RESEARCH PROTOCOL

MAAS 25

Manchester Asthma and Allergy Study (MAAS)

Age 25 plus follow up

STUDY PROTOCOL

Version 1.2

Contents

1) RESEARCH TEAM & KEY CONTACTS

Chief Investigator: **Name:** Professor Clare Murray **Address:** 2nd Floor ERC, Wythenshawe Hospital, Southmoor Road, Wythenshawe, M23 9LT. **Email:** clare.murray@manchester.ac.uk **Telephone:** 0161-291-5876	***Co-investigator(s):*** **Name:** Professor Angela Simpson **Address:** 2nd Floor ERC, Wythenshawe Hospital, Southmoor Road, Wythenshawe, M23 9LT. **Email:** Angela.Simpson@manchester.ac.uk **Telephone:** 0161-291-5876:
Sponsor(s): **Name:** The University of Manchester **Sponsor contact:** Ms Stacey Body Research Governance Officer **Address:** Faculty of Biology, Medicine and Health, 4.64 Simon Building, University of Manchester, M13 9PL. **Email:** FBMHethics@manchester.ac.uk **Telephone:** 0161 275 5436	***Lead R&D Trust contact(s):*** **Name:** Ms Elizabeth Mainwaring, **Address:** Research Office 1st Floor Nowgen Centre 29 Grafton Street Manchester M13 9WU. **Email:** R&D.applications@mft.nhs.uk **Telephone:** 0161 276 3340
Co-investigator(s): **Name:** Dr Lesley Lowe **Address:** North West Lung Research Centre, Wythenshawe Hospital, Southmoor Road, Wythenshawe, M23 9LT. **Email:** lesley.lowe@manchester.ac.uk **Telephone:** 0161 291 5053	***Co-investigator(s):*** **Name:** Mrs Gina Kerry **Address:** North West Lung Research Centre, Wythenshawe Hospital, Southmoor Road, Wythenshawe, M23 9LT. **Email:** gina.kerry@manchester.ac.uk **Telephone:** 0161 291 5036

Collaborator **Name:** Professor Stefano Guerra Professor of Medicine, Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, UA Department of Medicine **Address:** Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, University of Arizona College of Medicine, Tucson, AZ 85724-5030A, USA **Email:** stefano@arizona.edu **Telephone:**	***Collaborator*** **Name:** Professor Adnan Custovic Professor of Paediatric Allergy **Address:** St Mary's Campus Medical School Imperial College London W2 1PG **Email:** a.custovic@imperial.ac.uk **Telephone:** **020 7594 3274**
Collaborator **Name:** Dr Sara Fontanella Non-Clinical Lecturer in Biomedical Modelling **Address:** Sir Alexander Fleming Building, South Kensington Campus, United Kingdom **Email:** s.fontanella@imperial.ac.uk **Telephone:**	

2) INTRODUCTION

Asthma is the most common long-term condition of childhood, the cause of which is unknown. It runs in families, but genetic studies have shown it is not due to a defect in a single gene, and the genetics of asthma is highly complex. Environmental factors are also important, and include pollution, allergens, tobacco smoke and viruses, but precise causes remain elusive.

Most asthma starts early in life and probably arises because of interactions between genetic and environmental factors. Population based birth cohort studies are the ideal study design to understand causes of asthma as information is collected prospectively before disease develops, facilitating longitudinal analysis. There are several birth cohorts in the UK, including the Manchester Asthma and Allergy Study (MAAS), around which this application is based. This cohort was recruited from 1995 from Wythenshawe and Stepping Hill Hospitals (n=1184) and sequential clinical follow up (a combination of questionnaires, lung function and blood tests)

occurred at ages 1, 3, 5, 8, 10-12, 13-16 and 18+years. Data and clinical samples from these follow ups have been adopted by a research tissue bank, to facilitate longitudinal analysis; the findings have contributed to many published papers.

The aim of the current study is to invite the MAAS cohort participants to attend for a further follow up visit at age 25 years plus, to complete questionnaires, lung function and blood tests. This will be a single visit lasting approximately 2 hours, conducted either at Wythenshawe Hospital, or as a home visit, postal or online if preferred. It is expected it will take 2 years to see all participants and complete the study. The data collected will be analysed to identify the predictors of and risk factors for persistence of childhood asthma (including environmental exposures, biomarkers and genetic factors)

3) BACKGROUND

Asthma and other allergic disorders are the most common chronic diseases in childhood and a major burden on health care services. Wheeze is one of the commonest causes of emergency hospital admissions and one of the most frequent medical reasons for time off school and work. Asthma and Lung UK estimate that 5.4 million people in the UK are currently receiving treatment for asthma: 1.1 million children (1 in 11) and 4.3 million adults (1 in 12). Asthma is considered incurable and may persist through the lifetime of many patients. Furthermore, exacerbations may need treatment with oral steroids, with potential long-term morbidity (https://www.asthmaandlung.org.uk/about-us/our-latest-work/our-asthma-reports).

Asthma consumes a large share of economic resources. It is estimated that asthma costs between 1% and 2% of the total healthcare budget in direct costs in terms of provision of medical care, and there are equally large indirect costs incurred by time lost from work and reduced productivity. The NHS spends around £1 billion a year treating and caring for people with asthma and in 2008/09 up to 1.1 million working days were lost due to breathing or lung problems.

Persistence of childhood asthma has been now conclusively linked to chronic lung function deficits that (a) track into adult life, (b) increase susceptibility to the subsequent development of chronic obstructive pulmonary disease (COPD), and (c) carry a substantial morbidity and mortality burden[1]. Thus, understanding the natural course of childhood asthma and preventing its persistence into adult life are tasks of paramount importance. Yet, for a significant proportion of children with childhood asthma, symptoms can resolve after the onset of puberty[1 2], but the factors that confer this resilience to persistent asthma remain largely unknown. At the present time, there are neither established prediction models nor available biomarkers for early risk stratification of long-term *sequelae* of childhood asthma.

The Manchester Allergy and Asthma Study (MAAS) is a population-based birth cohort specifically designed to study risk factors for the development of asthma and allergies[3]. Recruitment began in antenatal clinics at Wythenshawe and Stepping Hill Hospitals in 1995 and over a two-year period over 1100 parents consented to their children being followed up from birth. Clinical follow up to assess whether children have developed asthma or allergic disease is complete for age 1, 3, 5, 8, 10-12, 16 and 18+ years[4-8]. The most recent follow up at age 18+ years was completed by 595 participants (462 in person, 52 home visits, 16 postal, 65 online). Previous visits included parentally completed validated respiratory questionnaires (ISAAC) and clinical assessment of the children including skin prick testing and blood sampling. One unique facet of this cohort is the measurement of lung function from age 3 years using specific airways

resistance (sR_{aw}). At age 5, 8, 10-12, 16 and 18+ years the participants have also been able to perform more complex lung function testing[9 10].

Data on risk factors since birth have been collected, including environmental exposures with measurements of inhalant allergens in domestic dust (mite, cat and dog) as well as levels of endotoxin and estimates of environmental pollutants[8 11]. Information on dietary intake is available from age 5 years[12 13]. DNA has been collected on most children (from blood or saliva), and genotyping has been completed, thus allowing environmental and genetic risk factors to be investigated, and the possibility of gene-environment interactions[14-16].

Those with asthma and allergic disease have been shown in some studies to be more likley to have attention deficit hyperactivity disorder (ADHD); it is not clear whether this is due to shared genetic risk factors, or other factors. Screening for ADHD tendencies using a validate questionnaire will allow us to investigate this link further.

Club (formerly Clara) cell secretory protein (CC16, also known as CC10 and CCSP) is a homodimeric pneumoprotein that is encoded by the SCGB1A1 gene on chromosome 11q12.317. It is produced mainly by club cells and non-ciliated epithelial cells in the airways and can be readily measured in circulation18. Although the biological functions of CC16 have not been conclusively established, growing epidemiological and experimental evidence indicates that this protein exerts critical protective properties against airway inflammation and the development of obstructive lung disease[18]. In several cohorts, low levels of CC16 in circulation have been associated with lung function deficits in asthmatics[19 20,] and impaired FEV_1 growth in childhood and accelerated FEV_1 decline in adult life[20]. Data from the Tucson Children's Respiratory Study has shown that low circulating CC16 by school age is associated with strong risk for persistence of childhood asthma into adult life[17]. The evidence supports CC16 as a strong resilience factor against persistent disease and long-term lung function deficits in children with asthma.

The aim of the current study is to carry out a further assessment of individuals within the MAAS cohort, now in their mid-twenties. We will ask the participants to complete tests of lung function and allergies and to complete questionnaires, so that these data in adulthood can be integrated with data collected through childhood to build prediction models for asthma and for lung function and to identify biomarkers for adverse outcomes for respiratory health.

4) STUDY OBJECTIVES

4.1 Primary Question/Objective:

To identify the predictors of and risk factors for persistence of childhood asthma

4.2 Secondary Question/Objective:

1. To investigate the genetic, environmental and temporal factors which predict lung function, asthma and phenotypes and endotypes of wheeze
2. To determine predictors and biomarkers for development of lung function deficits into young adult life (e.g. CC16).
3. To investigate the genetic, environmental and temporal factors which predict onset and persistence of eczema, hay fever and food allergies
4. To investigate the determinants of symptom severity and exacerbations of wheezing illness.
5. To investigate the molecular mechanisms underlying genetic, environmental and temporal factors which predict onset and persistence and severity of eczema, hay fever, food allergies and exacerbations of wheezing illness.

6. To describe the patterns of sensitisation (to inhalant and food allergens) through childhood to adulthood and determine their associates
7. To model indoor and outdoor pollutants in relation to wheeze and atopic outcomes
8. To validate the clinical outcomes collected from questionnaire data with information collected from the GP record (such as prescriptions issued and hospital attendances)
9. To identify determinants of circulating CC16 from birth to adulthood.
10. To describe the association between self-reported ADHD symptoms and asthma and other allergies, and explore associated genetic, environmental and temporal factors

5) STUDY DESIGN & PROTOCOL

5.1 Participants

The participants of the MAAS birth cohort were identified in utero. Parents were screened at 'booking' antenatal visits (during the first 8–10 weeks of pregnancy) by using skin-prick testing and a structured questionnaire. Recruitment started on 1 October 1995 and finished on 1 July 1997. Overall, 1184 children were born into the study. The data on the prevalence of and the risk factors for asthma and other allergic diseases have been described in detail previously. Subsequently children have completed clinical follow up at ages 1, 3, 5, 8, 10-12, 13-16 and 18+years. Since the start of the study (n=1184), 146 participants have withdrawn from further follow up, 107 have been lost to follow up or moved abroad. For the remaining 831, we have maintained contact with cohort members by sending annual birthday cards and requesting they forward new addresses when they move house, email addresses and mobile phone numbers, if they wish to remain in contact with the study.

All active cohort members will be contacted and invited to take part in the 25+ follow-up (approx. 800) with 500 being a realistic figure to complete. All participants will be offered an in-person Clinic Visit, to take place at Wythenshawe Hospital, MFT (**Clinic Visits**). A home visit may be offered to participants (within a 50-mile radius) unable to attend Wythenshawe Hospital (**Home Visit**); this will include completion of questionnaires, measurement of spirometry (including bronchodilator reversibility) and FeNO using a portable device, performance of skin prick tests to inhalant allergens only, and collection of a blood sample. If they are unable to attend Wythenshawe hospital and cannot be offered a home visit, questionnaires can be completed online or by post as an alternative (**Online Visit**). Where possible, participants completing Online Visits will be offered the opportunity to perform home spirometry following video training on the technique, with a spirometer that will be posted to the participant (subject to sufficient funds being available).

5.2 Study Intervention and/or Procedures

This is an observational study. The study will comprise a single visit lasting approximately 2 hours. As this is a birth cohort study, all participants have attended previous visits and completed all these types of tests previously. During the visit the study participants will complete questionnaires, lung function tests, skin prick tests and have blood taken. In order to take part in the study, it is necessary to complete the questionnaires. All other tests are optional, as stated in the Patient Information Sheet and the Consent Form.

Participants will be asked to follow these instructions, where possible: *If you are on inhalers, you will be asked **not to take your inhalers for 4 hours before the test**, or 12 hours if you*

use long-acting inhalers, if possible. You will also need to ***refrain from using antihistamines for 72 hours****, if possible. We ask that you do not eat or drink anything (except plain water) for two hours before your visit*

All tests described below will be offered to those attending for a Clinic Visit. Results will be entered directly into the electronic Case Report Form which will be constructed in a University of Manchester approved software (Qualtrics or REDCap), and contain the fields outlined below. Where tests are also offered for Home Visits (HV) or Online Visit (OV) these are marked (HV) or (OV) accordingly. Tests include:

1. Height, weight and body composition; blood pressure, heart rate and pulse oximetry. **(HV)**
2. Skin prick testing to a panel of inhalant and food allergens (including house dust mite, cat, dog, grass, trees, mould, milk, egg, peanut, hazelnut, walnut, Brazil nut, cashew and peach). **(HV, inhalant allergens only)**
3. Lung function
    - **a.** Fractional Exhaled nitric oxide (FeNO)- a non-invasive method of evaluating airway inflammation. **(HV)**
    - b. Airways Oscillometry - Airways resistance and reactance will be measured using the THORASYS tremoFlo® or similar, in accordance with department SOP. In brief, participants will be seated with their head in the neutral position. Wearing a nose-clip, participants will be instructed to firmly hold their cheeks, as to minimize the upper airway shunt artefact, and breathe tidally through the device. Measurements consist of 16 seconds recordings and the procedure will be repeated in triplicate.
    - c. Airway resistance and static lung volumes will be measured pre and post bronchodilator, using whole body plethysmography, to assess airway calibre, total lung capacity and air trapping. This is a highly sensitive and accurate method of measuring lung function and provides essential diagnostic information. We have previously performed these tests at age 13-16 years.
    - d. Spirometry and bronchodilator reversibility **(HV)**: Spirometry enables us to measure the volume and flow generated by a forced expiration and has been done at each visit since age 5 years. Flow measurements as they relate to lung volume give an indication of any flow limitation in the small airways. Measurement of spirometry before and after the administration of a bronchodilator (400µg salbutamol via a metered dose inhaler and large volume spacer) is the most commonly used test for the diagnosis and monitoring of lung disease. Where possible, participants who do not want to attend clinic and are too far away for a home visit (see below) will be offered the opportunity to perform home spirometry following video training on the technique, with a spirometer that will be posted to the participant (subject to equipment being available). **(OV)**
4. Questionnaires regarding current and previous asthma and allergy symptoms, exacerbations, medications, hospital admissions and diagnoses will be asked. **(HV and OV)**
    - a. Respiratory Questionnaire, based on the European Community Respiratory Health Survey Questionnaire (ECRHS), with additional questions from

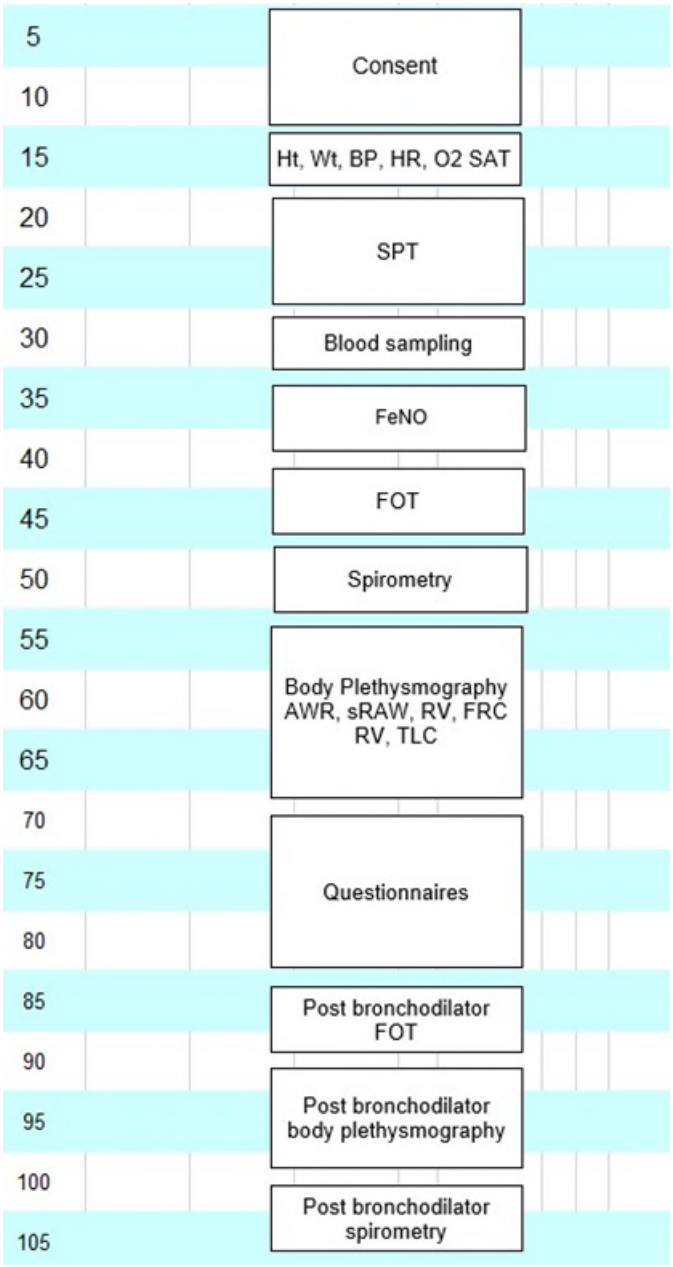
International study of Asthma and Allergies in childhood (ISAAC) for continuity, and previous asthma exacerbations and prescriptions, where participants will be asked to check on the NHS app where possible.

   b. Health Survey– SF-12.
   c. food allergy questionnaire (based on the EUROPREVALL questionnaire).
   d. Asthma Control Test – (ACT).
   e. Adult ADHD self-report Scale (ASRS).

5. Outdoor Environment and Pollution Monitoring questionnaire (previously administered at age 10-12 years; a short questionnaire about where participants lived and went to school during childhood, so that we can model exposure to pollutants and the effects on lung function and asthma). **(HV and OV)**
6. Up to 20mls of blood will be taken by the research team. **(HV)** This will be collected in the clinic for a clinic visit and at home for a home visit. The measurement of the FBC will be done in the clinical laboratories at Wythenshawe Hospital (MFT, the site of the study visit). The remaining sample will be processed in the research laboratories at Wythenshawe Hospital (MFT) and stored in the freezers pending further analysis or shipment. This will be for measurement of IgE, RNA and proteins (including CC16). Cells will be separated so that peripheral blood mononuclear cells (PBMCs) can either be analysed immediately or cryopreserved in liquid nitrogen for future cell culture and functional studies. Aliquots will be sent securely packaged via courier to research collaborators with whom we will have a Material Transfer Agreement, in the UK and abroad, once funding for this work has been secured. Samples will be shared in line with contractual requirements for analysis for this study where collaborators have not yet been identified

Data analysis will be conducted by University of Manchester Researchers and also by collaborators at Imperial College London, and University of Arizona, with whom we will have Material Transfer Agreements.

7. GP information: Participants will be asked to consent for the research team to access their primary care records to extract information on healthcare utilisation, diagnoses and medication prescriptions (this has been done previously up to age 10 years, and consent was sought at age 18+ years). **(HV and OV)**
8. We will also ask participants to complete an Equality, Diversity and Inclusion (EDI) survey, to help us comply with our policy of ensuring equality, diversity, and inclusivity in our work, in line with NIHR policy. This will not be linked to the research data but will be stored anonymously.



9. Samples will be analysed in the laboratories of the University of Manchester and the Manchester University NHS Foundation Trust. In addition, samples will be analysed in the laboratories of collaborating institutions in the UK, EU and outside the EU. Samples will be sent to collaborators at the University of Arizona, Tucson, Arizona, USA.
   ICH-GCP and Standard Operating Procedures will be adhered to when collecting, handling and processing all biological samples.
10. Genetic analysis: At previous follow up visit, study subjects have donated samples of blood for genetic analysis and gifted their samples, to be tested for possible new genetic associations in relation to asthma and allergy, carried out by the Manchester Asthma and Allergy Study group, (which may include researchers outside of the hospital) in the future. Extensive genotyping has already been completed on these samples and much genetic analysis has already been done and published. It is not necessary to collect further blood samples for genetic analysis (as whole genome genotyping has been

already done), but we propose to use existing genotyping data and link this to the clinic outcomes collected at the age 25 years+ follow up, as listed in the secondary objectives above (in particular, secondary objectives 1 and 3)

5.3 End of study

The end of the study will be when final participant has completed all the study procedures, and after the main analysis of biological sample has been completed. This is expected to be on or before December 2027. Following the end of the study, the data will be cleaned, and the database will be locked. The samples will be stored for up to 12 months after the end of the study date under the REC approval for verification and checking of the research data only.

Following declaration of the end of the study, the study will be adopted by a research tissue bank:- Manchester Allergy, Respiratory and Thoracic Surgery (ManARTS) Biobank REC: 20/NW/0302, IRAS: 285126 North West - Haydock Research Ethics Committee). This will facilitate further sample analysis and data analysis within a research ethics and governance framework.

6) STUDY PARTICIPANTS

6.1 Inclusion Criteria: (IRAS A17-1)

All participants who are part of the MAAS cohort and have not previously withdrawn from the study.

6.2 Exclusion Criteria: (IRAS A17-2)

MAAS participants who previously withdrawn.

6.3 Recruitment: (IRAS A27-1 – A35)

All participants (who have not previously withdrawn from the study of been lost to follow up) will be contacted and invited to take part in the 25+ follow-up (approx. 800) with 500 being a realistic figure to complete.

Previous participants who have not withdrawn from MAAS will be sent a copy of the participant information sheet (PIS) describing what is involved in the visit. First contact will be made by email where an address has been previously provided, or by text message with link if mobile number has been provided, or by post (if neither email nor phone number have been provided). They will be invited to book an appointment via an online interface (e.g. Sign in Scheduling), or by telephone or email. Further contact will be made 1-2 and 3-4 weeks after the first contact if no appointment has been made. Those that have not booked their visit after 5-6 weeks will be contacted directly by phone by the study team.

For those who chose not to attend the visit in person a version of the consent form will be completed online prior to completing the questionnaires online (or postal version can be sent if preferred).

The Chief Investigator will be responsible for the informed consent of participants and will ensure that any person with delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent will be obtained from participants using the Patient Information Sheet (PIS) and Consent Form (CF). The researcher will discuss the study procedures and answer any questions the participant may have. The participant's right to refuse taking part in the study without giving reasons will be respected. A contact point (MAAS study e-mail address and telephone number) will be provided where they may obtain further information about the study.

A paper copy of the consent will be given to the participant to sign in person; the original will be stored in the site file, a copy will be given to the participant, and the third copy will be stored in the hospital record. Participants can consent to complete some part of the visit and omit others.

6.4 Participants who withdraw consent [or lose capacity to consent]:

Participants will also be free to withdraw from the study at any time without giving reasons and without prejudicing their further treatment, as participation in the research is voluntary, without their care or legal rights being affected. Data and samples already collected will be retained in the study.

7) OUTCOME MEASURES

The primary outcome will be the prevalence of asthma in the cohort, as defined by responses to the respiratory questionnaire. This will be related to other clinical outcome measures and measures of environmental exposures, biomarkers and genetic markers

The secondary outcome measures will include:

1. prevalence of eczema, hay fever and food allergy as defined by questionnaires
2. prevalence of allergy to inhalant allergens (dust mite cat and dog and pollen) and to foods
3. classes of trajectories of measures of lung function (to identify predictors)
4. classes of wheezing illness - defined by frequency of episodes and exacerbations
5. measurement of CC16 in relation to asthma and lung function outcomes
6. classes of exposure to outdoor air pollutants - to relate to clinical outcomes.

8) DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

Only data that is essential for the purposes of the study will be collected.

All members of the research team who handle the data will be appropriately trained and familiar with the policies governing the confidentiality and security of the data collected during the study.

8.1 Data Collection Methods

Where possible, participants will complete questionnaires electronically, Data will be entered directly into a secure anonymised electronic online database. For home visits and in the event of a network failure the questionnaire data will be collected on paper and entered into the online database by a member of research staff at a later time point. Only the study ID will be recorded onto the paper copy, with no identifiable information. This will be via a UoM approved system (either be UoM Qualtrics or REDCap).

Skin test and Lung Function data will be collected on paper or printed from the respective device and entered into the online database by a member of research staff at the end of the visit. Blood results will be copied from the MFT electronic patient record (Hive) into the online database.

Validation of the data will be carried out during the study by members of the research team (e.g. via appropriate range and consistency checks).

8.2 Data Management

The University of Manchester is the data controller for the project

A Data Information Governance Risk review and an IG checklist has been conducted within the University of Manchester to facilitate the assessment of risks associated with processing participant data in this study. GDPR requirements and the DPIA will be reviewed annually.

A copy of relevant lung function and skin test results will be sent to the GP with a copy to the participant

8.3 Data Protection and Security

Each subject will be issued a unique identity number (UID) which will be used on all data (but not the consent form which will contain only the name). This pseudonymisation key will be generated by the data manager for the study team. The key linking the UID to the subject will be stored securely but separate to the clinical research data. Researchers from outside the University of Manchester will not have access to the key. The clinical research data will be stored under the UID and not the participant's name

Paper-based files will be kept in a locked filling cabinet in a locked office that requires staff swipe card access to the building and the room. Consent forms which contain the name of the participant (but not the UID in line with University of Manchester policy) will be stored separately from other paper documents (which will be labelled with the UID, but not the name). Computerised data will be stored on University of Manchester secure servers and will be password protected and within locked offices. Access is restricted to study team members.

Research data will be stored on a password protected database (either UoM Qualtrics or REDCap) with limited access only by study personnel. The data from the outdoor air quality questionnaire (Previous Addresses and School Details) will be stored on a separate password protected database (either UoM Qualtrics or REDCap) to the other questionnaire data. For those who consent to be contacted about future research, contact details with personal data will be stored separately on a password protected database in the secure Research Data Storage (RDS) at University of Manchester. Backups of the data will occur by the University IT support, in line with University policies.

Biological samples will be coded with the UID and barcoded locations of the samples will be recorded prior to storage, in a secure room with limited access.

In line with university record retention policy, consent forms for this study (non-interventional low risk studies) will be retained until 2 years after the end of the study. As the study will then be adopted by the Research Tissue Bank, consent forms will be passed to the research tissue bank at this time; the study data will be transferred in encrypted Excel files to the ManARTS Biobank trust servers using ZendTo.

Archiving – After the study ends, data will be archived in line with University of Manchester SOPs. Digital and hard copy data will be archived with Iron Mountain off site storage.

9) STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis

We will use linear or logistic regression models to assess the associations between parameters, reporting odds ratios (ORs) with 95% confidence intervals (CIs), with Bonferroni correction. We will use latent profile modelling to derive trajectory classes based on the development of outcomes over time. We will use weighted multinomial logistic regression models to ascertain early-life risk factors associated with each clinical trajectory. The posterior probability of

membership for each trajectory class will be used as weights to reflect uncertainty of class assignment; results will be reported as relative risk ratios (RRR) with 95% CIs.

Analysis of data will be completed using appropriate statistical packages e.g. SPSS, STATA, R, unix and python. Where appropriate statistical advice will be sought from collaborators at the University of Manchester and other collaborating institutions

9.2 Sample Size

As this is a population-based birth cohort, only those born into the study (n=1184) can be recruited, minus those who have withdrawn from further follow up (n=146).

we anticipate that approximately 500 will attend. 595 attended the last follow up.

A sample size of 500 would enable the accuracy of the prevalence of a particular outcome to within +/- 2% or +/- 3% depending on the prevalence estimate (i.e. the 95% confidence interval for the prevalence would extend from prevalence -2% to prevalence +2%).

10) MONITORING AND QUALITY ASSURANCE

This study will be subject to the audit and monitoring regime of the University of Manchester.

11) PEER REVIEW

The follow up of the cohort will be funded by a peer reviewed grant from the North West Lung Centre Charity and has been through the peer review process of the charity.

An application for additional funding has been submitted as part of a collaborative multinational project to the National Institute of Health. Although the grant scored highly (in the top 4% of grants reviewed), we have not yet had confirmation of funding. The data and sample collection can proceed without this funding, as it is needed for the CC16 measurement in blood samples which may be done on stored samples at a later date.

Previous cohort follow ups have been funded by the Medical Research Council and were peer reviewed as part of this process.

Relevant grants: Medical Research Council (MRC) G0601361 (2007-2012), MR/K002449/1 (2013-2014) and MR/L012693/1 (2014-2018), and MR/S025340/1 (2020-2024).

Participant and Public Involvement: Within the Manchester Asthma and Allergy Study, we have worked closely with NIHR Manchester BRC patient and public involvement and engagement centre, Vocal (https://research.cmft.nhs.uk/facilities-services/vocal). A focus group of MAAS participants was held in August 2024 to gauge participant views on conducting a further review of their health and lifestyle, and on accessing data from their health records. Information from the focus groups helped us to design the protocol, participant information sheets and consent form. Specifically, focus group participants had positive memories of taking part as children and were keen to attend a further visit, but felt reimbursement of travel expenses was appropriate. They appreciated that home visits would be available as well as online visits (with the possibility of home spirometry, which was well received), but reported that would be more likley to attend when back in Manchester visiting family. They reported that an online booking system would be more convenient, and they would value a prompt within the PIS to check with family about postcodes and addresses of homes and schools from childhood for the outdoor pollution questionnaire. On discussion of accessing their primary care records to extract information on

healthcare utilisation, diagnoses and medication prescriptions, they agreed that asking them to share information via the NHS app would be a desirable option as this allowed them to control what was shared. They asked to be copied in on study results sent to GP; for those who chose to register for the MyMFT app (linking to MFT new electronic patient record) the letter will also be visible on there. They were keen to receive an updated newsletter of study results and to include links to scientific papers (as ~ 50% had jobs in science).

12) ETHICAL and REGULATORY CONSIDERATIONS

12.1 Approvals

The study protocol will be submitted to the NHS Research Ethics Committee via the IRAS process. The study will be authorised by the Health Research Authority according to the legal requirements in England.

The selection of the subjects will not start before the approval of the Ethics Committee has been obtained and the study authorised by the Health Research Authority.

The study will be conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practices guidelines and following all other requirements of local laws.

a. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
b. All correspondence with the REC will be retained.
c. The Chief Investigator will notify the REC of the end of the study.
d. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

12.2 Risks

This is an observational study with no intervention, and it takes place at a single visit.

Blood sampling is a safe procedure and is unlikely to cause any problems.

Events that may be regarded as expected complications associated with the investigations are shown in the table below.

We do not anticipate any major ethical issues with this study. All research methods employed in this study have been previously applied in both healthy volunteers and patients with asthma. All the clinical procedures performed in this study are validated.

Tests performed during Clinic visit or Home Visits will be conducted by experienced researchers. All participants will be asked if they have any drug allergies at the start of the visit in line with MFT Medicines Policy, and this will be recorded in the hospital medical record.

Procedure	Known complications
Spirometry	Cough, breathlessness, light headedness
Airway Resistance, lung volumes	Cough, breathlessness, light headedness
Bronchodilators (salbutamol)	Tachycardia, tremor, cough, nausea, headache. This will be dispensed from the Trust Pharmacy and Trust SOPs will be followed in relation to the dispensation and provision of this to

	participants. Participants will be provided with a copy of the medicine information leaflet if this administered.
Oscillometry	breathlessness, light headedness, cough
FeNO	breathlessness, light headedness, cough
Skin Prick Testing	Wheals, itching. If this develops, we will offer antihistamine cream, in line with clinical practice. This will be dispensed from the Trust Pharmacy and Trust SOPs will be followed in relation to the dispensation and provision of this to participants. Participants will be provided with a copy of the medicine information leaflet if this administered.
Blood testing	Minor bruising, light headedness. It is possible that a participant could faint during blood tests; should this happen, it will be managed appropriately by the research staff

13)STATEMENT OF INDEMNITY

The University of Manchester has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

14)FUNDING AND RESOURCES

The Manchester and Allergy Study will use equipment already available in the North West Lung Research Centre, purchased with previous grants and owned by MFT. This stored in the Manchester and Allergy Study clinic and lung function rooms, and is maintained by the medical electronics department at MFT, and calibrations are completed by the research physiologist in line with study SOPs

This includes:

a. Blood Pressure, Heart Rate and O2 Sats will be measured on a DASH 2500 Patient Monitor.
b. Height will be measured using a stadiometer, weight and body composition with a Tanita bioelectrical impedance analyser.
c. a Vyaire Whole Body Plethysmograph
d. Tremoflo Airwave Oscillometry Device.

We will purchase (from the North West Lung Centre Charity grant):

e. a NIOX VERO for the measurement of exhaled nitric oxide
f. associated consumables such as mouthpieces and filters,
g. FBC consumable and measurement costs
h. Skin prick test allergen solutions and consumables
i. Monetary gift voucher as token of appreciation for attending (£10), and parking costs/travel expenses

Subject to equipment being available, where possible, participants who do not want to attend clinic and are too far away for a home visit will be offered the opportunity to perform home spirometry following live video training on the technique, with a handheld spirometer that will be posted to the participant. We will supply packaging so that the spirometer can be returned. It will then be made available for use in other BRC supported studies.
We have salary for a part time band 7 research nurse to plan and conduct the visits (from the North West Lung Centre Charity grant.)

The study will also be supported by the Manchester National Institute for Health and Care Research (NIHR) Manchester Biomedical Research Centre (BRC).
At the end of the study, the equipment will be used in other BRC supported studies.

15) PUBLICATION POLICY

Our expectation is that after data analysis, information from this study will be widely disseminated in the medical and scientific community. This will be achieved through a series of peer reviewed publications and meeting abstracts at local, national and international events. Information will also be distributed more informally through discussion with collaborators. We have an excellent track record of having research highlighted in regional, national and international media. The identity of study participants will be anonymised, and their names will not appear in any publications.

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List of abbreviations

MAAS	*Manchester Asthma and Allergy Study*
CC16	*Club Cell Secretory Protein*
COPD	Chronic Obstructive Pulmonary Disease
ISAAC	*International Study of Asthma and Allergies in Childhood*
BP	*Blood Pressure*
HR	*Heart Rate*
O_2Sat	*Oxygen Saturation*
LF	*Lung Function*
sR_{aw}	*Specific Airway Resistance*
R_{aw}	*Airway Resistance*
RV	*Residual Volume*
TLC	*Total Lung Capacity*
FRC	*Functional Residual Capacity*
FeNO	*Fractional Exhaled Nitric Oxide*
AOS	*Airwave Oscillometry System*
FOT	*Forced Oscillation Technique*
SOP	*Standard Operating Procedure*
ECRHS	*European Community Respiratory Health Survey*
SF-12	*Short Form 12 Health Survey*
ACT	*Asthma Control Test*
MFT	*Manchester University NHS Foundation Trust*
FBC	*Full Blood Count*
IgE	*Immunoglobulin E*
sIgE	*Specific Immunoglobulin E*

PBMC	*Peripheral Blood Mononuclear Cells*
SPT	*Skin Prick Test*
ICH GCP	*International Conference on Harmonisation-Good Clinical Practice*
PIS	*Patient Information Sheet*
CF	*Consent Form*
CRF	*Case Report Form*
UoM	*University of Manchester*
GDPR	*General Data Protection Regulation*
DPIA	*Data Protection Impact Assessment*
AE	*Adverse Event*
SAE	*Serious Adverse Event*