**Research proposal**

**Pilot OVERNIGHT study: A nOVEl approach to impRoviNg symptoms for people with pre-COPD usInG Hepa fiLTers**

# Project Team Roles & Responsibilities

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| **Role** | **Title** | **Name** | **Position** | **Affiliations** |
| Principle investigator | Dr. | Xin Dai | Research fellow, ECRHS 4 study coordinator | Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry & Health Sciences. |
| **Responsibilities** |
| Dr. Dai will be the lead investigator and study coordinator. She will be responsible for the overall conduct of the study, co-ordination of governance and management with senior investigators, working with the investigators to update study protocols, working with industry partners (Hepa filter manufacturer and air sensor supplier) to ensure they are adhered to protocols and timelines to produce the equipment. She will also lead the publication of results in high impact journals and dissemination and transfer for future larger RCT. |

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| **Role** | **Title** | **Name** | **Position** | **Affiliations** |
| Investigator | A/Prof. | Caroline Lodge | NHMRC emerging Leadership Fellow level 2,Dame Kate Campbell Fellow | Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry & Health Sciences. |
| **Responsibilities** |
| A/Prof Lodge is PI of the Australian arm of the multisite ECRHS. The current proposal is based on ECRHS. She will closely supervise the lead investigator Dr. Dai to action all key items in the study including designing study methodology, paper writing, stakeholder communication and scientific presentation. |

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| **Role** | **Title** | **Name** | **Position** | **Affiliations** |
| Investigator | Prof. | Shyamali Dharmage | Dame Kate Campbell & NHMRC Leadership Fellow,Head of the Allergy and Lung Health Unit,Deputy Director (Research) of the Centre for Epidemiology and Biostatistics | Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry & Health Sciences. |
| **Responsibilities** |
| Prof Dharmage is a world-recognised leader in Life Course Epidemiology of Allergy and Chronic Respiratory Diseases. She is highly-experienced in mentoring PhDs and ECRs. Prof Dharmage will provide strategic oversight and guidance to the CI team of this program. |

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| **Role** | **Title** | **Name** | **Position** | **Affiliations** |
| Investigator | Dr. | Rachel Tham | Research Fellow | 1. Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry & Health Sciences.
2. Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences.
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| **Responsibilities** |
| Dr. Tham is an environmental epidemiologist. She will be responsible for monitoring and modelling air quality using air sensors in this study. She will provide essential input into study design and interpretation of results.  |

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| **Role** | **Title** | **Name** | **Position** | **Affiliations** |
| Investigator | Dr. | Dinh Bui | Research Fellow | Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry & Health Sciences. |
| **Responsibilities** |
| Dr Bui has developed a novel model of lung function trajectories for predicting COPD risk. His work led to the new pre-COPD field of research, the basis of this study. He will use this knowledge to assist in identifying participants with pre-COPD, collecting and analysing data. He will also contribute to the study design and assist with paper write up. |

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| **Role** | **Title** | **Name** | **Position** | **Affiliations** |
| Investigator | Dr. | Anurika De Silva | Biostatistics Research Fellow | Methods and Implementation Support for Clinical and Health (MISCH) research Hub, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry & Health Sciences. |
| **Responsibilities** |
| Dr. De Silva is a biostatistician who will review the data collection forms and study database, review procedures for data management including data checking and cleaning, attend regular study group meetings, and write a detailed statistical analysis plan. Dr. De Silva will also conduct a full evaluation of the data including summarising the available data and the statistical analysis of the final study results. Dr. De Silva will be involved in the presentation of results both at conferences and in scientific papers on which they will be named as a co-author. |

# Resources

Our research will be conducted in University of Melbourne (UoM) and participants’ homes. We will recruit participants from European Community Respiratory Health Survey (ECRHS). This research is supported by UoM (E-MCR Project Catalyst Grant, Application ID: EMCRPC31). ECRHS is funded by National Health and Medical Research Council (NHMRC) (APP2008019).

# Background

## 3.1 Literature review and rational

COPD is a major public health problem. According to the 2016 Global Burden of Disease Study, COPD is the third leading cause of death, responsible for around three million deaths annually [1]. In Australia, COPD prevalence for adults aged 45 years or older is 4.8%, or over 4.64 million people [2]. COPD diagnosis is confirmed by demonstrating irreversible airflow limitation on spirometry, with a post-bronchodilator (post-BD) forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) ratio <0.7 [3]. By the time COPD is diagnosed, extensive and irreversible lung damage has occurred [4]. Pre-COPD is an early stage of disease that is currently not formally diagnosed. It is a new under-researched paradigm recognised by international respiratory researchers [5]. Given the transition from pre-COPD to COPD occurs over a long period of time, the pre-COPD phase represents a critical period for interventions to prevent the transition to COPD. Currently, no interventions have been established.

Besides cigarette smoking, recent studies from high income countries have reported increased risk of COPD in those exposed to household air pollution (HAP) [6-8]. HAP from heating and cooking comprises harmful gases and particulate matter (PM) [9]. Other HAP sources include from attached garages, barbeques, dust, aeroallergens, traffic, industry, and landscape fire smoke [10]. HAP is a major issue in Australia with less attention.

High efficiency particulate air (HEPA) filters work by removing particulate matter > 0.3µm in diameter with 99.95% efficiency. Evidence has suggested that lower exposure to airborne PM and allergens may reduce symptoms in people with respiratory diseases and may even stop progression of lung function loss [11, 12]. We aim to conduct a feasibility randomised controlled trial (RCT) on HEPA filter use in participants with pre-COPD. Our future aim is to perform a larger RCT of HEPA filter use to demonstrate the efficacy for stopping or slowing COPD development, in those with pre-COPD. The planned larger trial will require further funding and will be the subject of a new ethics application at a later date.

## 3.2 Research questions

1. To determine if the use of a HEPA filter is feasible and deliverable and to determine: barriers to participation/follow-up; feasibility of study assessment procedures; necessary time and resources required to deliver the intervention and assessments; willingness to participate in intervention/control group; adherence to filter use; risks/adverse effects of using filters.
2. To determine if application of a HEPA filter for pre-COPD participants in their bedrooms during night-time improves respiratory symptoms and sleep quality when compared with participants who use sham filters.

## Expected outcomes

Our proposed research will determine feasibility for a larger RCT to generate novel evidence for pre-COPD interventions to reduce the burden of COPD. This is the first clinical trial in the under-researched area of pre-COPD.

# Project design

## 4.1 Research project setting (physical sites, online forums and alternatives)

Our research will take place in participants’ homes. Participants will complete online surveys and/or telephone interviews. The returned data will be analysed at the University of Melbourne (UoM).

## 4.2 Participants

We will recruit participants from the Melbourne arm of the European Community Respiratory Health Survey (ECRHS). ECRHS is the largest international study of respiratory health in adults. It began with 10,000 participants invited in each of 29 centres in 14 countries. There have been three completed follow-ups and we have just commenced ECRHS IV on the Melbourne cohort. Respiratory symptoms and spirometry (lung function) have been measured at all follow-ups. The Australian ECRHS centre was established in Melbourne in the 1990s. ECRHS IV is the current follow-up and participants are now aged 50-75 years. Our proposed research will start during clinical testing phase of Melbourne ECRHS IV.

## 4.3 Power

A total of 20 participants will be recruited. Anticipating a 70% recruitment rate and using an exact method (Clopper-Pearson binomial), a sample size of 28 eligible participants is required to provide a 95% confidence interval of the true underlying recruitment rate of 51–87%. Assuming 20 participants are recruited and anticipating a 90% retention rate at 3 months and adherence rate of 80%, a 95% confidence interval of the true underlying retention rate would be 68-99% and adherence rate would be 56-94%.

## 4.4 Participants recruitment strategies and timeframes

Inclusion criteria: Participants will be identified as having pre-COPD based on both respiratory symptoms and lower baseline lung function. Respiratory symptoms will be identified from the ECRHS IV short survey, including questions on current wheeze, current asthma, current asthma medication, current nasal allergy, chronic cough, chronic phlegm, and use of inhaled steroid medication. Lower baseline lung function will be identified as lower 50 percentile of pre-bronchodilator FEV1/FVC using GLI equation lung function reference at ECRHS IV. We will recruit the firs 20 eligible participants who consent to be involved.

Exclusion criteria: Participants do not meet the spirometric criteria for COPD (post-bronchodilator FEV1/FVC <0.7)[13] at ECRHS IV.

We would like to send invitations to eligible participants’ mobile phones, emails, postal addresses and/ or distribute to participants when they attend for ECRHS IV clinical tests. We will follow up the invitations by telephone calls and emails. We would like to start recruitment once we have ethics approval, aiming for April – May, 2024.

## 4.5 Approach/es to provision of information to participants and/or consent

An informed consent with explanation will be provided to participants regarding the purposes of the research and intended use of data, before they start our proposed study.

## 4.6 Randomisation

Participants who meet the inclusion criteria and consent to the proposed study will be randomised using randomly permuted blocks of varying sizes in a 1:1 ratio, stratified by smoking, atopy, and ventilation. The randomisation list will be computer-generated by an independent statistician and carried out centrally to ensure concealment. The randomisation schedule will be uploaded and stored on the study’s REDCapTM database at the University of Melbourne.

## 4.7 Intervention and control (HEPA/placebo filter)

HEPA filter air purifiers will be placed in participant’s bedrooms to be used during the night over 3 months. HEPA filters are portable and capable of cleaning air in a standard room. Participants will be instructed to use the filters every night. Those randomised to the control group will receive placebo filters, with the internal HEPA filter and carbon filters removed. Placebo filters will, however, run as per HEPA filters including similar noise, airflow, and appearance.

## 4.8 Data collection/Gathering

Primary outcomes: For feasibility, adherence and acceptance, we will collect data from the recruitment, air quality monitors, and online surveys.

Recruitment

* Percentage of potential participants who meet the inclusion criteria in this cohort.
* Percentage of eligible participants willing to be randomised.
* Barriers to participation in the study.

Online surveys

* Number of participants using filters during study.
* Problems encountered with assessment procedures.
* Barriers to filter use.
* Number of participants assessed every four weeks.

Air quality monitor

* Number of participants following filter instructions. A drop of over 60% in PM levels will be defined as HEPA filter adherence amongst those with active filters. This will be assessed after study completion and unblinding.

Secondary outcomes: Changes of respiratory symptoms and sleep quality. We will collect data from online questionnaires.

Questionnaires

* St George’s Respiratory Questionnaire for COPD patients (SGRQ-C) – 14-item questionnaire designed to measure the impact of obstructive airways disease on overall health.
* Respiratory Symptom Questionnaire (RSQ) – 4-item questionnaire to assess respiratory symptoms and their impact on daily activity.
* Functional Outcomes of Sleep Questionnaire (FOSQ-10) – 10-item questionnaire to measure the impact of sleepiness on the ability on daily activities in adults.

We will conduct feasibility and adherence check via online survey by sending SMS/email and using air quality monitors after study commencement at 3, 7 and 14 days, at one month, and every month thereafter. Firstly, an SMS/email will be sent with a link. If there is no response, we will conduct telephone interviews. Baseline respiratory symptoms will be collected using SGRQ-C and RSQ; baseline sleep quality will be collected using FOSQ-10, monthly respiratory symptoms will be collected using RSQ. All participants will repeat the SGRQ-C and FOSQ-10 at the end of 3 months.

## 4.9 Blinding

The study will be double blinded. Both researchers and participants will be blinded to filter type. Once the HEPA filters are delivered to The University of Melbourne, an independent investigator will record the series numbers linked to intervention/placebo, an independent biostatistician will provide a randomisation list, an independent investigator will send HEPA filter with specific series number based on randomisation list to participants. The statistical analysis plan will be written and published on our research centre’s website while blind to group allocation. Main statistical analyses will be performed blinded to group details.

## 4.10 Data management

Dr. Dai is the PI for the research project, and she is also the study coordinator for ECRHS IV Australian arm and she will take responsibilities for data management (establishment of the REDCapTM survey and data collection; transferring data from University of Melbourne REDCapTM to University of Melbourne secure research drives, keeping and storing the data). She will be assisted in these processes with advice and guidance from A/Prof Lodge (PI of the ECRHS IV) and Prof Dharmage (CI on previous ECRHS follow-ups and PI of 3 respiratory cohort studies based at University of Melbourne). A/Prof Lodge will be working closely with Dr. Dai to create the REDCapTM platform and be involved in the mailout and data collection and transfer.

**4.10.1 Store data**

Data will be initially collected into REDCapTM, a secure collection system advocated by the University of Melbourne. The data on the secure REDCapTM OVERNIGHT (ON) project will only be accessible for the project team through specific individual password entry. Only 2-3 members of the team will have full access rights - eg able to modify data instruments and download data. The REDCapTM ON project will contain identifying participant information including names, dates of birth, and email addresses. This will enable us to send survey links to individuals through their previously collected email addresses. These addresses have been collected during earlier follow-ups from the European Community Respiratory Health Survey (ECRHS) and were supplied by participants to researchers for the current purpose- contacting the participants for further study processes including new follow-ups. The only identifying data the participant will send back to us on the REDCapTM ON surveys are first names and dates of birth. We will use these fields to verify that the person filling out the survey is in fact the ECRHS participant. If there is a discrepancy between the information given by the potential participant and the date/name recorded in our data, then we will contact the participant by telephone or email to resolve this discrepancy. If the data does not belong to an ECRHS participant, it will not be used in this follow-up and will be removed from the REDCapTM database.

Once data collection is complete for the REDCAP ON project, all collected data will be downloaded from REDCapTM and stored on secure University of Melbourne drives. For other collection methods that may arise: Any surveys collected by telephone will be entered electronically into the same REDCapTM platform. Paper surveys will be returned by a provided certified mail envelope. Any paper surveys collected will also be entered into the REDCapTM platform, and then the paper surveys will be safely destroyed.

All collected data will be removed from REDCapTM and transferred to secure university servers at the end of the project. The participant details (named, address, etc) will be stored in a separate file to the other data and linked only with a participant id. Only named University of Melbourne researchers on this application will have access to these data.

**4.10.2 Transfer data**

Though ECRHS is an international study, we don’t plan to transfer data to European centres as this study is designed and conducted independently by Melbourne arm.

**4.10.3 Use and disclose of data**

As our proposed study is a sub-study of ECRHS, our data management will comply with the formal data access and Usage policy - Data Protection Act 1998(UK) and processes all personal information in accordance with the following 8 Data Protection Principles:

* be obtained and processed fairly and lawfully and shall not be processed unless certain conditions are met
* be obtained for a specified and lawful purpose and shall not be processed in any manner incompatible with that purpose
* be adequate, relevant and not excessive for those purposes
* be accurate and kept up to date
* not be kept for longer than is necessary for that purpose
* be processed in accordance with the data subject's rights
* be kept safe from unauthorised access, accidental loss or destruction
* not be transferred to a country outside the European Economic Area, unless that country has equivalent levels of protection for personal data Staff and students of the College, or others who process or use any personal information for the College, must ensure that they follow these principles at all times (not applicable to this study)

**4.10.4 Destroy and achieve the data**

Our data will be kept for at least 7 years after the most recent publication.

## 4.11 Data Analysis

Dr. De Silva, a biostatistician within the Methods and Implementation Support for Clinical and Health (MISCH) research Hub, which provides high level clinical research support including in the design and analysis of RCTs, will devise a formal detailed statistical analysis plan for the study prior to unblinding to group allocation. The analysis will include all participants according to their randomised allocation (intention-to-treat (ITT)) and reporting of the findings will follow CONSORT guidelines [14]. Continuous data will be summarised using mean (standard deviation) or median (25th – 75th percentile), and categorical data will be summarised using frequencies and percentages. The proportion and corresponding two-sided 95% confidence intervals (CIs) calculated using the exact (Clopper-Pearson binomial) method will be presented for the primary outcomes on feasibility. Results of feasibility outcomes will be presented for all randomised patients combined. For secondary outcomes: respiratory symptoms measured using the SGRQ-C, and sleep quality measured using the FOSQ-10 score, at 3 months, will be analysed using linear regression models adjusted for baseline scores. Respiratory symptoms (RSQ) will be analysed using a constrained longitudinal data analysis (cLDA) model [15] The response will consist of all RSQ scores (at baseline, and every 4 weeks) and the model will include factors representing treatment, time (categorical), and treatment-by-time interaction, with the restriction of a common baseline mean across treatment groups. All analysis models for secondary outcomes will be adjusted for the stratification factors smoking, atopy status and ventilation.

## 4.12 Identified risks and risk migration

**Identified risks:** Participants may be distressed if they know they are identified as pre-COPD cases. Discussion of pre-disease status is a potentially sensitive topic. These participants have been adversely affected by chronic respiratory diseases for long time.

Other than this, our intervention HEPA filter air purifiers are widely used in community and very safe for participants.

**Risk migration:** To address potential distress that may arise from pre-COPD or other questions, we have established a destress management plan and provided contact details in the plain language statement for lifeline and beyond blue.

## 4.13 Strength and benefits

We have a unique opportunity to investigate the feasibility of using HEPA filters for pre-COPD in our Melbourne arm of the ECRHS cohort. ECRHS participants are being recruited for the current follow-up and we have updated contact details. Furthermore, our participants are aged 50-75 years; an ideal age to detect pre-COPD. The current follow-up (ECRHS IV) commences clinical testing in January 2024.

Our approach will inform a larger RCT that will significantly progress the research field towards implementation of an effective solution to pre-COPD area and has strong potential to significantly improve health care practice and policy. If the effectiveness of HEPA filter use can be confirmed in a larger trial, they will be a low cost, easy way to prevent pre-COPD progressing to COPD.

# Results, outcomes and Future Plans

Project outcomes will be reported at conferences and through publication in high quality journals. All information will be in aggregate form with no possibility of individual participant identification. A summary of aggregate information about the study will be provided to ECRHS participants in the form of a short newsletter via their personal emails at the conclusion of the study. We will translate our research into a larger RCT. If successful, our trial and subsequent larger trial will pave the way for future research at the community level.

# Reference

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