken E, *et al*. Exposure to traffic and early life respiratory infection: a cohort study. *Pediatr Pulmonol* 2015;50:252–9.
28 Litonjua AA, Gold DR. Early-Life exposures and later lung function. add pollutants to the mix. *Am J Respir Crit Care Med* 2016;193:110–1.
29 Ierodiakonou D, Zanobetti A, Coull BA, *et al*. Ambient air pollution, lung function, and airway responsiveness in asthmatic children. *J Allergy Clin Immunol* 2016;137:390–9.
30 Habre R, Moshier E, Castro W, *et al*. The effects of PM2.5 and its components from indoor and outdoor sources on cough and wheeze symptoms in asthmatic children. *J Expo Sci Environ Epidemiol* 2014;24:380–7.
31 Neophytou AM, White MJ, Oh SS, *et al*. Air pollution and lung function in minority youth with asthma in the gala II (Genes-Environments and admixture in Latino Americans) and SAGE II (study of African Americans, asthma, genes, and environments) studies. *Am J Respir Crit Care Med* 2016;193:1271–80.
32 Belanger K, Holford TR, Gent JF, *et al*. Household levels of nitrogen dioxide and pediatric asthma severity. *Epidemiology* 2013;24:320–30.
33 Belanger K, Gent JF, Triche EW, *et al*. Association of indoor nitrogen dioxide exposure with respiratory symptoms in children with asthma. *Am J Respir Crit Care Med* 2006;173:297–303.
34 Kattan M, Gergen PJ, Eggleston P, *et al*. Health effects of indoor nitrogen dioxide and passive smoking on urban asthmatic children. *J Allergy Clin Immunol* 2007;120:618–24. S0091-6749(07)00962-1 [pii].
35 McConnell R, Islam T, Shankardass K, *et al*. Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect* 2010;118:1021–6.
36 Hansel NN, Breysse PN, McCormack MC, *et al*. A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. *Environ Health Perspect* 2008;116:1428–32.
37 McCormack MC, Breysse PN, Matsui EC, *et al*. In-Home particle concentrations and childhood asthma morbidity. *Environ Health Perspect* 2009;117:294–8.
38 Delfino RJ, Wu J, Tjoa T, *et al*. Asthma morbidity and ambient air pollution: effect modification by residential traffic-related air pollution. *Epidemiology* 2014;25:48–57.
39 Yitshak-Sade M, Yudovitch D, Novack V, *et al*. Air pollution and hospitalization for bronchiolitis among young children. *Ann Am Thorac Soc* 2017;14:1796–802.
40 Darrow LA, Klein M, Flanders WD, *et al*. Air pollution and acute respiratory infections among children 0-4 years of age: an 18-year time-series study. *Am J Epidemiol* 2014;180:968–77.
41 Strickland MJ, Klein M, Flanders WD, *et al*. Modification of the effect of ambient air pollution on pediatric asthma emergency visits. *Epidemiology* 2014;25:843–50.
42 Gaffin JM, Hauptman M, Petty CR, *et al*. Differential effect of school-based pollution exposure in children with asthma born prematurely. *Chest* 2020;158:1361–3.
43 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–9.
44 Thébaud B, Goss KN, Laughon M, *et al*. Bronchopulmonary dysplasia. *Nat Rev Dis Primers* 2019;5:78.
45 Ehrenkranz RA, Walsh MC, Vohr BR, *et al*. Validation of the National Institutes of health consensus definition of bronchopulmonary dysplasia. *Pediatrics* 2005;116:1353–60.
46 Phipatanakul W, Bailey A, Hoffman EB, *et al*. The school inner-city asthma study: design, methods, and lessons learned. *Journal of Asthma* 2011;48:1007–14.
47 Oostveen E, MacLeod D, Lorino H, *et al*. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *European Respiratory Journal* 2003;22:1026–41.
48 Standardization of spirometry, 1994 update. American thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107–36.

49 Guilbert TW, Morgan WJ, Krawiec M, *et al*. The prevention of early asthma in kids study: design, rationale and methods for the childhood asthma research and education network. *Control Clin Trials* 2004;25:286–310.
50 Bateman ED, Hurd SS, Barnes PJ, *et al*. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143–78.
51 Adamkiewicz G, Spengler JD, Harley AE, *et al*. Environmental conditions in low-income urban housing: clustering and associations with self-reported health. *Am J Public Health* 2014;104:1650–6.
52 Gillooly SE, Zhou Y, Vallarino J, *et al*. Development of an in-home, real-time air pollutant sensor platform and implications for community use. *Environmental Pollution* 2019;244:440–50.
53 Kinney PL, Aggarwal M, Northridge ME, *et al*. Airborne concentrations of PM(2.5) and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. *Environ Health Perspect* 2000;108:213–8.
54 Cyrys J, Heinrich J, Hoek G, *et al*. Comparison between different traffic-related particle indicators: elemental carbon (EC), PM2.5 mass, and absorbance. *J Expo Anal Environ Epidemiol* 2003;13:7500262 [pii]:134–43.
55 Celedón JC, Milton DK, Ramsey CD, *et al*. Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. *J Allergy Clin Immunol* 2007;120:144–9.
56 King EM, Filep S, Smith B, *et al*. A multi-center ring trial of allergen analysis using fluorescent multiplex array technology. *J Immunol Methods* 2013;387:89-95.
57 Boehlecke B, Hazucha M, Alexis NE, *et al*. Low-Dose airborne endotoxin exposure enhances bronchial responsiveness to inhaled allergen in atopic asthmatics. *J Allergy Clin Immunol* 2003;112:1241–3.
58 Noss I, Wouters IM, Bezemer G, *et al*. β-(1,3)-Glucan Exposure Assessment by Passive Airborne Dust Sampling and New Sensitive Immunoassays. *Appl Environ Microbiol* 2010;76:1158–67.
59 Phipatanakul W, Koutrakis P, Coull BA, *et al*. The school inner-city asthma intervention study: design, rationale, methods, and lessons learned. *Contemp Clin Trials* 2017;60:14–23.
60 Lai PS, Sheehan WJ, Gaffin JM, *et al*. School endotoxin exposure and asthma morbidity in inner-city children. *Chest* 2015;148:1251–8.
61 Gaffin JM, Hauptman M, Petty CR, *et al*. Nitrogen dioxide exposure in school classrooms of inner-city children with asthma. *J Allergy Clin Immunol* 2018;141:2249-2255.e2.
62 Sheehan WJ, Permaul P, Petty CR, *et al*. Association between allergen exposure in inner-city schools and asthma morbidity among students. *JAMA Pediatr* 2017;171:31–8.
63 Fleming TR, Labriola D, Wittes J. Conducting clinical research during the COVID-19 pandemic: protecting scientific integrity. *JAMA* 2020;324:33–4.
64 McCormack MC, Breysse PN, Hansel NN, *et al*. Common household activities are associated with elevated particulate matter concentrations in bedrooms of inner-city Baltimore pre-school children. *Environ Res* 2008;106:148–55. S0013-9351(07)00185-5 [pii].
65 Wildfire JJ, Gergen PJ, Sorkness CA, *et al*. Development and validation of the Composite Asthma Severity Index--an outcome measure for use in children and adolescents. *J Allergy Clin Immunol* 2012;129:694–701.
66 Spilsbury JC, Frame J, Magtanong R. Sleep environments of children in an urban U.S. setting exposed to interpersonal violence. *Behav Sleep Med* 2015:1–17.
67 Pabayo R, Molnar BE, Street N, *et al*. The relationship between social fragmentation and sleep among adolescents living in Boston, Massachusetts. *J Public Health* 2014;36:587–98.
68 Gruchalla RS, Gan V, Roy L, *et al*. Results of an inner-city school-based asthma and allergy screening pilot study: a combined approach using written questionnaires and step testing. *Ann Allergy Asthma Immunol* 2003;90:491–9.
69 Solé D, Vanna AT, Yamada E, *et al*. International study of asthma and allergies in childhood (Isaac) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8:376–82.
70 Chervin RD, Hedger K, Dillon JE, *et al*. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med* 2000;1:21–32.
71 Liu AH, Zeiger R, Sorkness C, *et al*. Development and cross-sectional validation of the childhood asthma control test. *J Allergy Clin Immunol* 2007;119:817–25.
72 Asher MI, Keil U, Anderson HR, *et al*. International study of asthma and allergies in childhood (Isaac): rationale and methods. *Eur Respir J* 1995;8:483–91.
73 Braun-Fahrländer C, Wüthrich B, Gassner M, *et al*. Validation of a rhinitis symptom questionnaire (Isaac core questions) in a population of Swiss school children visiting the school health services. *Pediatric Allergy and Immunology* 1997;8:75–82.
74 Szefler SJ, Mitchell H, Sorkness CA, *et al*. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *The Lancet* 2008;372:1065–72. S0140-6736(08)61448-8 [pii].
75 PROMIS Pediatric Scale v1.0 - Global Health-7, 2016. Available: https://www.healthmeasures.net/ [Accessed 05 Jun 2016].
76 PROMIS Pediatric - Profile-25 v2.0: HealthMeasures.net, 2016. Available: https://www.healthmeasures.net
77 Kroenke K, Spitzer RL, Williams JBW, *et al*. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics* 2009;50:613–21.