

Joint Research Management Office (JRMO) Research Protocol for Research Studies

Full Title	Short-term air pollution exposure and risk of airway inflammatory response in children
Short Title	CHERISH (Children's HEalth, Respiratory Inflammation and SHort-term air pollution)
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REC Reference <i>Research Ethics Committee</i>	QME25.1220
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2. Glossary

ARTP: Association for Respiratory Technology + Physiology
 ATS: American Thoracic Society
 BMI: Body Mass Index
 CARRii: Centre for Applied Respiratory Research Innovation and Impact
 CC16: Clara cell protein 16
 CI: Chief Investigator
 CHERISH: Children's HEalth, Respiratory Inflammation and SHort-term air pollution
 CHILL: Children's Health in London and Luton
 CRF: Case Report Form
 DEFRA: Department for Environment, Food & Rural Affairs
 DNA: Deoxyribonucleic acid
 ERS: European Respiratory Society
 EUPATI: European Patients' Academy on Therapeutic Innovation
 FeNO: Fractional exhaled Nitric Oxide
 GDPR: General Data Protection Regulation
 HRA: Health Research Authority
 HTA: Health Technology Assessment
 ICC: Interclass correlations
 ICL: Imperial College London
 IL-6: Interleukin-6
 IL-8: Interleukin-8
 MPO: Myeloperoxidase
 MRC: Medical Research Council
 NO2: Nitrogen Dioxide
 PE: Physical Education
 PI: Principal Investigator
 PPI: Patient and Public Involvement
 PMG: Project Management Group
 QMREC: Queen Mary University of London Research Ethics Committee
 QMUL: Queen Mary University of London
 SAB: Scientific Advisory Board
 SOP: Standard Operating Procedure

STEM: Science, Technology, Engineering, and Mathematics
WIPH: Wolfson Institute of Population Health

3. Signature page

CI Agreement

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of GCP, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

CI Name: Abigail Whitehouse



Signature:

Date: 14/10/25

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research,, the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for the statistical work in this protocol is accurate and take responsibility for statistical analysis and oversight in this study.

Statistician's name: _____

Signature: _____

Date: _____

4. Summary and synopsis

Short title	CHERISH (Children's HEalth, Respiratory Inflammation and SHort-term air pollution)
Methodology	Randomised mixed factorial design with one within-subject factor (exposure condition: active vs. rest) and air pollution as a continuous variable.
Objectives / aims	<p>Objective 1: Provision of an air pollutant database covering all exposure days and one week prior to exposure days at participating school sites and children's home addresses.</p> <p>Objective 2: Assess and compare the acute health effects (changes in lung function and airway inflammation) of primary school-aged children exercising in school playgrounds selected to have a mix of air quality characteristics.</p> <p>Objective 3: Examine the relationship between variations in daily air quality and the physiologic and immunologic responses observed.</p> <p>Objective 4: Provision of a free outreach and engagement workshop for all schools, using Breathe London real-time, user-friendly air quality data to empower schools to monitor their own air quality.</p>
Number of participants	330
Inclusion and exclusion criteria	<p>Inclusion</p> <ul style="list-style-type: none"> • Girls and boys • Aged 8 to 11 • Attending schools in Central and East London that have been recruited to the study <p>Exclusion</p> <ul style="list-style-type: none"> • Not able to engage with PE lessons on safety grounds, reported by their parents. • Children with learning or physical disabilities sufficient for them to be unable to give informed assent to the study, or to carry out study procedures.

Statistical methodology and analysis (if applicable)	Mixed effects models, considering repeated measurements within participants and variances between groups.
Study duration	24 months 1 st June 2025 – 31 st May 2027

5. Introduction

5.1. Background

The global burden of disease survey estimated air pollution contributed to one in eight deaths in 2019 (1). Urban areas such as London are a heterogeneous patchwork of different air pollutants, which all have different impacts on human health. Air pollution disproportionately impacts children due to their growing lungs. Understanding how different air quality environments affect children is vital to improving health guidance we provide to them and their families.

5.2. Rationale

Air pollution in one in four London school playgrounds exceeds the UK legal limit for NO₂ (2) with playgrounds in deprived areas exposed to 8% more NO₂ than the least deprived areas. Research has shown that air pollution stunts lung growth in primary school-aged children (3). The UK Government's Committee on the Medical Effects of Air Pollutants is currently reviewing the Air Quality Information System for public alerts and the issue of whether or when to ask public organisations such as schools to restrict exercise. Despite this, no research has explored the health impacts of exposure to air pollution in London's school playgrounds. The committee is calling for studies, such as CHERISH, to investigate the health effects of exercise in polluted school playgrounds to guide this critical government policy.

6. Study objectives

6.1. Primary hypothesis

Primary hypothesis: Exposure to air pollution in school playgrounds is associated with acute decrements in lung function following physical activity as measured by oscillometry resistance at R5.

Secondary hypothesis (ii): Exposure to air pollution during physical activity is associated with the induction of inflammation in children compared to rest.

6.2. Objectives

Objective 1: Provision of an air pollutant database covering all exposure days and one week prior to exposure days at participating school sites and children's home addresses.

Objective 2: Assess and compare the acute health effects (changes in lung function and airway inflammation) in primary school-aged children of exercising in school playgrounds selected to have a mix of air quality characteristics.

Objective 3: Examine the relationship between variations in daily air quality and the physiologic and immunologic responses observed

Objective 4: Provision of a free outreach and engagement workshop for all schools, using Breathe London real-time, user-friendly air quality data to empower schools to monitor their own air quality.

Primary endpoint

Airways resistance as measured by oscillometry R5

6.3. Physiological secondary endpoints:

- R5-R20.
- X5
- X5-X20

6.4. Immune response primary endpoint

- IL6

6.5. Secondary Immune response endpoint

- Th1/Cellular Immunity: Granzyme A, Granzyme B
- Acute/Innate Inflammation: IL-1b, IL-8, TNFa, MPO
- Th2/Type 2 Immunity: IL-4, IL-5
- Factors That Promote the Th2 Response (Alarmins): TSLP and IL-33
- Dual or Regulatory Role Mediators: IL-10
- TH17-Associated: IL-23
- Vascular/Endothelial Markers: VEGF, E-selectin
- Oxidative stress: Glutathione, LOPs

6.6. Control variables

- Physical activity measured by accelerometry
- Prior exposure to air quality measured as: PM₁₀ and PM_{2.5}, nitrogen dioxide (NO₂).

- Temperature, wind direction (if required)
- Prior exposure from Breathe network.

6.7. Biobanking

- Any nasal mucus samples not used in the analysis will be biobanked for secondary analysis.
- We shall target Child Action for a follow-on grant to analyse biobanked samples.

7. Study population

School Selection

We shall purposely recruit schools from the CHILL and Breathe networks (Central and East London) to ensure a gradient in NO₂ between the two groups of five schools. Breathe London have provided historical data which shows that we are able to provide the required air quality contrasts by working with schools already within their network.

Participant Selection

Children will be recruited via a school bag approach where information sheets and consent forms are sent home via school SMS systems and in children's school bags. Additional information/opportunity to ask questions will be provided via playground information sessions, talks at parent's evenings, school newsletters, and class talks.

7.1. Inclusion criteria

- Girls and boys
- Aged 8 to 11
- Attending Central and East London schools recruited to the study

7.2. Exclusion criteria

- Not able to engage with PE lessons on safety grounds reported by their parents.
- Children with learning or physical disabilities sufficient for them to be unable to give informed assent to the study, or to carry out study procedures.

8. Study design

Randomised mixed factorial design with one between-subjects factor with a within-subjects factor (exposure condition: active vs. rest) and air pollution as a continuous variable.

9. Study procedures

9.1. Participant pathway summary

Students will be recruited via a school bag approach - where study documents are sent to parents in children's school bags. To ensure informed consent, further support will be provided in the form of playground information sessions, parent talks, school assemblies, school newsletters, and class talks - informing children and parents about the study and providing opportunity to ask questions.

Parents and participants will provide informed consent/assent after they have time to consider their involvement (minimum 24 hours) and ask any questions. Following provision of written informed consent, participants' parents/guardians will complete a short baseline and demographic questionnaire and provide their address to support air pollution exposure estimates.

Following provision of written informed consent, the CHERISH study team will visit the schools on two occasions, separated by a minimum washout period of two weeks. The study team will set up in a spare classroom. Tables will be wiped down and individual stations with bottles of sterile saline solution will be set out along with oscillometers and FeNO devices. When consented children enter the room, they will be asked initial assent questions (SOP 1). Once they have provided their assent, they will have their height and weight measured (SOP 2) and will then undergo the nasal sampling and lung function assessment (SOP 4 and SOP 8, respectively). All children will perform a FeNO test (SOP 3). They will also be provided with activity monitors.

The children will then take part in either the 90-minute PE lesson led by West Ham United Foundation or the science workshop led by Centre of the Cell. The sessions will be designed to keep children at either sedentary or moderate levels of physical activity. Schools will be randomised in terms of the order in the which the two sessions are delivered (i.e., PE followed by science workshop or science workshop followed by PE). All children will take part in both sessions.

At the end of the session children will undergo a second round of lung function testing and will hand back their activity monitors.

The next day the study team will attend the school again and they shall perform the assent questions, lung function assessment, and the sample collection in an identical way to the pre-exposure assessment.

Screening, Recruitment & Informed Consent

Central and East London schools will be selected from the Breathe London Network or CHILL study as this ensures they already possess the required air quality monitoring infrastructure to report air pollution. 10 schools will be recruited with

varied air pollution concentrations (as determined by historic air quality data from Breathe London).

An average of 33 participants will be recruited at each school according to the criteria in section 7.1.

Study Intervention

	09:00	10:30	11:30	12:30	24 hours after
	Classroom	Playground	Playground	Classroom	Classroom
Assent	x				
Baseline Survey	x				
Activity monitor		x	x		
FeNO	x				
Oscillometry	x			x	x
Nasal lavage	x				x

All physiological measures will be performed to the most recent ATS, ERS and ARTP guidelines.

9.2. Abstaining from medication.

Participants will continue to use all their routine asthma medication (e.g. preventer inhalers) during the study. In agreement with ERS spirometry guidance, participants will be asked to abstain from using reliever medication for six hours prior to performing lung function assessment. If participants need to use their medication in the six hours prior to the first spirometry testing of an assessment visit they will take part in the study and researchers will record the use of medication.

If participants need to use their inhaler during the testing protocol a member of the research team will immediately seek out the school first aid trained member of staff. The use of an inhaler should be marked on the CRF. If the symptoms resolve, the school policy will be followed. If the school plan is that the participant rejoins PE (and the participant agrees and wishes to rejoin) they can return to the PE lesson gradually and under observation. The participant should follow the testing pathway unless they opt out and withdraw assent.

If the participant is known to have asthma and haven't brought their inhaler, they can only take part if the school policy is that they would be allowed to take part in a normal exercise class.

9.3. Exercise and exposure protocol:

To control for variations in air quality, exposure will occur for 90 minutes between 10:30am and 13:30pm on weekdays. Between pre- and post- health assessments, trained coaches will lead an educational outreach PE session designed to maintain a consistent level of exercise intensity, monitored by Actigraph physical activity monitors.

We propose standardising exercise intensity to control physiological variation such as cardiovascular and ventilatory drift and to standardise inhaled doses of PM and gaseous pollutants over the 2-hour period and reflect a typical PE lesson. Moderate intensity is chosen, as prior research by the authors has shown that children spend break time performing moderate-to-vigorous levels of physical activity, ensuring a safe level of intensity, and reflecting children's typical exercise levels and therefore ensuring maximum relevance of the findings.

Sample Collection and Laboratories

The nasal lavage samples will be collected at the school sites and subsequently biobanked. They will be transferred to Blizzard laboratories in cooler boxes (4°C) by a member of the research team. Upon arrival, samples will be stored within HTA approved facilities at -80°C. All transport, storage and disposal protocols will adhere to the College's SOPs, which can be found on the QMUL Governance site.

See *Laboratories Section 14* for details of laboratory procedures for examining the samples.

Participant Withdrawal

Three options are provided to participants should they wish to withdraw:

- May withdraw from a specific part of the study (e.g. one of the lessons – PE or science outreach) but continue with the rest of the study, in which case data is retained.
- May withdraw at any point and continue no further, data for before this point is retained.
- May withdraw and request all data removed - in which case all data for this participant is removed from the study.

The sample size for this study has been chosen to account for up to a 15% dropout rate without reducing the power of the statistical analysis below 85%.

End of Study

We define the end of the study as the final interaction with a sample at the laboratory. Therefore, the study ends once all included samples have been examined and associated data is recorded.

9.4. Study Timeline

GANTT CHART		Responsibility	Comments	Mar-25	Jun-25	Sep-25	Dec-25	Mar-26	Jun-26	Sep-26	Dec-26	Mar-27	Jun-27
Study administration	Set up study meeting/ teams	AW											
	Confirm protocol	AW/JS											
	Study Sponsorship	AW/JS											
	Research ethics	AW/JS											
	Study documents	AW											
	Set up testing equipment	JS											
	Set up study website	JS											
Health assessment	Final report	AW											
	School Recruitment	JS											
	Participant recruitment	HV											
	Participant exposure period	JS											
	Health data processing	JS											
	Data linkage	HH											
Air quality monitoring	Analysis	HH											
	Analysis of historical AQ data	MM/HH											
	Data collection	MM											
	Data preparation	MM											
Sample processing	Data linkage	HH											
	Consumable purchases	IM											
	Sample processing	IM											
	Data linkage	HH											

10. Statistical considerations

10.1. Randomization

We shall randomise to activity or sedentary conditions at the school level. This will be done prior to school visits via sealed envelopes containing one of the two conditions. The envelopes will be sealed before the start of the study by someone not part of the study team.

10.2. Sample size

A total of ten schools will be recruited to this study. Ten schools will be purposively recruited using historical air quality data from Breathe London to get higher and lower NO₂ pollution schools. This strategy will provide the largest air pollution gradient possible between the school playgrounds.

An average of 33 children will be recruited at each school ensuring 165 children are recruited to each group. We expect 10% drop out in each group.

For power calculation, we set significance level= 0.05, mean value = 0.572 and standard deviation = 0.14 for respiratory resistance (R5). If we want to see 5% change in R5, with total of 330 children (33 per school) and clustered within 10 schools (active vs rest), we then will have a power of 90.21%. Even if we will have a dropout rate of 10 to 15%, we will have a power of 85.28%.

5% change in R5 was chosen as it is a clinically relevant change in airway restriction. This is especially true in the specific context of school playground exposures which occur daily in school environments.

10.3. Method of analysis

Mixed effects models, considering repeated measurements within participants and variances between groups.

10.4. Descriptive analysis

After data quality check, we will prepare data description tables including number of observations, mean and standard deviation of variables. We will also use graphical methods (e.g. scatterplots) to get insight in the correlation between different exposure variables and the associations between specific exposures and health endpoints.

10.5. Statistical modelling

We will use a mixed effects regression model to estimate the effects of different pollutants on changes in health outcomes, defined as the difference in various measures (e.g. R5 and R5–R20) between pre-exposure and post-exposure (at 0, 2, or 24 hours). For each endpoint, one key post-exposure time point will be selected based on the time of maximal effect observed in previous controlled exposure studies; for example, for R5 this will be 24 hours post-exposure.

We will provide estimates of the effects of pollution exposure and physical activity (within participants). Levels (e.g. integrated average concentration report as interquartile ranges) of each pollutant will be included in the model. We shall include pollutant as a continuous variable. The effects of different pollutants will be compared based on statistical significance and effect sizes calculated for selected exposure contrasts.

Two-pollutant models will also be specified to evaluate which pollutant has the strongest association with each health endpoint. In our models, we will account for potential confounders that may be present, as the exposure contrast cannot be entirely predicted by design. We may therefore include meteorological variables (e.g. temperature, relative humidity, and wind direction during the exposure) as well as individual characteristics such as age, gender, asthma severity, and allergies.

To account for repeated measures, random intercepts for participants will be included in the models, and random slopes will be explored if model convergence permits.

Covariates will be included in the model to account for repeated measures (health outcome at baseline) and to adjust differences between groups (BMI as a Z-score, ethnicity, age, gender, asthma status).

To account for possible clustering effects (children nested in schools) we shall first run null models to evaluate the interclass correlations (ICC) if the ICC effect is large at the school level we shall include two hierarchical levels by including school and student as random effects in the model.

All mixed models will be implemented in R (version 4.1.3 or newer; R Development Core Team), using functions from the lme4 and nlme packages.

11. Ethics

The study will be sponsored and managed by QMUL and supported by Imperial College London, [according to MRC guidance](#).

This study has received QMUL REC approval (reference QME25.1220). The study will be carried out according to the principles of the Helsinki Agreement 2013.

11.1. Risks / benefits

11.1.1. Risks to participants: Asthma attack or unwell

There are risks associated with exposing children to high air pollution via exercise protocols. Such activities may increase the likelihood of accidental events, with asthma attacks being the most likely. Between 8 and 15% of children recruited to the study are likely to have asthma, based on UK prevalence.

11.1.2. Risk mitigation: Asthma attack or unwell

To mitigate potential accident events during the study we will take the following precautions (SOP 6):

- The study will only proceed after University Research Ethics Committee approval and sponsor indemnity.
- Our protocol has been devised with people living with asthma, children, parents and respiratory paediatric clinicians.

- Participants will only be recruited if their parents report them fit enough to participate in PE lessons.
- Participants will have respiratory health assessments prior to the PE lesson.
- Usual medication will be continued (e.g. prescribed preventer inhalers).
- The exercise intensity and locations have been selected to be typical of school PE lessons, as such participants will not be exposed to unusually high air pollution.
- Basic rescue asthma medication (salbutamol and large volume spacer) should always be available at assessment sites. If required, first aid will be administered by appropriate school staff
- If participants need to use their inhaler during the testing protocol the testing will end immediately. A member of the research team will immediately seek out the school first aid trained member of staff . The use of an inhaler should be marked on the CRF. If the symptoms resolve, the school policy will be followed. If the school plan is that the participant rejoins PE (and the participant agrees and wishes to rejoin) ,they can return to the PE lesson gradually and under observation. The participant should follow the testing pathway unless they opt out and withdraw assent.
- We shall remind children who report having rescue inhalers, bring them to school on the visit days. If the participant is known to have asthma and haven't brought their inhaler, they can only take part if the school policy is that they would be allowed to take part in a normal exercise class.
- Participants will be closely monitored during the exercise protocol and will be repeatedly encouraged to provide feedback about their physical state during the exercise.
- A risk register and an adverse events register will be maintained for the duration of the study.
- Accidents will be discussed with the Chief Investigator and reported promptly to the Sponsor as per Good Clinical Practice regulations and reviewed at study Project Management Group.

11.1.3. Response to Asthma attack or unwell participants:

This section should be read alongside SOP 06 and the field-testing risk assessment. If a participant has an asthma attack during the protocol the testing will end immediately. a member of the research team will immediately seek out the school first aid trained member of staff. The use of an inhaler should be marked on the CRF. If the symptoms resolve, the school policy will be followed. If the school plan is that the participant rejoins PE (and the participant agrees and wishes to rejoin) they can return to the PE lesson gradually and under observation. The participant should follow the testing pathway unless they opt out and withdraw assent.

In the event of a participant feeling unwell, the research team will:

- Calmly reassure the participant and encourage the participant to make themselves suitably comfortable.
- The participant will be observed for any signs of distress or breathing difficulty.
- Alert the nearest member of school staff
- Seek first aid trained member of school staff
- If required, first aid will be administered by appropriate school staff
- School first aid/safeguarding protocols will be followed.

11.2. Risks to participants: Accidental personal data release

As with all human participant research there is a risk of inadvertent release or loss of personal data through incorrect storage of electronic or hardcopy data or through incorrectly transferring or handling data.

11.3. Risk Mitigation: Accidental personal data release

To mitigate this, we shall follow best practice guidelines provided in SOPs by our Clinical Trials Unit (SOP 7). Paper records will be stored securely in locked filing cabinets in password locked rooms in the pass-protected Centre for Primary Care in the Wolfson Institute of Population Health. Electronic records will be stored in a password-protected study database on a secure server in QMUL. In the study database, personal details (name, address, date of birth) will be kept separate from research data, which will be identified by a unique study reference number. In tables of data, participants will only be identified by number not by initials or name. Data management procedures will be completed in compliance with the GDPR and trial regulations. Survey reported data will be stored in the QMUL data safe haven, where data will be held in a UK server and access will be facilitated by two factor authentication. Survey software with integrated data validation checks and audit trails will be used to record study data. Any data transfers between QMUL and Imperial College London will be completed via encrypted Secure File Transfer Protocol. All data will be backed up weekly to ensure data is safeguarded from accidental loss.

11.1. Annual Safety Reporting

The CI will send an Annual Progress Report to the QMREC and the sponsor using the Health Research Authority (HRA) template on the anniversary of the QMREC “favourable opinion”.

11.2. Benefits

Participants:

Participants will receive free respiratory health assessments. They shall also receive a free lesson from West Ham United multisport coaches and a 'snotty science' STEM science workshop explaining how air pollution impacts their health.

Society:

This study will give evidence to support policy change when it comes to planning of play spaces and provide evidence on the direct impact of where our children play in relation to traffic pollution exposure. By having this evidence, we will be able to better inform families and the wider public on appropriate actions to take. There is also the potential to feed into wider policy on health advice such as that given on high air pollution days by DEFRA.

Academic outputs of the study will be fed directly back into the far-reaching education projects that are stemming from the Barts-funded and established Children's Environmental Health Service.

12. Public involvement

As the study progresses the PPI group will be invited to project management group (PMG) meetings. The group will collaborate as advisors and partners in the study and are invited to provide unsolicited advice. To ensure the PPI group can provide meaningful advice and guidance the CI will regularly keep them informed of study developments via email. The meetings will follow the EUPATI (European Patients Academy on Therapeutic Innovation) roadmap (<https://bit.ly/3bugCMk>) discussing themes of: Research design and planning, research conduct, operations, dissemination and communication.

13. Data handling and record keeping

13.1. Data management

OneDrive will be used to store electronic case report forms all data will be held on GDPR compliant databases with integrated data validation checks and audit trails (SOP 7). All collected data will be held on backed up encrypted servers. Any data transfers between ICL and QMUL will be performed via Secure File Transfer Protocols. Paper records, CRFs and consent forms and recruitment logs will be held locally in double locked locations in Yvonne Carter Building 58 Turner St E1 2AB (QMUL).

Data Sharing: we will comply with MRC policy on data sharing. A copy of study data will be held on the HDRUK BREATHE secure data hub

<https://www.breathedatahub.com>. BREATHE's mission is 'Better respiratory health through better connected data'.

13.2. Source Data

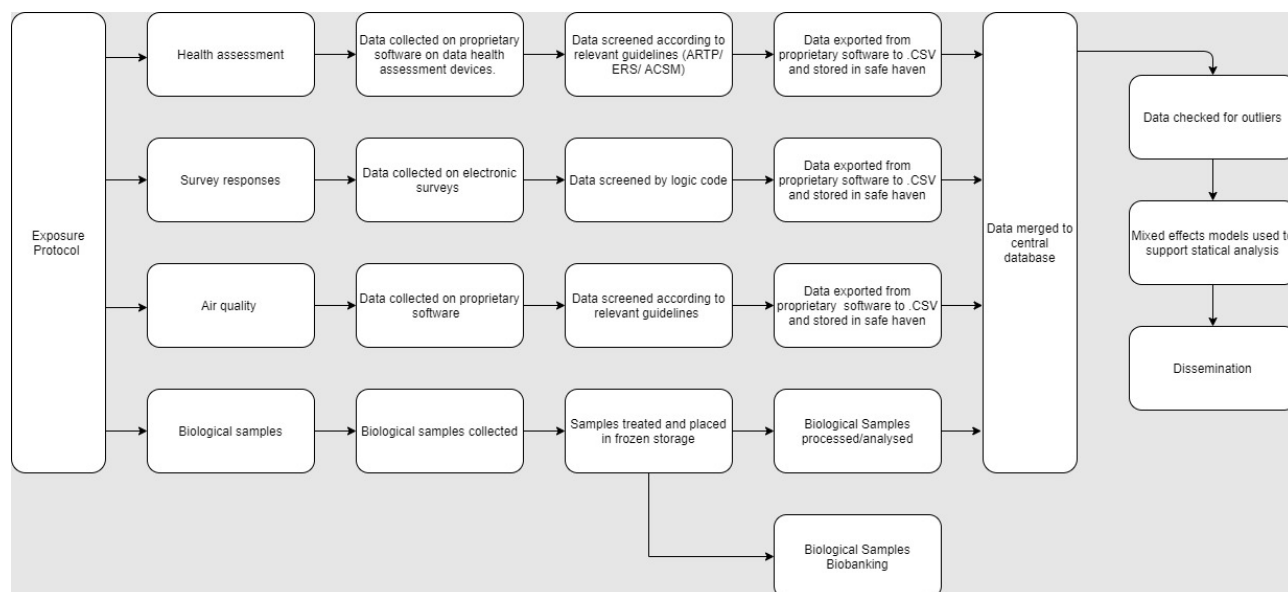


Figure 1. Representation of data flow

Quantitative data will be generated from patient surveys, health assessments, biological samples, and air quality.

Participant identifiable data will be held within QMUL secure OneDrive.

All data will be generated, collected, and stored according to MRC policy and the findable, accessible, interoperable, and reusable (FAIR) principles.

13.3. Confidentiality

We shall follow best practice guidelines provided in SOPs by our Clinical Trials Unit. Paper records will be stored securely in locked filing cabinets in password locked rooms in the pass-protected Centre for Primary Care (WIPH). Electronic records will be stored in a password-protected study database on a secure server, in QMUL. In the study database, personal details (name, address, date of birth) will be kept separate from research data, which will be identified by a unique study reference number. In tables of data, participants will only be identified by number not by initials or name. Data management procedures will be completed in compliance with the GDPR and trial regulations. Survey reported data will be stored in the QMUL data

safe haven, where data will be held in a UK server and access will be facilitated by two factor authentication. Survey software with integrated data validation checks and audit trails will be used to record study data. Any data transfers between QMUL and Imperial College London will be completed via encrypted Secure File Transfer Protocol. All data will be backed up weekly to ensure data is safeguarded from accidental loss.

13.4. Record retention and archiving

In accordance with the UK Policy Framework for Health and Social Care Research, research records will be kept for 20 years after the study has completed while personal records will be stored for five years after the study has been completed. At the completion of the study data will be moved to a trusted archive centre. At the end of the retention period data will be destroyed in accordance best practice guidelines at the time of destruction.

14. Laboratories

14.1. Sample preparation and collection

Nasal mucus samples will be collected via nasal lavage (SOP 4). Nasal lavages will be performed at two time points, pre and 24-hour post at the school sites. Samples will be biobanked in 5 mL aliquots at -80°C at ICL under Human Tissue Act licence 12521 (local Human Tissue Act lead, Dr Ian Mudway).

Samples will be collected in disinfected facilities at the field-testing site. Screens will be used to ensure participant privacy.

14.2. Laboratory procedures

Samples will be assessed using a case-controlled study design. The sample will consist of children who report any form of respiratory disease. We shall then randomly select a healthy comparator cohort, which is matched for 1) age 2) sex 3) Ethnicity 4) air pollution.

Samples across the interval pre- to 24-hour post will be used to assess neutrophilic biology, oxidative stress pathways, and epithelial injury.

We hypothesise that short-term exposure to ambient air pollution-primarily driven by NO₂ and traffic-related co-pollutants induces epithelial stress, leading to neutrophil

recruitment and activation, and the release of inflammatory mediators and effector molecules.

The inflammatory response will be characterised through measurement of:

Primary outcome:

- IL6 (key role in Th17 polarisation)

Secondary outcome:

- Th1/Cellular Immunity: Granzyme A, Granzyme B
- Acute/Innate Inflammation: IL-1b, IL-8, TNFa, MPO
- Th2/Type 2 Immunity: IL-4, IL-5
- Factors That Promote the Th2 Response (Alarmins): TSLP and IL-33
- Dual or Regulatory Role Mediators: IL-10
- TH17-Associated: IL-23
- Vascular/Endothelial Markers: VEGF, E-selectin
- Oxidative stress: Glutathione, LOPs

Nasal lavage samples will also be retained as a downstream resource for secondary analysis that aligns with ongoing work by JS and AW.

14.3. Sample storage and transfer

Samples will be transferred from the collection sites in London to QMUL in cooler boxes (4°C) using authorized courier services. Upon arrival samples will be stored within HTA approved facilities at -80°C. All transport, storage and disposal protocols will adhere to the College's SOPs, which can be found on the QMUL Governance site.

15. Safety reporting

Accident events occurring between visits/questionnaires/sample collections will not be recorded or reported as they are not the aim or focus of this study.

The CI's (Dr James Scales, Dr Abi Whitehouse) may take urgent safety measures to ensure the safety and protection of the study subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the QMREC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (*via* telephone) of this event immediately.

The CI has an obligation to inform both the Main QMREC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management

Office [JRMO]) must be sent a copy of the correspondence with regards to this matter.

16. Monitoring and auditing

The Sponsor or delegate retains the right to audit any study, study site, or central facility. In addition, any part of the study may be audited by the funders where applicable.

For further explanation of monitoring and auditing this section should be read along with the documents:

- SOP 1) Consent and assent**
- SOP 2) Height and weight**
- SOP 3) FeNO**
- SOP 4) Nasal lavage**
- SOP 5a) Activity monitoring**
- SOP 5b) Device preparation**
- SOP 6) Participant unwell or injured**
- SOP 7) Data management and quality control**
- SOP 8) Oscillometry**

Dr Abi Whitehouse and Dr James Scales will be responsible for the data management, storage, record keeping, coding, data linkage, and metadata generation. All researchers have up to date GCP and Data Governance training. All data will be managed according to European Union General Data Protection (GDPR) guidelines.

QMUL studies adhere to the NHS Research Governance, Framework for Health and Social Care, the Data Protection Act, and the Human Tissue Act. We follow QA and QC protocols are developed by the PCTU.

We shall hold a trial Master file recording all key study documents and study discussions, ethical review board reports, and staff training logs. Detailed meta-data will be kept. Methodologies and analyses will be summarised in readme files, including information on variables names, missing data labels, definition of acronyms, etc. For example, sample tracking records, SOPs, and information on QA/QC procedures, stored as pdfs on secure servers with metadata tables linking relevant documentation to datasets. For new data acquisitions/ collations data dictionary/metadata describing data content will be created embedded in the data or stored separately. Methods and analysis techniques will be documented and stored in relevant study folders.

17. Study committees

Study Team Meetings

The study team will meet weekly chaired by JS to discuss day-to-day delivery of the project, and report to the PMG.

Project Management Group (PMG)

Monthly project management meetings will be chaired by AW and will consist of the co-applicants, collaborators, and research associates. Queen Mary University London (QMUL) will lead the health assessment and analysis with HW project managing the programme. Breathe London (ICL) will lead the exposure data collection and processing and laboratory assessments. Ongoing statistical support will be provided by HH. An open invite will be extended to the SAB and a CARRii PPI group representative

Scientific Advisory Board (SAB):

We present an exceptional team that has worked closely together to successfully conduct large scale research programmes. However, in recognition of the early career status of the applicant we propose to convene a SAB at least four times a year; we propose it be chaired by Professor Chris Griffiths, from QMUL Center for primary care. Prof Griffiths currently leads the CHILL study. Other members of the board include Prof Klea Katsouyanni, who will provide statistical guidance. In the first instance the board's role is to monitor and advise on study conduct and progress on behalf of the Sponsor and Barts Charity. However, the board are all known to the research team and will meet more frequently than a traditional SAB to provide more detailed support and guidance to the study team.

18. Finance and funding

This work is funded by Barts Charity under grant code: G-002887

19. Insurance and indemnity

The insurance that Queen Mary has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

20. Dissemination of research findings

Dissemination is a standing item on the PMG agenda, ensuring interim study findings are rapidly and effectively communicated. Our PPI group will co-write or review all study outputs for dissemination via traditional and social media throughout the study.

The outputs of this study fall into four key areas and in order to fully support all of them, we will work not only with PPI groups (Namely, Mums for Lungs and CARRii PPI Group) to co-design the dissemination plan, but also to work on ways to ensure that the results of the study can be viewed by all in an accessible manner.

Policy:

We envisage that the results of this study will be directly relevant to policy makers. As AW and ISM sit on the UK governments Committee for Medical effects of Air pollutants, we know the UK government is specifically looking for studies which describe the health impacts of air pollution on children in school playgrounds to inform the UK governments air quality warning system. We shall ensure we present our findings to the committee.

Academic:

This study will deliver key outcomes on the question of the short-term health impacts of traffic derived pollution exposure in our most vulnerable age-group. Previous research has looked at this in adults but to date the immediate responses have been less well clarified within a paediatric population. This will then feed into the wider body of evidence on short-term health effects in children.

- We will deliver a set of high impact publications in primarily environmental health journals and present our findings at international conferences.
- We shall make our data available on open access via HDRs BREATHE, a UK respiratory health data repository lead by our collaborators.
- We shall explore feasibility of combining our data sets with other comparable short exposure studies including IONA (WT-7325450) and the London Underground study (MR/S035613/1).

Clinical:

While this study will look at all children within the schools, there is likely to be a proportion that have underlying health conditions therefore we hope to be able to see smaller effects in these children.

We plan to use the results of this study to support clinician education providing specific advice regarding vulnerable children with respiratory illness. This will be embedded in the air pollution mitigation advice training that has been recommended by multiple parties in relation to reducing the health impacts of air pollution exposure in children with wheeze and asthma.

Public:

This research proposal and study have been developed due to a recurrent and pressing need to fulfil a research gap that has been noticed by parents, schools, and the wider public, namely looking at the impact that our play spaces have on children's health. Therefore, a major focus of our communications will focus on disseminating the results in an accessible way.

- In the spirit of Breathe London's open access air quality data we shall provide summary data to schools and community groups via the Breathe London website.
- We shall provide outreach workshops to schools, led by outreach experts at QMUL's Centre of the Cell.
- We shall prepare press releases to support use in social media platforms and public facing websites.

We will engage closely with the media teams at QMUL and Barts to support this process.

21. References

1. Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet [Internet]. 2020 Oct 17 [cited 2025 Sep 19];396(10258):1223–49. Available from: <https://www.thelancet.com/action/showFullText?pii=S0140673620307522>
2. Sheridan CE, Roscoe CJ, Gulliver J, Fecht D, Preux L de. Inequalities in Exposure to Nitrogen Dioxide in Parks and Playgrounds in Greater London. International Journal of Environmental Research and Public Health 2019, Vol 16, Page 3194 [Internet]. 2019 Sep 1 [cited 2025 Sep 19];16(17):3194. Available from: <https://www.mdpi.com/1660-4601/16/17/3194/htm>
3. Mudway IS, Dundas I, Wood HE, Marlin N, Jamaludin JB, Bremner SA, et al. Impact of London's low emission zone on air quality and children's respiratory health: a sequential annual cross-sectional study. Lancet Public Health. 2019 Jan 1;4(1):e28–40.